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Protocol

Enhanced Patient Activation in Cancer Care Transitions: Protocol for a Randomized Controlled Trial of a Tailored Electronic Health Intervention for Men With Prostate Cancer

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Abstract

Background: Prostate cancer has increased in incidence worldwide and is the leading cause of cancer death in 24 countries. The most common treatment is radical prostatectomy. However, surgery is associated with postoperative complications such as urinary incontinence and sexual dysfunction, causing decreased quality of life. If survivors are encouraged to be more active in self-care management, the symptom burden may decrease and quality of life may improve. An electronic health (eHealth) intervention based on motivational behavioral theory has been developed for this purpose.

Objective: This study aimed to compare the effectiveness of standard care in combination with a tailored eHealth and mobile health self-management support system, electronic Patient Activation in Treatment at Home (ePATH), with standard care of adverse effects of prostate cancer treatment (urinary incontinence and sexual functioning) in men undergoing radical prostatectomy. The secondary aim was to test the effect on patient activation, motivation, overall well-being, and health literacy over time in and between groups.

Methods: A pragmatic multicenter, block-randomized controlled trial with 2 study arms, standard care (control) and eHealth-assisted standard care (intervention), for patients undergoing radical prostatectomy. For 80% power, a sample of 242 men will need to be recruited.

Results: Recruitment started in January 2018 and is expected to be completed by August 2019. Data collection will be completed in August 2020. The first cross-sectional results from this trial are anticipated to be published in January 2020.

Conclusions: With the increasing number of prostate cancer survivors, attention should be paid to rehabilitation, psychosocial care, and support for endurance of self-care to reduce suffering from adverse treatment effects, poor quality of life, and depression because of postoperative complications. This project may increase knowledge of how patients can be supported to feel involved in their care and returning to as normal a life as possible. The anticipated effects of ePATH could improve health outcomes for individuals and facilitate follow-up for health care professionals.

Trial Registration: International Standard Randomised Controlled Trial Number: 18055968; http://www.isrctn.com/ISRCTN18055968 (Archived by WebCite at http://www.isrctn.com/ISRCTN18055968).

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KEYWORDS

medical informatics; eHealth; mHealth; motivation; patient activation; prostate cancer; self-management

Introduction

Background

Prostate cancer is increasing in incidence worldwide, in both developed and developing countries, and it has been ranked as the eighth most common cause of cancer death globally. A growing and aging population must be considered as a contributing factor [1]. In Sweden, over 10,000 men are diagnosed with prostate cancer every year [2]. As novel diagnostic methods and treatment approaches have significantly improved cancer survival, the number of people living with disabilities after cancer treatment is also increasing [3]. The most common treatment is radical prostatectomy (RP), which shows >95% survival 15 years postsurgery [4]. Prostate cancer survivors commonly experience long-term consequences related to adverse effects of treatment, which can reduce quality of life. Specific adverse effects following local treatment (ie, RP and high-dose radiotherapy) include urinary leakage, loss of libido, and erectile dysfunction [5-7]. Further symptoms affecting functioning in everyday life, such as psychological distress, depression, fatigue, and muscular weakness, are prevalent [8], and an increased risk of suicide is evident in the first 12 months after diagnosis [9,10]. Thus, promoting support for management of long-term physical side effects for men with prostate cancer is of utmost importance.

In 2015, the Swedish government launched a national reform to standardize cancer care pathways with the goal of speeding up cancer treatment, increasing patient involvement and satisfaction with cancer care, and reducing waiting times and regional inequalities [11]. Each patient is assigned a contact nurse who will act as a primary caregiver contact throughout the treatment period and improve care coordination, availability, and patient participation throughout the care trajectory in line with the national reform. Yet, patients have reported unmet information needs along their cancer trajectories [11-13], especially lack of information about cancer treatment and its adverse effects, as well as a need for self-management support in the aftermath of surgery [14,15].

Adverse Effects of Prostate Cancer Treatment

Health-related quality of life in men with prostate cancer is closely associated with urinary and sexual bother and dysfunction following prostate cancer treatment. Urinary incontinence (UI; incomplete emptying, frequent dysuria, urgency, weak stream, straining, or nocturia) is common, which may affect functioning in daily life by hindering return to work and participation in social and physical activities, events, or sports [6,7]. Sexual dysfunction after prostate cancer treatment is a multifaceted problem with UI in relation to sexual activities, various orgasmic disturbances, penile shortening, and *de novo* deformity. Concerns about possible recurrence of the cancer [7] are mixed with feelings of dissatisfaction with body image, reduced physical function, emotional lability, and decreased masculine self-esteem [5]. Thus, psychological factors in relation to sexuality as well as the importance of involving the partner should be acknowledged during the rehabilitation phase [16].

Prostate Cancer Rehabilitation

Recovery after prostate cancer treatment focuses on urinary function, sexual function, and the return to daily life. Currently, pelvic floor muscle training (PFMT) is recommended for UI following prostate cancer treatment. However, previous research shows varying effects of PFMT [17], and there is controversy regarding whether postoperative PFMT is effective for achieving urinary continence. Only 2 of 21 studies from the Cochrane review by Campbell et al (2012) [17] showed that postoperative PFMT had a statistically significant benefit. Two systematic reviews [18,19] that investigated preoperative PFMT showed inconsistent results on common side effects, including erectile dysfunction and incontinence. Chang et al [18] found evidence to suggest that preoperative PFMT improves early but not long-term continence rates. The etiology of UI after RP is multifactorial, and the mechanisms for how PFMT improves postoperative continence in men have not been fully elucidated, which may explain the inconsistent results. Furthermore, adherence to PFMT exercises and optimal frequency and number of repetitions are still sparsely studied.

Rehabilitation of sexual function is often pharmacological. However, survivors of prostate cancer are less likely to gain a proper effect from medical treatment [20]. Medical treatment is directed toward erectile dysfunction, and oral treatment with phosphodiesterase-5 inhibitors (PDE5Is) is the first-line choice. Although treatment with sildenafil (a PDE5I) is often successful, discontinuation rates for medical treatments of erectile dysfunction, including sildenafil, are found to range from 50% to 60%. Thus, a high number of men choose not to continue using the medication despite treatment being efficacious [21,22]. The current literature suggests that penile rehabilitation should start as early as possible, preferably the day after surgery. This means that PDE5Is may be most effective if treatment is initiated as soon as the diagnosis and surgery dates are confirmed [23]. However, the problem is complex, and it is likely that medication alone is simply not enough [21]. Literature shows that hypoactive sexual desire following RP occurs in 60% to 80% of men. This could partly be because of a psychological impact of the cancer on mental health and body image [24]. Although there is a place for medical and surgical therapies in erectile function recovery and or preservation, psychological and sexual counseling may be equally important in sexual rehabilitation after RP [24]. Therefore, alternatives such as sexual therapy techniques (sexual communication and stimulation) have been suggested [25].

Exercise is increasingly seen as significant in prostate cancer rehabilitation as a strategy to enhance sexual function as well as improve feelings of masculinity and reduce the distress men experience after prostate cancer [26]. The national

recommendations on physical activity in cancer are 20 min of endurance training daily, along with aerobic training or household work 1 hour per week [27]. A meta-analysis [28] shows that introducing exercise in the rehabilitation may reduce the loss of muscle mass, fatigue, and psychological morbidity that may arise from cancer treatment. First-degree evidence shows that exercise improves quality of life, fatigue, and body strength. A systematic meta-review suggests that exercise also has an effect on incontinence in men with prostate cancer [29], and PFMT together with exercise might have a positive effect on sexual activity [28,30]. Altogether, there is a growing body of literature suggesting that single interventions are not enough to address the complexity of adverse effects of prostate cancer treatment. Rather, a combination of multiple interventions, including PFMT, exercise, cognitive behavioral therapy, psychoeducation, and peer support, is suggested to be the most effective in decreasing distress and improving health-related quality of life [28,30,31].

Web-Based and Mobile Electronic Health Apps

Electronic health (eHealth), referring to health services delivered or enhanced through the internet and related technologies [32], has the potential to meet patients' needs for tailored information and provide person-centered self-management support and encouragement for sustained healthy behaviors [33]. Increasingly, medical and public health practices are supported by mobile devices (mobile health, mHealth) that allow for bidirectional communication or on-demand access to health services, extending the accessibility of support beyond temporal and physical boundaries [34,35]. Despite the opportunities provided by mHealth apps for remote support and communication and an abundance of apps on the market, only a few apps focus on supporting patients during cancer treatment and follow-up [36]. Existing studies suffer from poorly validated information, and there is still a lack of rigorous trials regarding quality of life and postoperative rehabilitation in prostate cancer. Ongoing studies in Canada [37], the United Kingdom [38], and Sweden [39] explore the effects on early detection or follow-up care of introducing e & mHealth prostate cancer care with a focus on increased patient participation and interaction. However, different theoretical frameworks and intervention strategies are used to approach this goal.

This protocol describes the third phase of the electronic Patient Activation in Treatment at Home (ePATH) project, which started in 2015, targeting the care trajectory of cancer patients. The first phase explored prostate cancer patients' need for support, during cancer treatment and follow-up, that facilitates self-management activities and a proactive interaction with health care professionals [14]. The second phase encompassed development of the content and functionality of the eHealth- and mHealth-assisted self-management support system, ePATH, by applying user-centered design, testing and optimizing in iterative cycles to satisfy patient requirements, and adapt to the context [40,41].

The aim of the third phase was to compare the effectiveness of a tailored eHealth- and mHealth-assisted self-management support as a complement to standard care, with standard care. Primary outcomes are postoperative adverse effects (ie, urinary and sexual bother and function) in men undergoing RP. The secondary outcomes are physical activity, patient activation, motivation, health literacy, and overall well-being, which may be associated with the primary outcomes and have a mediating or confounding effect on the intervention.

The hypotheses of the study are the following:

1. The ePATH self-management support system will have a greater effect than standard care on patient-reported outcomes of UI and sexual bother and function at 1, 3, 6, and 12 months after RP.
2. The ePATH self-management support system will have a greater effect than standard care on (1) physical activity, (2) patient activation, (3) motivation, (4) health literacy, (5) overall health and well-being, and (6) endurance and adherence to self-care at 1, 3, 6, and 12 months after RP.

Methods

Design

This protocol describes a pragmatic multicenter block-randomized controlled trial with 2 study arms for patients undergoing RP: standard care (control arm) compared with standard care in combination with the ePATH self-management support system (intervention). A pragmatic trial design has been chosen to test whether the intervention (ePATH) works under normal conditions in routine clinical practice [42]. The protocol conforms to Standard Protocol Items: Recommendations for Interventional Trials guidelines (Table 1).

Participants

All men diagnosed with prostate cancer at the study sites in Southeast Sweden where the chosen treatment is RP (open, laparoscopic, or robot-assisted) will be eligible. Inclusion criteria include being able to speak, read, and understand Swedish, having or being able to get a mobile BankID (the leading solution for electronic identification used in Sweden) for safe handling of personal information, having access to an email address, and being computer literate.

Recruitment

Consecutive recruitment of patients will take place at 3 surgical and urology clinics in southeast Sweden. Eligible patients are to be identified by the contact nurses at the 3 study sites. In this study, the contact nurses will act as the communication channel among the researchers, the clinics, and the patients. The patients will receive both verbal and written information about the study in conjunction with diagnosis. Within 1 to 2 weeks, the contact nurses will contact each patient and ask about interest in participating in the study, and those who volunteer will submit their written consent form to the contact nurse (site B) or send their written consent in a prestamped, addressed envelope to 1 of the researchers (AH; site A and C; Figure 1). The researcher (AH) will send the Web-based baseline questionnaire to the patients. Afterward, the patients will be randomized to the 2 study arms. Patients randomized to the intervention group will receive an email informing them that an account has been created in ePATH. Patients randomized to the control group will receive an email telling them that no account has been set

up (Figure 1). Due to the nature of the intervention, blinding of contact nurses or patients is not possible. None of the researchers are involved in patient care.

Table 1. Overview of timepoints, enrollment and assessments.

Study period	Timepoint						
	Enrollment: 4 weeks pre-RP[a]	Baseline: 2 weeks pre-RP	Discharge: 3-7 days post RP	Follow-up 1 month	3 months	6 months	12 months
Enrollment							
Eligibility criteria: speak, read, and understand Swedish; Active email address; Planned RP surgery; Computer literacy; Access to computer, tablet, and mobile phone; Mobile BankID, or willing to apply for mobile BankID	X[b]	—[c]	—	—	—	—	—
Information about the study	X	—	—	—	—	—	—
Informed consent (written)	—	X	—	—	—	—	—
Allocation: cluster randomization; Intervention: standard care+ePATH[d]; Control: standard care	—	X	—	—	—	—	—
Journal data: cancer severity, length of hospital stay, type of surgery, postoperative complications	—	—	T_0[e]	—	—	—	—
Assessment							
Demographic data	—	T_0	—	—	—	—	—
Expanded Prostate Cancer Index Composite	—	T_0	—	T_1	T_2	T_3	T_4
Pelvic floor muscle training	—	—	—	T_0	T_1	T_2	T_3
Physical rehabilitation	—	—	—	T_0	T_1	T_2	T_3
Physical activity (SGPALS[f])	—	T_0	—	T_1	T_2	T_3	T_4
Sexual rehabilitation	—	—	—	T_0	T_1	T_2	T_3
Patient Health Questionnaire	—	T_0	—	—	T_1	T_2	T_3
Needs Satisfaction Frustration Scale	—	T_0	—	—	—	T_1	T_2
Patient Activation Measure	—	T_0	—	—	T_1	T_2	T_2
Cancer Behavior Inventory	—	T_0	—	—	T_1	T_2	T_3
General health (RAND-1[g])	—	T_0	—	T_1	T_2	T_3	T_4
Sleep Condition Indicator (short version)	—	T_0	—	—	T_1	T_2	T_3
Fatigue Severity Scale	—	T_0	—	—	T_1	T_2	T_3
Communicative and critical health literacy	—	T_0	—	—	—	T_1	T_2
Total questionnaire items	—	67	—	33	53	71	77

[a]RP: radical prostatectomy.

[b]X: procedure will be done.

[c]Not applicable.

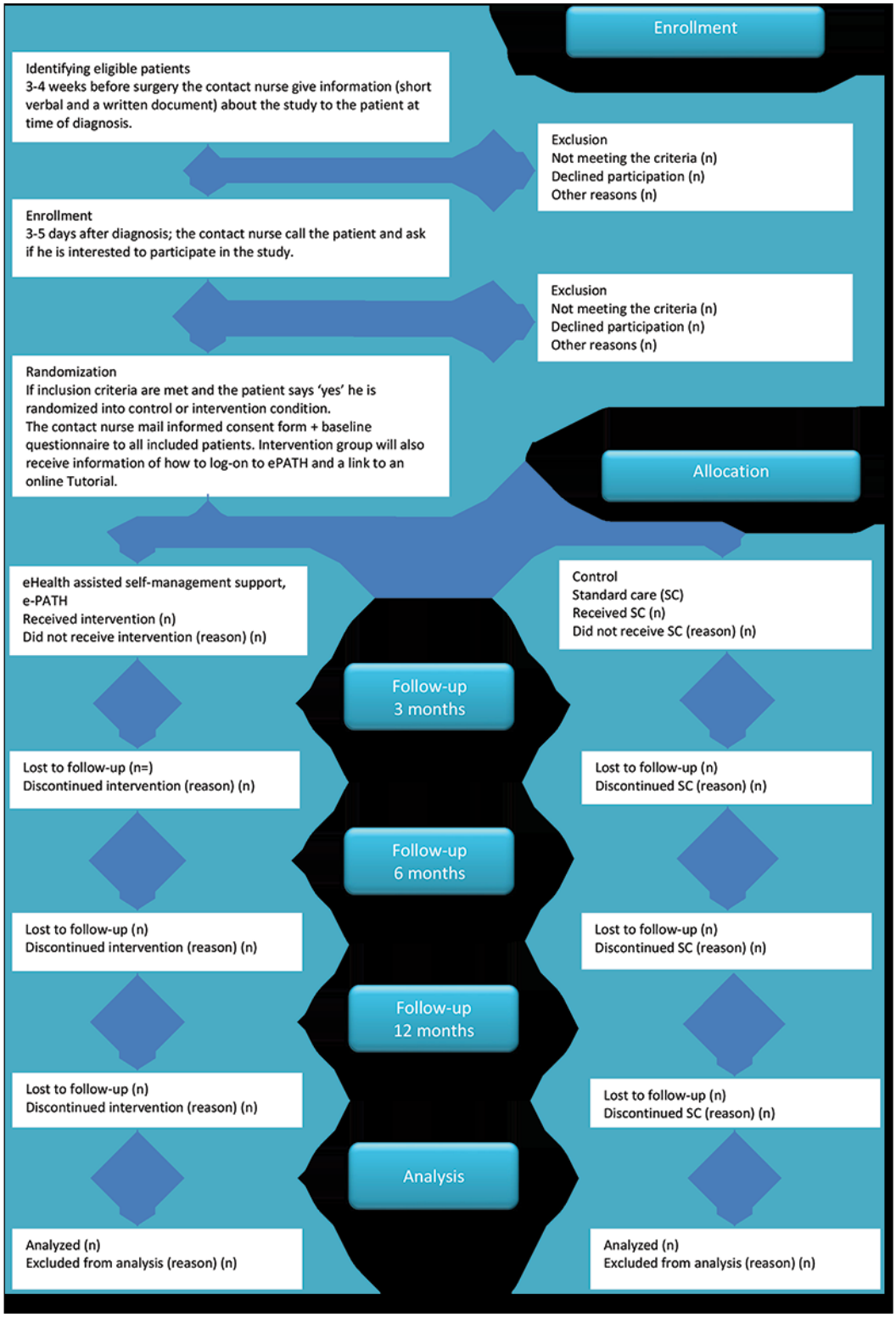
[d]ePATH: electronic Patient Activation in Treatment at Home.

[e]$T_{0...4}$: Time point for baseline (=0) or follow-up (=1-4) assessment.

[f]SGPALS: Saltin-Grimby Physical Activity Level Scale.

[g]RAND-1: 1 item from Veteran's RAND 12-Item Health survey.

Figure 1. The CONSORT diagram shows how patients' recruitment and flow through the randomized trial of two groups including attrition rate will be reported. (n) denotes the number of patients included and lost at each step.



Sample Size

Considering an effect size of 0.5 and a maximum of 4 domains (urinary, bowel, sexual, and hormonal) on the Expanded Prostate Cancer Index Composite with a 2-sided 5% significance level and a power of 80%, a sample size of 121 patients per group will be necessary given an anticipated dropout rate of 25% [43].

Randomization

A computer-generated block randomization list will be produced by an independent statistician, who is not involved in the trial, to allocate participants to the 2 study arms. The statistician will retain information about block sizes and the randomization list for the duration of the study. The order will be concealed from the researchers through the use of sequentially numbered, opaque, sealed envelopes. The envelopes will be opened

consecutively by 1 of the researchers (CWe) when patients have been included and allocated to the study arms. The researchers involved in the study will be blinded to block sizes.

The Electronic Patient Activation in Treatment at Home Intervention

ePATH is conceptually based on a theoretical framework, self-determination theory [44], and the assumption that promoting autonomy, competence, and relatedness are factors that foster intrinsic motivation and engagement in sustained self-management. Patient activation in self-care entails understanding one's own role in the care process, having the knowledge, skills, and confidence to perform the required behaviors [45], and creating the social support necessary for the initiation and maintenance of the desired behavior [44,46]. In ePATH, autonomy is supported by an engaged patient-nurse interaction, enabling patients to make a selection of self-care activities. Relatedness is supported through the message function, which will enable a 2-way communication with the contact nurse. Support for autonomy, competence, and relatedness in ePATH is expected to enhance patients' motivation to engage in self-care.

ePATH is developed as a Web-based tool and also comprises a mobile app for mobile phones. The system makes use of national services for safe authentication for citizens (mobile BankID) and health care staff (e-legitimation, SITHS). ePATH provides access to tailored comprehensive information about diagnosis and treatment, a rationale as to why self-care is needed, health care contacts, a list of medications, and, finally, a set of self-care activities, with self-selected goals and ratings related to the activities.

ePATH contains functionality, enabling the patient to communicate with his or her health care contacts, report self-care activities (eg, PFMT or physical exercise), symptoms of relevance for diagnosis (eg, UI, sexual bother and functioning, distress, and fatigue), and follow-up on reported data over time. Notifications to exercise or take medication can be activated to provide the patient with support and reminders.

Self-care activities in ePATH focus on PFMT, psychosexual self-management, and exercise, as these activities are directed at the main symptoms after surgery. Self-care activities for UI include PFMT in the form of Kegel exercises (ie, contraction and relaxation of the pelvic floor muscles) 3 times per day to increase strength. A suggested physical exercise program including endurance training (jogging, running, etc) and resistance training (weight lifting, sit-ups, planks, etc) will be available. The intensity of exercise is determined based on the physical condition of the patient and can be assessed by the patient using the revolutions per minute Borg scale in the app; examples of suitable activities have been developed in collaboration with a physiotherapist [47-48]. For most men, sexual function is affected by the surgery. To increase the patients' understanding of the postoperative situation and rehabilitation options, ePATH provides information about medical treatments and self-care activities for the sexual rehabilitation. There is also a diary function, where the men can write down their feelings, experiences, and thoughts related to sexual bother and function.

Intervention Group

The intervention group is treated in accordance with the standard guidelines for RP at the clinic and the group has access to the ePATH self-management support system. Information about ePATH and how to navigate the app is provided in a written pamphlet. For those participants who so wish, a face-to-face meeting with the contact nurse or researcher may be arranged for practical guidance and training. Contact nurses at each of the 3 study sites have likewise been trained in how to navigate in the ePATH as well as in the protocol to ensure standardized follow-up.

At inclusion, the contact nurse and the patient review self-care activities and tailored goals of self-care. Patients have the possibility to evaluate and adjust goals and activities during the care trajectory through the message function in ePATH, over the phone, or in person during follow-up visits. Furthermore, the nurses check that patients are aware of the functions of ePATH: how to send messages, register activities performed and medications taken, make notes, and activate reminders.

Control Group

Men randomized to the control group receive standard care following RP, with verbal and written information about PFMT (Kegel exercises), the diagnosis, the surgical procedure, and symptoms related to treatment (ie, urinary symptoms and affected sexual function). Follow-ups after discharge are in accordance with normal procedures at the clinics, with visits to an urotherapist or sexologist, a contact nurse, and a surgeon. As study sites are located in different counties, standard care is organized differently at each site (Figure 2).

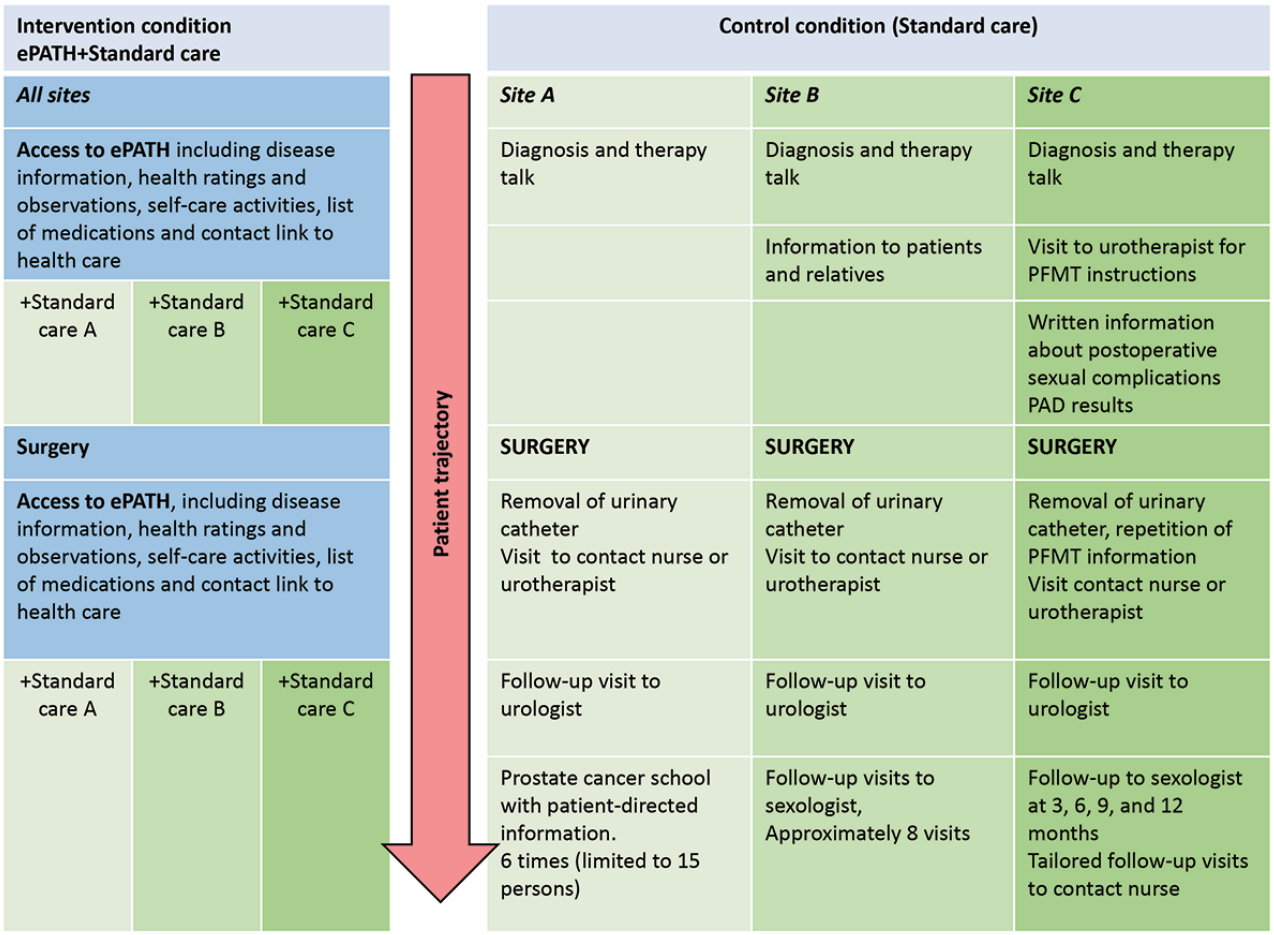
Outcome Measures

Participants in both study arms are asked to complete questionnaires at baseline and at 1, 3, 6, and 12 months after surgery. The contact nurses extract information on cancer severity (Gleason score), surgical procedure (open, laparoscopic, or robot-assisted), length of hospital stay, and possible postoperative complications that affected discharge from the patients' medical records. A detailed time schedule of assessments and questionnaires is presented in Table 1.

At baseline, sociodemographic questions about age, marital status, educational level, and household income are included.

Primary outcomes are patients' urinary and sexual bother and function, measured by use of the Expanded Prostate Cancer Index Composite-26 item, which contains 26 items to measure patient function and bother after prostate cancer treatment in urinary, bowel, sexual, and hormonal domains. Higher scores represent better health-related quality of life [43]. A total of 2 items concerning frequency of performed PFMT and support of sexual rehabilitation will also be included. See Textbox 1 for secondary outcomes.

Figure 2. Patient trajectories at the 3 different study sites of the ePATH intervention.



Analysis

Descriptive statistics will be presented with measures of central tendency and dispersion, as well as frequencies or percentages. The effectiveness of the intervention will be evaluated separately for the 2 hypotheses. As the trial involves repeated measures of data, a linear mixed model will be used to analyze the primary and secondary outcome measures. For ordinal outcome variables, a generalized estimating equation will be employed. The latter model will be used to evaluate the effect of the intervention on UI and sexual health at 1, 3, 6, and 12 months. An interaction term will be introduced into the model to examine the heterogeneity effect. A generalized linear model will be employed for intraindividual analysis of log data within the intervention group to evaluate associations between endurance and adherence to PFMT and postoperative outcome over time. We will perform residual analyses to assess model assumptions and goodness of fit. Assumption of normality will be checked using skewness and normal probability plot when necessary. An intention-to-treat analysis will be performed for the data. Patterns of missing data and dropout will be examined and, if necessary, multiple imputation will be used on the basis of the nature of the missing data. All statistical tests will be carried out at the 5% significance level (2-sided).

Intervention Fidelity

To enable research to be implemented into clinical practice, it is important to report both internal and external contextual details on how the intervention has evolved during the research process. It is rare that a protocol for a randomized controlled trial is followed faithfully when delivering interventions outside laboratories or similar controlled environments. Therefore, it is necessary with flexible interventions that can be adapted to the target group and the unique circumstances of each clinical setting [57]. To describe those aspects as thoroughly as possible, we will follow the Template for Intervention Description and Replication checklist [58] (Table 2). We will carefully evaluate the intervention and its use to strengthen external validity through interviews with patients, retrieving log data from the ePATH app, and dropout analysis. We will also keep in close contact with the test clinics by phone, email, and visits throughout the study to make any necessary adaptions and modifications. All adjustments and contextual factors at the management level at the 3 study sites that may account for variations in implementation outcome will be documented and evaluated.

Textbox 1. Secondary outcomes.

- Physical activity will be evaluated using a single-item measure of physical activity: the Saltin-Grimby Physical Activity Level Scale [47,48]. The respondent rates the time spent in physical activity per week on a 4-point scale: sedentary, some physical activity, regular physical activity and training, or regular hard physical training. An item about support received in physical rehabilitation will also be included.
- Patient activation is a latent trait that comprises knowledge, skills, motivation, and confidence a patient has regarding self-management of his or her illness, and it will be measured using the Patient Activation Measure-13 (PAM-13). PAM-13 contains 13 items that specifically measure patient active engagement in self-care [45]. Each item has 5 response categories with scores from 1 (strongly disagree) to 4 (strongly agree) and no score for not applicable.
- Motivation or self-determination, defined as perceived autonomy, social belonging, and belief in one's own competence, will be measured using the Swedish short version of the Needs Satisfaction and Frustration Scale, comprising 6 items. Each item has 7 response options ranging from 1 (very often) to 7 (very seldom) [49].
- Health literacy will be measured using the Japanese Communicative and Critical Health literacy scale [50] comprising 5 items with 5 response options ranging from *never* to *always* [51]. A total score is calculated by collapsing the 5 response options into 3: never or seldom (1,000), sometimes (100), and often or always (1). These are then classified as lack of (1,000), problematic (100), and sufficient (1) health literacy, respectively.
- Overall, well-being will comprise the following measures:
  - The Sleep Condition Indicator Short Form, a screening tool for sleep difficulties with 2 items (score 0-4). A total score is calculated, with a lower score indicating poorer sleep [52].
  - The Patient Health Questionnaire-9, comprising 9 items (score 0-3) and representing depression as defined in Diagnostic and Statistical Manual of Mental Disorders-4th edition. A higher score indicates worse mental health. There is a tenth item covering the overall experienced difficulty of items 1 to 9 [53].
  - The Cancer Behavior Inventory-B , a measure of self-efficacy, comprising 12 items [54]. Confidence in one's own capability is rated on a scale from 1 (not confident at all) to 7 (totally confident). A total score is calculated, and higher scores indicate greater coping efficacy.
  - The Fatigue Severity Scale, containing 9 items, with response alternatives from 1 (do not agree at all) to 7 (fully agree). A total score is calculated, and a higher score indicates greater fatigue [55].
  - General health, measured using a single item, with 5 response alternatives ranging from excellent (1) to poor (5), RAND-1 [56].
- Endurance in self-care and adherence to pelvic floor muscle training (PFMT) will be assessed through a single item asking how many times a day PFMT has been performed. For the intervention group, there is also a possibility to use ratings of practice in the ePATH. *Log data* will be retrieved from the ePATH, where the patients in the intervention group have the possibility to rate their self-care activities such as physical exercise (specified as type of activity, intensity, and time spent doing the activity), PFMT (frequency, duration), symptom burden, and health.

Patients' usage of the ePATH self-management support system will be determined through extraction from the data logs to study user interactions with the different modules in the ePATH. Logistic regression will be performed to identify patterns of use, that is, associations between system use and patient characteristics. Such information is crucial in adapting the eHealth service to different patient groups.

Semistructured patient interviews will be conducted with a subsample of patients in the intervention group to provide deeper insight into how ePATH may support and promote adherence to self-care, strengthen patient health literacy, motivation, and the competences needed to manage self-care. We will also explore hindrances to self-care activities such as distress, anxiety, or insufficient or lack of support. Given the importance of understanding factors contributing to attrition, we will also interview patients who did not actively adapt to the ePATH. All interviews will be audio-recorded, transcribed verbatim, and analyzed using qualitative content analysis. These actions strengthen the external validity of the study, facilitating translation to other clinical settings.

Ethical Considerations

The Regional Research Ethics Committee in Linköping (No 2016/484-31; 2017/512-32; 2018/147-32) has approved this study. For confidentiality, all communications and registrations of data in ePATH are transmitted through secure connections: Mobile BankID for patients and SITHS-login for care providers. All questionnaire and interview data will be anonymous and stored in accordance with the European Union legislation General Data Protection Regulation. Only the researchers will have access to data. Log data from the ePATH app will be stored in encrypted servers at Linnaeus University. Super administrators who have been responsible for the development and updates of ePATH will have access to the coding files of the app.

Potential Harms

Criticism may be directed at the contact nurses if there are problems in the functioning and operability of ePATH. To avoid this situation, it will not only be emphasized that this is a research project where the views of the patients are valuable to improve ePATH but also that the contact nurses are merely users of the same eHealth tool: they are not responsible for it. If patients have criticisms, these should be addressed to the researchers. The intervention is unlikely to cause any harm to the participants, but there is a risk that patients may feel lost or deserted when the study ends. Therefore, ePATH will remain open for the intervention group patients to use after the 12 months have passed.

Table 2. Template for Intervention Description and Replication checklist for the electronic Patient Activation in Treatment at Home intervention.

TIDieR[a] item	Description
1. Brief name	ePATH[b]
2. Why	To compare the effectiveness of a tailored eHealth[c] intervention (ePATH) on the basis of self-determination theory with standard care. Primary outcome is postoperative symptoms in men undergoing radical prostatectomy. Secondary outcomes are patient activation, motivation, overall well-being, and health literacy over time in and between groups.
3. What materials	User manual (paper) and Web-based mobile app for both patients and health care staff (only available in Swedish).
4. What procedure	During use of ePATH, interactions with health care staff and registration of self-care activities are carried out on an individual basis.
5. Who provided	The intervention was developed as a codesign project with health care researchers, technicians, patients, and health care staff. Researchers with theoretical knowledge of self-determination theory and backgrounds in social and behavioral science, cancer care, and as registered nurses will provide the contact nurses with a training session of approximately 2½ hours. One such session will be held at each study clinic and include how to log in to and use ePATH, how to add targeted information, and how to communicate through the app. All study sites will receive a manual with a written, supplementary tutorial to ePATH, information about the study, the cornerstones of the intervention, the process of enrollment, and a checklist over the contact nurses' responsibilities regarding enrollment and collecting data from the medical records of participants. The contact nurses also get to practice hands-on during introductory sessions. To ensure the patient's ability to perform the intervention, that is, self-care activities, patients are provided with a user manual for ePATH, and the contact nurses will contact all patients in the intervention group to make sure that they can log in to ePATH.
6. How	Delivery of the intervention takes place on an individual basis, depending on the patients' needs. The patients start using ePATH approximately 1 to 2 weeks before surgery, depending on how soon they get their surgery scheduled.
7. Where	On the Web and mobile phone in patient homes.
8. When and how much	The intervention is based on self-care activities and engagement of the patients in their own homes. The enactment of the intervention is monitored through ratings in the app, communication, and follow-up questionnaires. The patients themselves decide to what extent they wish to use ePATH.
9. Tailoring	Contact nurses, in their close communication with each patient, have the possibility to add self-care packages that are relevant for the individual. These packages can be changed and tailored over time.
10. Modification	Researchers have close communication with the contact nurses about adaptions, to facilitate the use of ePATH in the clinical reality. All adaptions and modifications (what, when, and why) are thoroughly documented by the researchers.
11. How well (planned)	Step-by-step inclusion documents have been developed together with each clinic to suit its routines. Inclusion of patients is followed continuously by the research team and there is an ongoing dialogue with the contact nurses about possible difficulties.
12. How well (actual)	Adherence by the patients (how well was the intervention received?), that is, how many performed the suggested self-care activities, how often and how long, is investigated through log data and individual interviews. Dropouts will be described in detail.

[a]TIDieR: Template for Intervention Description and Replication.

[b]ePATH: electronic Patient Activation in Treatment at Home.

[c]eHealth: electronic health.

Data Management

The researchers are not involved in any of the care provided before, during, or after surgery. Documents and digital data will be stored in accordance with Swedish legislation on how to file research data, the Archives Act (Arkivlagen, SFS 1990:782). All data will be reported at a group level.

Results

This project is supported by the Kamprad Family Foundation of Entrepreneurship Research and Charity (grant number 2015-0067), the Swedish Cancer Society (grant number CAN 2017/748), the Cancer Foundation in Kalmar County, and the Medical Research Council of Southeast Sweden (grant numbers FORSS-657211; FORSS-760131).

Recruitment started in January 2018 and is expected to be completed by August 2019. Data collection will be completed in August 2020. The first results from this trial are anticipated to be published in January 2020.

Discussion

This project addresses the posttreatment challenges of prostate cancer, which create special requirements on customized rehabilitation and psychosocial support. Many RP patients suffer from poor quality of life because of postoperative complications. Erectile dysfunction and urinary leaks are common and may be difficult to talk about openly. With the number of men living with cancer expected to increase, major attention needs to be paid to rehabilitation and psychosocial care as well as the creation of tools to help patients return to as normal a life as possible. ePATH for those living with prostate cancer, their

families, and health care professionals provides access to a digital tool that can provide individualized information, be a communication link, and support self-care and empowerment during the course of care and treatment. The project will also increase the knowledge of how patients can be supported in performing self-care and feeling involved in their own care. If the anticipated effects of ePATH are found, this could imply significantly improved health outcomes for individuals and may also facilitate follow-up for health care professionals.

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Authors' Contributions

ME initiated and conceptualized the ePATH. ME, KS, and AH contributed to the study design and methodology. CWa contributed to the design and technical development of the ePATH self-management support system. ME, KS, AH, CWe, and LN contributed to content and design and user-tested and refined the ePATH. ME, KS, AH, CWe, and LN ensured support for the project through meetings and information to staff at the study sites. CWe will perform the interviews. CWe, AH, and KS will implement the protocol. AH is responsible for design of the Web questionnaires and the surveys at baseline, 1, 3, 6, and 12 months. AH, ME, and CWe will analyze quantitative data. AH, KS, ME, CWe, and LN will analyze qualitative data. AH, KS, and ME drafted the protocol. All authors contributed to revisions and approved the final manuscript.

Conflicts of Interest

During the course of the research project, Linnaeus University is the official owner of the app.

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Abbreviations

eHealth: electronic health
ePATH: electronic Patient Activation in Treatment at Home
mHealth: mobile health
PAM-13: Patient Activation Measure-13
PDE5Is: phosphodiesterase-5 inhibitors
PFMT: pelvic floor muscle training
RAND: Research ANd Development, a non-profit corporation in the USA
RP: radical prostatectomy
SITHS: an e-legitimation through WebTrust Certificate Authority
UI: urinary incontinence

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Protocol

eHealth-Based Behavioral Intervention for Increasing Physical Activity in Persons With Multiple Sclerosis: Fidelity Protocol for a Randomized Controlled Trial

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Abstract

Background: The rate of physical activity is substantially lower in persons with multiple sclerosis (MS) than in the general population. This problem can be reversed through rigorous and reproducible delivery of behavioral interventions that target lifestyle physical activity in MS. These interventions are, in part, based on a series of phase II randomized controlled trials (RCTs) supporting the efficacy of an internet-delivered behavioral intervention, which is based on social cognitive theory (SCT) for increasing physical activity in MS.

Objective: This paper outlines the strategies and monitoring plan developed based on the National Institutes of Health Behavior Change Consortium (NIH BCC) treatment fidelity workgroup that will be implemented in a phase III RCT.

Methods: The Behavioral Intervention for Physical Activity in Multiple Sclerosis (BIPAMS) study is a phase III RCT that examines the effectiveness of an internet-delivered behavioral intervention based on SCT and is supported by video calls with a behavioral coach for increasing physical activity in MS. BIPAMS includes a 6-month treatment condition and 6-month follow-up. The BIPAMS fidelity protocol includes the five areas outlined by the NIH BCC. The study design draws on the SCT behavior-change strategy, ensures a consistent dose within groups, and plans for implementation setbacks. Provider training in theory and content will be consistent between groups with monitoring plans in place such as expert auditing of calls to ensure potential drift is addressed. Delivery of treatment will be monitored through the study website and training will focus on avoiding cross-contamination between conditions. Receipt of treatment will be monitored via coaching call notes and website monitoring. Lastly, enactment of treatment for behavioral and cognitive skills will be monitored through coaching call notes among other strategies. The specific strategies and monitoring plans will be consistent between conditions within the constraints of utilizing existing evidence-based interventions.

Results: Enrollment began in February 2018 and will end in September 2019. The study results will be reported in late 2020.

Conclusions: Fidelity-reporting guidelines provided by the NIH BCC were published in 2004, but protocols are scarce. This is the first fidelity-monitoring plan involving an electronic health behavioral intervention for increasing physical activity in MS. This paper provides a model for other researchers utilizing the NIH BCC recommendations to optimize the rigor and reproducibility of behavioral interventions in MS.

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KEYWORDS

fidelity; multiple sclerosis; behavior change; exercise

Introduction

Physical activity is low among adults in the United States and even lower among persons with multiple sclerosis (MS) [1,2]. This lower rate of physical activity is important because persons with MS might experience greater benefits from physical activity than the general population [3] if we can change this behavior. The standard approach for promoting physical activity in MS involves structured, supervised exercise training [4] and has resulted in considerable benefits [3], but the low rate of physical activity in people with MS has not changed over the past 25 years [1]. Researchers have recently advocated moving away from structured exercise training and focusing on behavioral interventions for changing the physical activity lifestyle in MS [5,6]. Such behavioral interventions teach people skills, techniques, and strategies for changing physical activity (ie, behavior-change techniques), which are typically based on a health behavior theory [5,6], and can be delivered through electronic health (eHealth; ie, provision of health-related services through the internet or related technologies). EHealth addresses major barriers to physical activity in persons with MS, namely, transportation and cost [7].

We recently completed a 6-month, phase II, randomized controlled trial (RCT) that examined the efficacy of a newly developed internet website that delivered information on behavior-change techniques aligned with social cognitive theory (SCT) [8] by using electronic learning (e-learning) for increasing physical activity and improving symptoms, walking impairment, and neurological disability [9]. Bandura's SCT is an evidence-based learning theory that highlights the unique role of observing behavior and increasing knowledge for effectively changing behavior through interactions between the person and the environment [8]. E-Learning is the process of extending learning and delivering instructional materials using digital media (eg, interactive videos through the internet) [10]. Participants with MS (N=47) were randomly assigned to the e-learning, behavioral intervention (n=23) or control (n=24) condition. Outcome assessments were administered before and after the 6-month study period. There were positive intervention effects on self-reported and objectively measured moderate-to-vigorous physical activity (MVPA) as well as fatigue, depression, and anxiety symptoms; walking mobility; and disability status. We included a small battery of fidelity metrics in that study. Compliance with weekly step-count entry was 99% and that with weekly coaching video chat sessions was 96%. Such evidence served as proof of principle for the design of a planned phase III RCT testing the effectiveness of this approach for improving physical activity and secondary outcomes as well as examining mediators based on SCT (eg, self-efficacy or goal setting) [11]. This phase III intervention fits within the evaluation phase of the Medical Research Council Framework for assessing the effectiveness of the intervention and understanding change processes [12], which is further described in the recently published protocol focusing on primary, secondary, and tertiary outcomes [11].

The undertaking of a phase III RCT requires an additional protocol and method for monitoring fidelity; yet, fidelity methods are infrequently and inconsistently reported for nonpharmacological intervention trials, in general [13]. We are not aware of any reported fidelity protocols for eHealth-based behavioral interventions aimed to increase physical activity in MS. Fidelity refers to the degree to which an intervention is delivered as planned or intended [13] and addresses both the internal and external validity of a study and its outcomes. This is pertinent in all phases of research, particularly phase III RCTs, wherein factors such as varying treatment dose and provider training can influence intervention delivery and study outcomes.

The National Institutes of Health Behavior Change Consortium (NIH BCC) treatment fidelity workgroup published recommendations for incorporating treatment fidelity practices into health behavior research [13]. These recommendations focus on five areas: study design, provider training, delivery of treatment, receipt of treatment, and enactment of treatment [13]. These five areas include goals, descriptions, and sample strategies that help guide researchers toward conducting rigorous research that is reproducible. The NIH BCC recommendations were published in 2004, and some studies published since have measured theoretical fidelity (ie, SCT), which is a primary concern in fidelity monitoring because the efficacy of programs depends on effects from the specific behavior-change foundations grounded in theory rather than extraneous variables [14,15]. Additionally, facilitator-specific adherence is emphasized in another physical activity intervention [16]. However, one recent literature review indicated that there was still little uniformity in the definition and implementation of fidelity protocols [17]. This is disappointing and supports the need for greater attention toward fidelity in the development and execution of interventions, but few researchers provide this information in study protocols and publications, particularly for MS.

This paper describes the fidelity protocol for the Behavioral Intervention for Physical Activity in Multiple Sclerosis (BIPAMS) study based on the five areas identified by the NIH BCC. Such a protocol paper is essential to clearly document our fidelity metrics and approaches (ie, rigor and reproducibility) and offer a guide for other researchers conducting eHealth behavioral interventions to change physical activity in persons with MS.

Methods

Overview and Participants

BIPAMS is a phase III RCT that will test the effectiveness of a behavioral intervention [11] for increasing physical activity and improving secondary outcomes in a large sample of people with MS residing in the United States. The primary outcome is accelerometry as an objective measure of minutes/day of MVPA over a 7-day period. The secondary outcomes are self-reported measures of physical activity, walking mobility, cognition, fatigue, depression, anxiety, pain, sleep quality, and quality of

life. The tertiary outcomes are mediator variables (eg, self-efficacy) based on SCT. We will recruit a sample of 280 persons with MS from across the United States through postal and electronic advertisements delivered using the National MS Society, North American Research Center on Multiple Sclerosis, and iConquerMS. We will further distribute advertisements in the MS Centers identified through the National Multiple Sclerosis Society website and request that the materials be distributed among persons living with MS who visit the centers for services. The advertisements will describe the study as one comparing two different approaches delivered through the internet for managing the consequences of MS and improving health indicators. Those interested in participation will contact the study project coordinator either by email or telephone; we will establish a toll-free telephone number owing to the nationwide recruitment effort. This initial email or telephone call will be followed up by a phone call from the project coordinator who will describe the study and its procedures, answer all questions, and conduct a screening for inclusion criteria. The inclusion criteria involve diagnosis of MS; free of relapse in the past 30 days; internet and email access; willingness to complete the questionnaires, wear the accelerometer, and undergo randomization; inactive status defined as not engaging in regular physical activity (30 minutes accumulated per day) on more than 2 days of the week during the previous 6 months; ability to ambulate with or without assistance (ie, walk with or without a cane or walker, but not a wheelchair); and age between 18 and 64 years. We will exclude all individuals with moderate or high risk for undertaking strenuous or maximal exercise using the Physical Activity Readiness Questionnaire (PAR-Q) [15]. During the initial phone contact with the project coordinator, participants will verbally respond to the PAR-Q, and those individuals who report no more than one Yes or affirmative response on the seven items on the PAR-Q will be considered at low risk and included for participation. All other individuals will be considered at moderate or high risk and excluded from participation and further advised to seek medical guidance before becoming more physically active. Participants (N=280) will be randomized into the behavioral intervention condition (BIPAMS; n=140) or a social contact, attention control condition focused on general wellness (WellMS; n=140).

Behavioral Intervention for Physical Activity in Multiple Sclerosis Intervention Protocol

As described previously [9], the BIPAMS behavioral intervention consists of two primary components, namely, a dedicated internet website and one-on-one video calls with a behavioral coach for increasing physical activity. The WellMS control condition provides an internet website and one-on-one video calls with a behavioral coach for discussion about self-managing MS symptoms through health behaviors other than physical activity (eg, diet and nutrition). A comparison of conditions is presented in Table 1. The conditions will be administered over 6 months and supported by trained behavioral coaches who will be uninvolved in screening, recruitment, random assignment, and outcome assessment. The coaches meet with participants on “content weeks” via one-on-one video calls using Skype (Microsoft Corp, Luxembourg); this starts with weekly calls and modules that taper off in frequency over time for both conditions. There is a 6-month follow-up period wherein participants will not access the study website or engage in video calls with behavior coaches. We will collect primary, secondary, and tertiary outcome data every 6 months over the 12-month period (ie, baseline, immediate follow-up, and 6-month follow-up). This study has been approved by an Institutional Review Board, and the trial is registered at ClinicalTrials.gov (NCT03490240).

Study Fidelity Protocol

The BIPAMS study fidelity protocol addresses all five areas of the NIH BCC, including both fidelity protocol and monitoring plans that ensure uniformity among providers and replicability. Our fidelity protocol and monitoring plans are based on previous work by author BCW involving behavior change in spinal cord injury [18]. The intervention includes both BIPAMS and WellMS conditions with differences in contact frequency and format that require some group-specific strategies; however, where possible, strategies and monitoring plans are uniform between groups. All fidelity monitoring will be completed through the formal study period, as this will confirm implementation of protocols as intended. The five stages of fidelity fit linearly in the research process, with study design occurring prior to the intervention; provider training occurring prior to and during the intervention; and treatment delivery, receipt, and enactment occurring during the intervention phase. The frequency, NIH BCC areas, and data sources of the BIPAMS fidelity-monitoring plan are outlined in Table 2.

Table 1. Description of intervention components for the BIPAMS and WellMS conditions.

Intervention component	BIPAMS[a]	WellMS[b]
Internet website		
Target	Physical activity	General wellness
Primary source of intervention content	Previous research by principal investigator	National Multiple Sclerosis Society
Theoretical underpinnings	Social cognitive theory	Social cognitive theory
Interactive video courses, n	10	10
Resource section	Yes	Yes
Learn more section	Yes	Yes
Physical activity tracker	Yes	No
Forum	Yes	Yes
Patient voices, n	24	10
Weekly email announcements	Yes	Yes
Weekly updates on the website	Yes	Yes
Tips of the week	Yes	Yes
News and events section	Yes	Yes
One-on-one video calls		
Occurrence, n	13	9
Semiscripted guide	Yes	Yes
Adverse event reporting	Yes	Yes
Other		
Pedometer	Yes	No
Goal setting	Yes	Yes
Log books/self-monitoring	Yes	Yes

[a]BIPAMS: Behavioral Intervention for Physical Activity in Multiple Sclerosis.

[b]WellMS: Wellness for Multiple Sclerosis.

Table 2. Overview of the study fidelity-monitoring plan.

Data source	Monitoring frequency	Areas of fidelity addressed				
		Study design	Provider training	Treatment delivery	Treatment receipt	Treatment enactment
Coaching call checklist	Monthly	Yes	Yes	Yes	No	No
Coaching call logs	Monthly	Yes	No	Yes	No	No
Auditing of coaching calls by expert	Weekly	Yes	Yes	Yes	Yes	No
Behavioral resource bank within treatment group	Quarterly	Yes	No	No	No	No
Review of participant website log-in	Weekly	No	No	No	Yes	Yes
Review of participant exercise log (BIPAMS[a]) or log book (WellMS[b])	Weekly/monthly	No	No	No	Yes	Yes
Team meetings to discuss participant progress and protocol adherence	Weekly	Yes	Yes	Yes	Yes	Yes

[a]BIPAMS: Behavioral Intervention for Physical Activity in Multiple Sclerosis.

[b]WellMS: Wellness for Multiple Sclerosis.

Fidelity of Study Design

The NIH BCC fidelity of study design area focuses on practices that ensure study procedures and implementation are in line with current theory and clinical processes. Study design fidelity goals include ensuring that conditions are congruent with relevant theory and practice, ensuring equivalent treatment dose within and across conditions, and planning for implementation setbacks.

The first study design goal includes the congruence of the conditions with relevant theory and practice. As such, both conditions include evidence-based SCT behavior-change strategies in the website components as well as one-on-one video calls. Importantly, the WellMS intervention focuses on wellness based on resources from the National Multiple Sclerosis Society, whereas BIPAMS focuses on physical activity based on previous research and clinical practice. The website content and coach training are consistent with SCT principles for behavior change, and these were efficacious in the phase II trial of BIPAMS [9]. Two fidelity strategies will be implemented to track the use of SCT during video calls. The first strategy involves checklists for each video call that focus on goal setting and self-efficacy to, for example, ensure the use of SCT principles. This strategy is carried out with every video call. In the second strategy, video calls will be randomly audited by an expert for a review of principles from SCT. Each coach will have one call per content week that will be audited by an expert in SCT and eHealth delivery (BCW and RWM). We define such an expert as a principal investigator on a current or previously funded eHealth behavioral intervention based on SCT. Auditing is done randomly each week in person (one call audited per coach); no coaching calls will be recorded in any phase of the study. Adherence to these fidelity measures will be actively monitored by the project coordinator through monthly audits of the checklists for each participant per coach (Multimedia Appendices 1 and 2). Further, there will be ongoing review of the website in order to ensure that all content is working and up to date. Table 3 provides further details on the resources and frequency of monitoring.

The second goal regarding the study design involves ensuring equal treatment dose within and between conditions. Both conditions include a standard video call schedule, although the frequency of these calls varies slightly between conditions (Table 3). Both conditions will receive a weekly reminder with updated website content and additional tips that align with the topic. Therefore, both conditions will have a standardized dose with slight variations between them. This is largely based on the differential content between conditions (ie, physical activity vs general health and wellness) and the desire for making the control condition credible, but not overwhelming in diverse content for participants. The monitoring plans include in-person auditing of random video calls by experts and within-team meetings. Full team meetings that include coaches from both groups will occur weekly, while intragroup meetings will occur during content weeks. Intragroup meetings include discussions of call notes and duration focused on similar dose (ie, coaching call length) within groups. We anticipate that call length and content will vary depending on participant needs, particularly initially, when participants are learning to use the technology and website, but generally, calls should last between 10 and 30 minutes.

The third study design goal involves a plan for implementation setbacks such as website problems or coaching-related illness or travel. Both BIPAMS and WellMS have multiple trained coaches to address this goal, which serves as backup during unanticipated or scheduled events. In the event of travel or illness, trained coaches will fill in for the missing coach and follow all procedures (check lists, expert audits, etc), and we will monitor the number of times coaches change or cover for one another.

Fidelity of Provider/Coach Training

The NIH BCC fidelity-monitoring plan further includes strategies that address preparation for uniform delivery of treatment by providers/coaches. Behavioral health interventions often require training in new skillsets, content, and protocols. The coaches (ie, providers) for the BIPAMS and WellMS conditions will interact directly with the participants regarding content discussion, accountability, and goal setting. The strategies and monitoring plan for fidelity of provider/coach training are outlined in Table 4 with standard training between groups except for content-specific materials (ie, physical activity vs wellness strategies).

Table 3. Fidelity of study design strategies and monitoring plan for BIPAMS.

Goal	Description from NIH BCC[a]	Strategies used		Fidelity-monitoring plan	
		BIPAMS[b]	WellMS[c]	BIPAMS	WellMS
Ensure intervention is congruent with relevant theory and practice	Operationalize treatment to optimally reflect theoretical roots; precisely define variables most relevant to "active ingredients" of the intervention	• Coaches use evidence-based behavior-change strategies during calls and messages (SCT[d]) • Integration of behavior-change strategies into website (SCT)	• Coaches use evidence-based behavior-change strategies during calls and messages (SCT) • Integration of behavior-change strategies into website (SCT)	• Monthly review of coaching call checklist • Auditing of random selection of calls by an expert on content weeks • Initial review of the website before beginning enrollment and quarterly audit of resources provided within website modules, resources, and learn more information sections	• Monthly review of coaching call checklist • Auditing of random selection of calls by an expert on content weeks • Initial review of the website before beginning enrollment and quarterly audit of resources provided within website modules, resources, and learn more
Ensure equal treatment dose within and across conditions	Ensure equal treatment "dose" (measured by number, frequency, and length of contact) is adequately described and is the same for each subject within a particular treatment condition	• Standard call schedule for all participants on weeks 1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 13, 16, and 20 • Weekly email reminder with updated website content	• Standard call schedule for all participants at weeks 1, 2, 3, 6, 8, 12, 13, 16, and 20 • Weekly email reminder with updated website content	• Auditing of random selection of calls by an expert on content weeks • Weekly meeting within the team to review materials and call duration logs	• Auditing of a random selection of calls by an expert on content weeks • Weekly meeting within the team to review materials and call duration logs
Plan for implementation setbacks	Address possible setbacks in implementations (eg, treatment providers dropping out)	Train multiple providers to ensure back up in the event of provider vacation, illness, or turnover	Train multiple providers to ensure back up in the event of provider vacation, illness, or turnover	Tracking log with the number of times providers change/cover and reason	Tracking log with the number of times providers change/cover and reason

[a]NIH BCC: National Institutes of Health Behavior Change Consortium.

[b]BIPAMS: Behavioral Intervention for Physical Activity in Multiple Sclerosis.

[c]WellMS: Wellness for Multiple Sclerosis.

[d]SCT: social cognitive theory.

Table 4. Fidelity of provider training strategies and monitoring plan for BIPAMS.

Goal and description from NIH BCC[a]	Strategies used		Fidelity-monitoring plan	
	BIPAMS[b]	WellMS[c]	BIPAMS	WellMS
Standardized training				
Ensure that training is conducted similarly for all providers	Standardized protocols and training materials: • Study design • Behavior-change theory (SCT[d]) • Fidelity protocol overview • Data-collection procedures • Data-quality procedures	Standardized protocols and training materials: • Study design • Behavior-change theory (SCT) • Fidelity protocol overview • Data-collection procedures • Data-quality procedures	Provider training records	Provider training records
Ensure provider skill acquisition				
Train providers to well-defined performance criteria	• Role playing • Mock delivery • Coaching call checklists	• Role playing • Mock delivery • Coaching call checklists	• Provider training records • Monthly audit of coaching call checklists	• Provider training records • Monthly audit of coaching call checklists
Minimize "drift" in provider skills				
Ensure provider skills do not decay over time	• Monitor random selection of coaching calls • Weekly meetings with PI[e] and intervention staff to discuss intervention strategies and resolve difficult situations as they arise • Standardize training of all providers: • Behavior-change theory training • Mock delivery	• Monitor random selection of coaching calls • Weekly meetings with PI and intervention staff to discuss intervention strategies and resolve difficult situations as they arise • Standardize training of all providers: • Behavior-change theory training • Mock delivery	• Auditing of random selection of calls by an expert on content week • Provider training records	• Auditing of random selection of calls by an expert on content weeks • Provider training records
Accommodate providers differences				
Ensure adequate level of training in providers of difference skill level, experience, or professional background	• Coaching call checklist • Monitor random selection of coaching calls • Standardized materials provided on website • Standardized scripts for each call	• Coaching call checklist • Monitor random selection of coaching calls • Standardized materials provided on website • Standardized scripts for each call	• Monthly audit of coaching call checklists • Auditing of random selection of calls by an expert on content weeks • Weekly meeting among providers to discuss material • Weekly meeting among providers and with PI to discuss material	• Monthly audit of coaching call checklists • Auditing of random selection of calls by an expert on content weeks • Weekly meeting among providers to discuss material • Weekly meeting among providers and with PI to discuss material

[a]NIH BCC: National Institutes of Health Behavior Change Consortium.

[b]BIPAMS: Behavioral Intervention for Physical Activity in Multiple Sclerosis.

[c]WellMS: Wellness for Multiple Sclerosis.

[d]SCT: social cognitive theory.

[e]PI: principal investigator.

The first goal within the fidelity of provider/coach training is standardized training; this ensures that training is conducted similarly for all providers. All coaches must have a bachelor's degree in Exercise Science, Psychology, Kinesiology, or a related health field. Both groups of coaches will be trained by the principal investigator on the study design, SCT, fidelity protocol, data collection, and data quality procedures. Provider training records (eg, meeting dates and time log) will be maintained by coaches across training goals in this area, and monthly auditing will be conducted by the project coordinator.

BIPAMS and WellMS coaches will be trained separately using well-defined performance criteria in order to ensure and enhance skill acquisition. Training is utilized as an essential tool that familiarizes coaches with intervention-specific content, behavior-change strategies, and comfort in communication via virtual media. First, coaches will be trained on condition-specific content by using the website and previous literature to ensure thorough knowledge of resources and content. Thereafter, new coaches will undergo SCT and behavior-change strategy training with the principal investigator and then transition into hands-on training. All coaches will complete role playing and mock delivery of all content, with feedback provided by the research team. Coaching call checklists will be used in mock deliveries and all calls, thereby ensuring that providers meet all the performance criteria. In the event of poor skill acquisition (ie, not meeting 100% of the auditing checklist criteria), the principal investigator will be notified, and coaches will undergo additional training.

Another goal of provider training is minimizing drift in provider skills. The one-on-one video calls in the BIPAMS study will be conducted for 6-month periods across four waves of participants; this underscores the importance of coaches to revisit materials weekly and ensure consistency in communication over time with each participant and across waves. Standardized training and auditing of random calls, as previously mentioned, will be utilized to control for drift in both groups. Coaches will utilize call scripts and checklists for every video call throughout the intervention, thereby providing approaches for self-monitoring, maintaining consistency, and recording any drift. Additionally, weekly meetings with the principal investigator and intervention staff to address difficult situations that arise will be critical. These meetings provide an opportunity to solve problems within and across conditions as a team in order to ensure the coaches are consistent within the content area and understand the issues that can arise between conditions.

Providers are often different in many ways including professional background, personality, and experience. To accommodate provider differences, the NIH BCC recommends that researchers ensure an adequate level of training among providers. To account for these differences, standardization of training, website content materials, and phone call scripts are included in both conditions to provide uniform treatments and interactions. Weekly meetings among team members (ie, coaches) and the principal investigator will be conducted to clarify and review materials throughout the training and implementation phases. Additionally, coaching call checklists and live monitoring of video calls by experts (BCW and RWM), as previously outlined, address this goal and keep providers focused on the intended active ingredients. Any specific questions addressed by providers in a unique manner will be discussed in weekly meetings among coaches, as participants often have similar experiences.

Fidelity of Delivery of Treatment

Fidelity of treatment delivery focuses on ensuring the intervention is delivered as intended. Many of the concerns within delivery of treatment overlap with strategies for training and study design, including controlling for provider differences and adhering to created protocols; however, this area further addresses differences within treatment conditions and minimizes contamination (Table 5).

Both conditions have a unique team of coaches that focus on either BIPAMS or WellMS content; therefore, coaches only coach one condition. Auditing of random one-on-one video calls by experts (BCW and RWM) will be the primary strategy for controlling provider differences during the treatment-delivery phase of this study. These expert-audited video calls include a specific checklist of expected provider actions such as goal setting, website resource use, and content comprehension. The expert auditors will further provide feedback on the handling of unique questions and conversation topics that require reframing back to the week's content and condition-specific goals. The expert auditors will not be blinded to groups due to necessary content checking such as asking about steps for BIPAMS and weekly content-specific goals for WellMS.

As mentioned previously, the BIPAMS and WellMS conditions differ in foci and content; however, both provider teams will meet together on a weekly basis to review content. Weekly in-person meetings to discuss website content and resources ensure that providers within each condition understand and deliver the intended materials. Additionally, coaching call logs will be reviewed to assess and address any differences in the dose or time spent on calls. All participants within each condition will receive the same materials on the website and have access to the same content. During the video calls, coaches will ask if participants reviewed all content and encourage participants to review materials missed as well as provide an overview of the topic.

Table 5. Fidelity of delivery of treatment strategies and monitoring plan for BIPAMS.

Goal	Description from NIH BCC[a]	Strategies used		Fidelity-monitoring plan	
		BIPAMS[b]	WellMS[c]	BIPAMS	WellMS
Control for provider differences	Monitor and control for subjects perceptions of nonspecific treatment effects (eg, warmth, credibility) across conditions	Monitor random selection of coaching calls	Monitor random selection of coaching calls	Auditing of random selection of calls by an expert on content weeks	Auditing of random selection of calls by an expert on content weeks
Reduce differences within treatment	Ensure that providers in the same condition are delivering the same intervention	Coaches meet weekly to discuss materials and discussion plans for calls	Coaches meet weekly to discuss materials and discussion plans for calls	Weekly meetings among providers to discuss material	Weekly meetings among providers to discuss material
Ensure adherence to treatment protocol	Ensure that treatments are being delivered in the way they were conceived with regard to content and dose	• Coaching call checklists • Coaching call logs and missed call protocol • Equal resources provided within the condition	• Coaching call checklists • Coaching call logs and missed call protocol • Equal resources provided within the condition	• Monthly auditing of coaching call checklists • Monthly auditing of coaching call logs and missed call protocol • Quarterly review of website resources to ensure all materials are available for both treatment groups	• Monthly auditing of coaching call checklists • Monthly auditing of coaching call logs and missed call protocol • Quarterly review of website resources to ensure all materials are available for both treatment groups
Minimize contamination between treatments	Minimize contamination	• Train all staff on theory and physical activity interventions underlying the study • Train staff on answering questions related to randomization and group allocation in an unbiased way • Train staff to identify topics of cross-contamination (ie, diet, emotions, and secondary conditions)	• Train all staff on theory, health, and wellness behaviors underlying the study • Train staff on answering questions related to randomization and group allocation in an unbiased way • Train staff to identify topics of cross-contamination (ie, physical activity and exercise)	• Provider training records • Auditing of random selection of calls by an expert on content weeks • Tracking log-documenting instances of cross-contamination for each content week	• Provider training records • Auditing of random selection of calls by an expert on content weeks • Tracking log-documenting instances of cross-contamination for each content week

[a]NIH BCC: National Institutes of Health Behavior Change Consortium.

[b]BIPAMS: Behavioral Intervention for Physical Activity in Multiple Sclerosis.

[c]WellMS: Wellness for Multiple Sclerosis.

Participants will be informed at the screening that the study is an RCT and that participants are randomly assigned into BIPAMS or WellMS conditions. A general overview of each condition will be provided to all participants per Institutional Review Board requirements to present necessary information to participants when they make an informed decision on participation; therefore, cross-contamination was critical to address. Once randomized, participants will be provided with the condition-specific website link and a unique username and password; the websites are hosted in separate locations (Multimedia Appendices 3 and 4). BIPAMS participants will create goals and receive content regarding increasing physical activity. WellMS participants will receive content on different topics each week including nutrition, gait, stress management, and sleep and will be encouraged to create goals that align with these content areas outside of physical activity. Providers will be trained to identify potential topics of cross-contamination; for example, a WellMS participant who sets a physical activity-related goal or a BIPAMS participant who sets a nutrition goal. Participants will be encouraged to set goals that align with the content of the BIPAMS or WellMS conditions, and coaches will be trained to answer questions in an unbiased way. A record and description of any cross-contamination instances will be kept by coaches.

Table 6. Fidelity of receipt of treatment strategies and monitoring plan for BIPAMS.

Goal	Description from NIH BCC[a]	Strategies used		Fidelity-monitoring plan	
		BIPAMS[b]	WellMS[c]	BIPAMS	WellMS
Ensure participant's comprehension	Ensure that participants understand the information provided by the intervention	• Web-based physical activity tracker that coaches can view • Use of open-ended questions and participant-led goal setting/action planning	• Print-based log book that providers will inquire about/receive during each chat • Use of open-ended questions and participant-led goal setting/action planning	• Weekly review of exercise tracker • Participant reports during auditing of random selection of calls by an expert on content weeks	• Inquiry about log book use at each chat • Participant reports during auditing of random selection of calls by an expert on content weeks
Ensure participants ability to use cognitive skills	Make sure that participants are able to use the cognitive skills taught in the intervention (ie, reframing, problem solving, preparing for high-risk situations)	• Use of open-ended questions and participant-led goal setting/action planning • Narrative coaching notes	• Use of open-ended questions and participant-led goal setting/action planning • Narrative coaching notes	• Auditing of random selection of calls by an expert on content weeks for coaches' use of techniques and responses to participant questions • Review of notes/questions during weekly intervention meetings	• Auditing of random selection of calls by an expert on content weeks for coaches' use of techniques and responses to participant questions • Review of notes/questions during weekly intervention meetings
Ensure participants ability to perform behavioral skills	Make sure that participants able to use behavioral skills taught in the intervention (eg, relaxation, food diaries, cigarette-refusal skills)	Initial call to ensure receipt and use of training materials and ensure participants understand all aspects of the website	Initial call to ensure receipt and use of training materials and ensure participants understand all aspects of the website	• Quarterly review of coach call logs for initial call • Review of participant log-in throughout the study	• Quarterly review of coach call logs for initial call • Review of participant log-in throughout the study

[a]NIH BCC: National Institutes of Health Behavior Change Consortium.

[b]BIPAMS: Behavioral Intervention for Physical Activity in Multiple Sclerosis.

[c]WellMS: Wellness for Multiple Sclerosis.

Fidelity of Receipt of Treatment

Fidelity of treatment receipt involves strategies and monitoring of a participant's ability to understand and adopt treatment-related behavioral skills and cognitive strategies. Working with people with MS can make identifying receipt of treatment issues challenging because of cognitive impairment. This is important, as cognitive impairment is not an exclusion criterion. The research team created strategies and a monitoring plan to document receipt of treatment based on the NIH BCC best practices and goals by assessing and optimizing participant comprehension of materials (Table 6). Receipt of treatment further encompasses the degree to which participants demonstrate knowledge of and ability to use treatment skills.

Participants in both conditions will complete an initial, one-one-one call with a behavioral coach and confirm receipt of intervention materials and instructions on access and use of the online platforms for content and video calls. The initial call plays a role in ensuring participants are able to access materials and use the information taught in the intervention. The use of video calls throughout the intervention will provide the coaches with opportunities to assess comprehension of materials using visual cues (eg, facial expressions and body language) and real-time interactions to inquire about participants accessing website and reviewing modules, resources, and patient videos. The project coordinator will also review participant website log-in activity (Multimedia Appendix 5) weekly throughout the study to document when participants access the website and the study materials on an ongoing basis.

This intervention further depends on participants' comprehension and ability to utilize digital media in delivering content and tracking goals. Participants in the BIPAMS condition will be provided a pedometer and log steps in a journal daily (Multimedia Appendix 6) and transfer step counts into the website at the end of each week. This will allow the research team to monitor receipt of treatment on a weekly basis through the website. Participants in the WellMS condition will be asked to log goals and notes in a paper-based log book (Multimedia Appendix 7) on a daily basis, but not to transfer them into the website. The research team will document whether the log books are used weekly and ask participants to send the log book after the 6-month intervention period.

Table 7. Fidelity of enactment of treatment strategies and monitoring plan for BIPAMS.

Goal	Description from NIH BCC[a]	Strategies used in BIPAMS[b]	Strategies used in WellMS[c]	Fidelity-monitoring plan for BIPAMS	Fidelity-monitoring plan for WellMS
Ensure participants use cognitive skills	Ensure that participants actually use the cognitive skills provided in the intervention in appropriate life settings	Review of coaching calls	Review of coaching calls	Monthly tracking of coaching notes	Monthly tracking of coaching notes
Ensure participants use behavioral skills	Ensure that participants actually use the behavioral skills provided in the intervention in appropriate life settings	• Review of use in calls • Web-based exercise tracker that coaches can view • Review of participant weekly log-ins	• Review of use in calls • Print-based log book that providers will inquire about/receive at each chat • Review of participant weekly log-ins	• Monthly tracking of coaching notes • Weekly website review by coaches • Study coordinator review of website participant log-in throughout the study	• Quarterly review of coach call logs for the initial call • Monthly tracking of coaching notes • Study coordinator review of website participant log-in throughout the study

[a]NIH BCC: National Institutes of Health Behavior Change Consortium.

[b]BIPAMS: Behavioral Intervention for Physical Activity in Multiple Sclerosis.

[c]WellMS: Wellness for Multiple Sclerosis.

Based on SCT, participants will be encouraged to be the leaders of their behavior change, with coaches available to provide knowledge and support. Provider training includes established practices in participant-driven goal setting and action planning that use open-ended questions, providing participants the opportunity to voice concerns and autonomy in leading the conversation. This strategy will allow the research team to ensure participants comprehend materials and are capable of using cognitive skills for creating unique goals. Narrative coaching notes for each video call and auditing of calls by an expert will be set in place to monitor the use of these strategies and participant reports.

Enactment of Treatment

The fifth area highlighted by the NIH BCC is enactment of treatment described as strategies aimed at monitoring and improving participant ability to perform treatment-related behavioral skills and cognitive strategies in relevant real-world settings. This area is particularly important in a longitudinal behavior change study like BIPAMS, as outcomes are focused on the degree to which participants apply skills learned as part of daily life. The goals for enactment of treatment focus on ensuring participants use both the cognitive and behavioral skills learned (Table 7).

Use of cognitive skills provided in the intervention in appropriate life settings will be documented and assessed in narrative coaching notes. Check-in video calls with participants will occur each week that new content is presented on the condition-specific website. The video calls will provide coaches with rich qualitative data regarding the use of cognitive skills learned as part of the conditions. Coaches will assess the use of behavioral skills during video calls through specific questions outlined in the coaching call scripts. As previously mentioned, BIPAMS and WellMS conditions have unique logging resources for self-monitoring new behaviors or tracking goals that will provide an additional means of monitoring treatment enactment. Participant website log-ins will be tracked in order to monitor enactment of new behaviors associated with follow through on intervention responsibilities such as review of content and weekly tips/updates.

Data Analysis

The NIH BCC treatment fidelity workgroup does not provide guidance on the analysis of treatment fidelity data [13]. Previous researchers have incorporated high versus low fidelity in study design, treatment, and data analysis [14,15]; however, they do not provide clear analysis plans for fidelity metric data. Therefore, we have created a data-analysis plan to describe each fidelity metric within and across BIPAMS and WellMS conditions using descriptive statistics, specifically mean (SD), percentages, and frequency counts (range).

Results

Enrollment began in February 2018 and will conclude in September 2019. Intervention delivery will conclude in March 2020. Data analysis and full study results are expected in the summer of 2020.

Discussion

BIPAMS is a phase III RCT of an internet-delivered behavioral intervention based on SCT and principles of e-learning for increasing physical activity among persons with MS. The BIPAMS study includes an intervention condition (BIPAMS) and control condition (WellMS) delivered through internet websites and supported by video calls with coaches trained in SCT and associated behavior-change strategies. The primary outcome is objectively measured MVPA. The secondary outcomes are self-report physical activity, walking mobility, cognitive function, fatigue, depression, anxiety, sleep quality, pain, and change in disability. The tertiary outcomes are self-efficacy, outcome expectations, goal setting/planning, and

facilitators/impediments. Another set of outcomes is treatment fidelity for optimizing and assessing the rigor and reproducibility of the BIPAMS intervention in MS. This paper highlights our approach for rigor and reproducibility when reporting the effects of the BIPAMS intervention condition on primary, secondary, and tertiary study outcomes.

We applied the NIH BCC goals and applicable strategies for establishing the fidelity of this phase III trial. The NIH BCC fidelity-monitoring scheme includes five areas, and we included all five areas for complete mapping and monitoring of the fidelity of the BIPAMS study. Strategies for ensuring and monitoring fidelity in the intervention will include standardized scripts, standardized call schedules, comprehensive provider training in content and theory, ongoing phone call monitoring by a trained expert, monitoring website usage, and monitoring of self-monitoring strategies. This protocol is specific for an eHealth/e-learning physical activity intervention for persons with MS; however, the underlying strategies and themes are applicable for other studies. This report provides guidance for other researchers conducting phase III RCTs that are focused on evaluating the validity of behavioral interventions; this is particularly important as interventions in phase III are intended to test effectiveness and be widely disseminated for clinical or practical applications.

Some interventions may benefit from using the modified NIH BCC guidelines that align with associated study objectives. One group of researchers previously used the NIH BCC model to create an approach to address fidelity in the context of rehabilitation research [19]. This involved collapsing the five areas from the NIH recommendations into three focal areas, namely, intervention and study design, resourcing, and implementation. These broader definitions are applicable to clinical rehabilitation research, wherein clinical staff may be incorporating research into existing practice, thereby removing control over provider training and therapy/intervention protocols. For example, one group of researchers conducted a physical therapist-led intervention and reported that the NIH BCC goals did not precisely match the unique circumstances that arose within a clinical setting [20]. That protocol paper included several iterations to create an implementation-specific protocol utilizing the NIH areas and further provided a model for researchers interested in validating unique, intervention-specific fidelity practices. Although fidelity protocols are pivotal in replicating studies, an additional resource that can assist future evidence-based intervention research is the Template for Intervention Description and Replication (TIDieR) [21]. Based on previous research, we assert that behavioral intervention studies should include fidelity protocols and monitoring as well as use of the TIDieR checklist in order to move the field forward to address threats to validity and provide clarity for replicating studies.

Fidelity protocols and monitoring provide a quantifiable means of monitoring the rigor of the BIPAMS study. Previous iterations of the study demonstrated preliminary efficacy for BIPAMS in improving MVPA and secondary outcomes (ie, fatigue severity, physical impairment, depression, and anxiety) [9]. This iteration of BIPAMS includes an intervention and control condition that receives an intervention; therefore, standardization between conditions and coaches is essential. Our focus on disseminating a rigorous fidelity-monitoring protocol using the NIH BCC recommendations represents a pivotal next step in reporting strategies that test the true replicability and effectiveness of the BIPAMS intervention. Such a protocol will provide a foundation for fidelity practices in physical activity RCTs for people with MS.

The BIPAMS study fidelity protocol has some limitations. The BIPAMS and WellMS conditions (Table 1) include different contents and overall dose, as BIPAMS includes 13 video calls and WellMS includes 9 video calls. Specifically, this contributes to barriers when comparing and interpreting fidelity between two active conditions like BIPAMS and WellMS that share primary components but do not mirror each other perfectly. Both conditions include self-monitoring components, but BIPAMS is performed on paper and uploaded virtually, whereas WellMS only includes a paper log. However, the theoretical underpinnings of the conditions are consistent with previous iterations and the dose is equal within groups (ie, all BIPAMS participants receive the same content and number of calls). The interventions were previously designed and the evidence-based materials were kept in a validated format, wherever possible. Our study does not directly assess cognitive skills or disease severity and participants may have cognitive deficits that contribute to receipt and enactment of treatment; however, personalization based on the severity of disease is addressed in one-on-one video calls with behavioral coaches. Lastly, there is a threat to assessing fidelity in all studies wherein participants may provide socially desirable responses to behavioral coaches that do not accurately reflect engagement in intervention. Despite those limitations, fidelity protocols and monitoring provide the opportunity for a research team to evaluate where differences due to intervention content versus issues with internal validity may influence outcomes and interpretations.

The NIH BCC treatment fidelity workgroup provides recommendations for strategies to incorporate fidelity practices in behavior-change interventions. The BIPAMS phase III RCT integrated strategies in study design, provider training, delivery of treatment, receipt of treatment, and enactment of treatment to preserve internal validity and enhance external validity. The goal of the BIPAMS study is to create and test an evidence-based behavior-change intervention that can be used in the community and widely benefit people with MS. The treatment-fidelity procedures outlined in this report provide a model for other researchers to create studies in all phases and fit within the aims and priorities of translational research.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Behavioral Intervention for Physical Activity in Multiple Sclerosis audit checklist.

[PNG File, 23KB - resprot_v8i3e12319_app1.PNG]

Multimedia Appendix 2

Wellness for Multiple Sclerosis audit checklist.

[PNG File, 17KB - resprot_v8i3e12319_app2.PNG]

Multimedia Appendix 3

Behavioral Intervention for Physical Activity in Multiple Sclerosis website homepage.

[PNG File, 248KB - resprot_v8i3e12319_app3.PNG]

Multimedia Appendix 4

Wellness for Multiple Sclerosis website homepage.

[PNG File, 282KB - resprot_v8i3e12319_app4.PNG]

Multimedia Appendix 5

Weekly website log-ins.

[PNG File, 124KB - resprot_v8i3e12319_app5.PNG]

Multimedia Appendix 6

Behavioral Intervention for Physical Activity in Multiple Sclerosis logbook page example.

[PNG File, 71KB - resprot_v8i3e12319_app6.PNG]

Multimedia Appendix 7

Wellness for Multiple Sclerosis logbook page example.

[PNG File, 42KB - resprot_v8i3e12319_app7.PNG]

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Abbreviations

BIPAMS: Behavioral Intervention for Physical Activity in Multiple Sclerosis
eHealth: electronic health
E-Learning: electronic learning
MS: multiple sclerosis
MVPA: moderate-to-vigorous physical activity
NIH BCC: National Institutes of Health Behavior Change Consortium
PAR-Q: Physical Activity Readiness Questionnaire
PI: principal investigator
RCT: randomized controlled trial
SCT: social cognitive theory
TIDieR: Template for Intervention Description and Replication
WellMS: Wellness for Multiple Sclerosis

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Protocol

Measuring Caloric Intake at the Population Level (NOTION): Protocol for an Experimental Study

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Abstract

Background: The monitoring of caloric intake is an important challenge for the maintenance of individual and public health. The instruments used so far for dietary monitoring (eg, food frequency questionnaires, food diaries, and telephone interviews) are inexpensive and easy to implement but show important inaccuracies. Alternative methods based on wearable devices and wrist accelerometers have been proposed, yet they have limited accuracy in predicting caloric intake because analytics are usually not well suited to manage the massive sets of data generated from these types of devices.

Objective: This study aims to develop an algorithm using recent advances in machine learning methodology, which provides a precise and stable estimate of caloric intake.

Methods: The study will capture four individual eating activities outside the home over 2 months. Twenty healthy Italian adults will be recruited from the University of Padova in Padova, Italy, with email, flyers, and website announcements. The eligibility requirements include age 18 to 66 years and no eating disorder history. Each participant will be randomized to one of two menus to be eaten on weekdays in a predefined cafeteria in Padova (northeastern Italy). Flows of raw data will be accessed and downloaded from the wearable devices given to study participants and associated with anthropometric and demographic characteristics of the user (with their written permission). These massive data flows will provide a detailed picture of real-life conditions and will be analyzed through an up-to-date machine learning approach with the aim to accurately predict the caloric contribution of individual eating activities. Gold standard evaluation of the energy content of eaten foods will be obtained using calorimetric assessments made at the Laboratory of Dietetics and Nutraceutical Research of the University of Padova.

Results: The study will last 14 months from July 2017 with a final report by November 2018. Data collection will occur from October to December 2017. From this study, we expect to obtain a series of relevant data that, opportunely filtered, could allow the construction of a prototype algorithm able to estimate caloric intake through the recognition of food type and the number of bites. The algorithm should work in real time, be embedded in a wearable device, and able to match bite-related movements and the corresponding caloric intake with high accuracy.

Conclusions: Building an automatic calculation method for caloric intake, independent on the black-box processing of the wearable devices marketed so far, has great potential both for clinical nutrition (eg, for assessing cardiovascular compliance or for the prevention of coronary heart disease through proper dietary control) and public health nutrition as a low-cost monitoring tool for eating habits of different segments of the population.

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KEYWORDS

wearable device; dietary monitoring; calorimetric assessment; machine learning; big data

Introduction

Obesity affects 650 million people worldwide and is strongly related to cardiovascular diseases, which are the main cause of death in Western countries [1,2]. Therefore, the monitoring of caloric intake and energy expenditure are crucial challenges for the maintenance of individual and public health. Monitoring of diet requires daily recording of each food consumed and its energy content (and sometimes other macronutrients). The instruments used for this purpose include food questionnaires, food diaries, and telephone interviews [3-5]. Questionnaires are self-administered instruments that are low cost and easy to use. Despite some recent attempts to increase the immediacy of their use, these tools keep showing limited accuracy [6]. The reason is that the quality of data collected depends on the precision of the respondent in reporting their food intake and relative serving size [1,2,7]. In addition, long-term diet monitoring by self-evaluation increases the risk of underestimating energy intake and reporting incorrect or incomplete information [8].

With advances in technologies, studies have started to employ electronic wearable devices for monitoring caloric intake [9]. Wearable devices seem to be the future of research on nutrition since they are expected to reduce the error related to subjective evaluation, guaranteeing an adequate, objective, and reliable estimate of caloric intake [4,9].

Wearable devices equipped with motion sensors usually detect feeding-related gestures, translate gestures into a number of bites, and then bites into energy intake through the use of algorithms whose rationale is based on the existence of a relationship between the number of bites and the number of calories eaten [9]. For example, the Bite Counter is worn on the wrist and counts the number of bites taken by the movement of the arm or wrist [10]. It essentially consists of a watch that records the movements associated with the action of biting, counting them. In accordance with recent studies, the bite counters currently in use seem to be accurate in identifying bites, but not in associating bites to the corresponding caloric intake [11,12].

The main reason they are poor in associating bites to calories is because of their poor analytics, which are usually not well suited to manage the massive sets of data generated from these devices and with a limited accuracy in predicting caloric intake [8,13-16]. Technology alone is not effective unless smart data analytics complements it. Using the cutting-edge advances in machine learning and through the dynamic exploitation of big raw data coming from the real-life use of wearable sensors, this project aims to provide a ready-to-implement algorithm for monitoring caloric intake accurately. These massive data flows will provide a detailed picture of real-life conditions and will be analyzed through an up-to-date machine learning approach with the aim to accurately predict the caloric contribution of individual eating activities independent of the wearable device chosen. This protocol describes the experimental study set up for the development of an algorithm able to estimate the caloric intake from kinetic data.

Methods

This section describes the protocol of the study "Measuring Caloric Intake at the Population Level" (acronym NOTION), approved by the Bioethics Committee of the University of Torino, Torino, Italy, on July 12, 2017 (#256091).

Data Collection

The study will last 14 months from July 2017 with a final report by November 2018. Data collection will occur from October to December 2017.

Volunteer Recruitment

The study will capture four individual eating activities outside the home over a 2-month period. Twenty healthy Italian people will be recruited from the University of Padova with email, flyers, and website announcements. The eligibility requirements include age 18 to 66 years, no eating disorder history, and absence of allergies and food intolerances. Potential participants will complete a Web-based initial form to collect a preliminary assessment of the fulfillment of the inclusion criteria. Those who appear eligible will meet with the research team members who will describe the study, answer questions, and obtain written informed consent to determine final eligibility. Participants will receive an eating activity schedule, a device, and written instructions.

Each participant will be required to eat a minimum of four meals on weekdays in a predefined cafeteria in Padova (northeastern Italy).

Collection of Anthropometric and Nutritional Information

To collect information about dietary habits and physical activity, a standard questionnaire will be administered to all enrolled participants [17] also considering the available online tools [18]. Furthermore, to have a baseline view on body composition of the participants, some anthropometric traits will be recorded. Height (m) and weight (kg) will be measured using a SECA 220 weighting scale with stadiometer (maximum capacity 220 kg; accuracy: 0.1 kg; 0.001 m), and the body mass index will be derived (kg/m^2); body density (g/cc) will be calculated by Durnin and Womersley equations, adjusted by age, using the logarithmic sum of four skinfolds using a Holtain 610 Caliper (accuracy: 0.1 mm): biceps, triceps, subscapularis, and iliac [8]. The Siri equation will be then used to calculate fat mass (%) and fat-free mass (%) [8]. The waist-hip ratio will be calculated by measuring their circumferences (in cm). Skinfold measurements will be performed by the dieticians' staff as recommended by official guidelines [9].

Experimental Phase

A selection of different types of prepackaged foods will be made by dieticians to simulate a complete Mediterranean daily diet

of 2000 kcal or less. The choice of prepackaged food is driven by the fact that bias regarding the energy content will be reduced because the caloric information reported on the labels will be compared to the values measured by the calorimeter. Two menus (menus A and B, Table 1) of Italian food items will be set up and randomly assigned to the volunteers. Volunteers will be asked to be present on two different days at fixed times to have breakfast and lunch on the first day, and snack and dinner on the second day. Each volunteer will wear two devices, one on each wrist, and eat the assigned food in two stages: first simulated and then the actual meal right after. During the simulated meal, the participants have to simulate a maximum of 10 bites for each food item without ingesting it. The operators will collect the bites in plastic bags, previously labeled with a unique alphanumeric code designed to allow the traceability of each bite along all the experimental phases from the collection to the final storage. During the actual meal, participants will be asked to eat the meal continuously and naturally. All stages will be videotaped. The several stages are shown in Figure 1.

Tools

Two digital cameras will be used to record each participant's mouth, torso, and tray during meal consumption. Four Garmin Fenix 5 watches containing an accelerometer and gyroscope will be used to record the movement of the wrists of each participant at 5 Hz. The FIT files generated by the watches will be converted using the java/FitToCSV.bat utility in the FIT SDK. They will contain all the relevant information for the analysis: triaxial accelerometer data x, y, z, pitch and roll angle, power, and time.

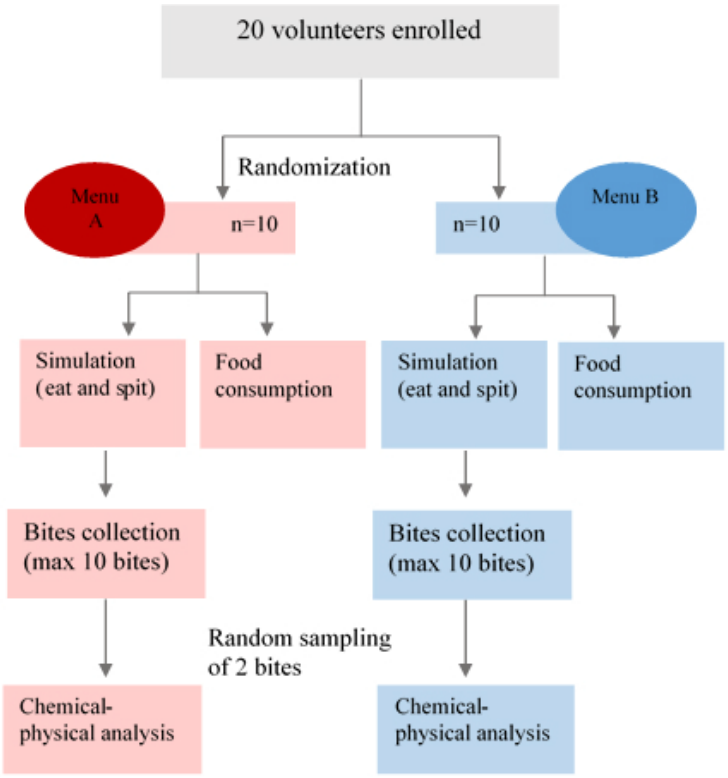
Gold standard evaluation of the energy content of selected foods will be obtained by calorimetric assessments made at the Laboratory of Dietetics and Nutraceutical Research of the Department of Cardiac, Thoracic and Vascular Sciences of the University of Padova, Padova, Italy.

For this purpose, all collected bites will be measured by mass, while two bites of each food item per participant will be randomly selected to measure volume and energy content. The mass of the bites will be measured using the Gibertini Crystal 100 scale. The volume measurement will be obtained measuring the liquid displacement due to the immersion of the sample in a graded cylinder (250 mL class A) filled with water. Caloric content of bites will be measured using a bomb calorimeter after the complete homogenization of a single bite [18]. Each sample will be analyzed in duplicate. Every 30 burns the benzoic acid standard will run to ensure the instrument calibration [19,20].

Table 1. Composition of the two menus (menus A and B) randomly assigned to the volunteers recruited in the NOTION study.

Menu and meal	kcal/portion
Menu A	
Breakfast	
Rusks and jam	114 kcal/41 g
Yogurt	186 kcal/170 g
Lunch	
Risotto with asparagus	471 kcal/300 g
Mozzarella	242 kcal/100 g
Snack	
Biscuits	278 kcal/55 g
Dinner	
Vegetable soup	135 kcal/310 g
Artichoke chicken	199 kcal/120 g
Menu B	
Breakfast	
Brioche	99 kcal/28 g
Yogurt	186 kcal/170 g
Lunch	
Tagliolini with mushrooms	546 kcal/300 g
Chicken meatballs with tomato sauce	135 kcal/120 g
Snack	
Sandwich	195 kcal/70 g
Dinner	
Eggplant parmigiana	309 kcal/300 g
Italian fresh cheese	269 kcal/100 g

Figure 1. NOTION study design and flowchart.



The calorimeter calculates the gross energy of the samples; therefore, to consider the metabolizable energy it will be necessary to correct the value by subtracting 1.25 kcal per gram of protein from gross energy.

Randomization and Sampling

Each volunteer will be assigned a menu through randomization, providing two balanced groups of 10 participants for each menu. A sampling strategy will be applied to select 2 of 10 bites collected during the simulated meal for chemical and physical analysis.

Randomization to Food Menus

With the aim to randomize each participant to a menu, the "blockrand" package of R will be used. This function creates random assignments for clinical trials, or any experiment, in which subjects are enrolled sequentially. Blocked randomization with a 1:1 ratio will be performed to ensure balance between the groups throughout the study.

Sampling of the Bites

Bites per food item and participant will be numbered progressively from 1 to 10 as they are collected. After random reordering, performed with the "sample" function of R, the first two will be sampled. Since sampling is scheduled in advance, and a participant could complete the meal in less than 10 bites, if the bite indicated in the reordered list be unavailable, then the next in the list will be considered (eg, assume that the list is 1,10, 3, 2, 7, 4, 8, 5, 9, 6 and the participant has finished the meal in five bites, then the first and third bites will be analyzed).

Data Processing

Bite Identification

A human rater will annotate an Excel file by watching the video and pausing it at times when a bite is seen to be taken, using frame-by-frame rewinding to identify the time when food or a beverage is placed into the mouth. Two human raters independently will label each food. Raters will be trained to standardize the process of labeling.

Sensor and Video Synchronization

To achieve synchronization without wires of cameras and wrist motion trackers, device clocks will be synchronized with the participants' watch times at the beginning of each data collection session. Participants will be asked to clap their hands at the beginning of each eating session. Watch times will be manually recorded for the periods of clapping. The peaks of the distinct sinusoidal patterns at the beginning of each acceleration signal will be visualized on the video and aligned between the wearable devices.

Signal Preprocessing

Working with sensor signals coming from wearable devices that monitor human movements involves the use of signal processing techniques to remove noise from the data [21]. As a result, the accuracy of a predictive model built on preprocessed data will depend on the choice of the most suitable filtering parameters. Another important aspect that should be considered is the computational cost of performing both sensor preprocessing and model fitting. There is great interplay between signal preprocessing and model performance. Different methods to preprocess sensor data will be evaluated and compared in terms of effectiveness to extract the maximum information at a low computational cost [21].

Row acceleration signals consist of movement, gravitational, and noise components. Separation of these becomes difficult during rotational movements [22]. These two components overlap in the frequency domain so cannot be completely separated by filtering. However, most of the acceleration of human body movements occurs below 0.2 to 0.5 Hz, and thus a reasonable estimate of separation will be carried out using a Butterworth low-pass filter with 0.3 Hz cutoff frequency [16,22,23]. Usually after applying the noise filter, feature extraction occurs for classification [23,24]. A vector of features will be obtained by calculating variables from the time and frequency domain on sliding windows with a percentage of overlap [25,26]. As an alternative to sensor preprocessing, we will apply the discrete-time Fourier transformation to each sensor data [27]. This choice is because data needs to be transformed into frequencies, so they are no longer dependent on time. Therefore, we will be able to decompose the time series into single values that correspond to every single variable in the classification model.

Algorithm

Machine Learning Techniques

The use of accelerometer data has recently emerged in several biomedical apps (eg, [28,29]). Researchers have developed apps, such as those for fitness wearables, with low-level software design to perform both signal processing and analysis operations. Supervised machine learning techniques have proven to be very useful in this context, with an excellent ability to recognize human movements [30,31]. Starting from these results, we will test several machine learning techniques to recognize the food items, and then estimate the caloric intake conditional on the identification of the food. We will formulate food recognition as a classification problem, where the classes represent the food items. We will evaluate different classifiers, among them random forest, bagging, weighted k-nearest neighbor, and support vector machine. Supervised learning training, with cross-validation techniques to access the best model in terms of accuracy, will be performed. Finally, an assessment of the model prediction will be made for test data.

Estimation of Caloric Intake

The purpose of this study is obtaining an estimate of caloric intake from the movements of the wrist. To achieve this objective, we will exploit accelerometer data because it is known to be a suitable adoption for this kind of problem [29,32]. Compared to past work, we will not limit ourselves to counting the number of bites [11], but we will try to identify the type of food to better predict its caloric value. We will explore several algorithms trained in a supervised way to obtain a recognition of food items from accelerometer data. Then, we will estimate a caloric intake starting from an identified bite with a supervised learning technique. We will use a two-step algorithm: first, we estimate which kind of food people eat, and then we predict a mean caloric intake for each bite identified conditional on the food item.

Results

Building an automatic calculation method for caloric intake independent of the black-box processing of the wearable devices marketed so far, has great potential both for clinical nutrition (eg, for assessing cardiovascular compliance or for the prevention of coronary heart disease through proper dietary control) and public health nutrition as a low-cost monitoring tool for eating habits of specific segments of the population.

From this study, we expect to obtain a series of relevant data that, opportunely filtered, could allow the construction of a prototype algorithm able to estimate caloric intake through the recognition of food type and the number of bites. The algorithm should work in real time and be embedded in a wearable device able to match bite-related movements and the corresponding caloric intake with high accuracy. The challenge will be refining the algorithm to recognize an extended number of foods on a large sample of multiethnic participants.

Discussion

Overview

The estimation of caloric intake is a topic of great interest in the field of nutrition [1,2]. Monitoring the consumption levels of food can be important for those who care about their body, but it becomes crucial when the impact of diet on the progression of some diseases, such as obesity, diabetes, and cardiovascular diseases, is the focus [33]. Several tools are currently available, but their effectiveness is limited to a gross measurement of the caloric intake, which is strongly influenced by the accuracy and the memory of the interviewee [1,2,7]. The main applications of automatic monitoring systems on nutrition intake are to avoid subjective influences in manual reports and to provide a comfortable and accurate way for controlling food intake in daily life. Although the instruments based on data recorded by motion sensors and wrist accelerometers overcome the limits related to the lack of objectivity in the quantification of foods and portions, they cannot completely fill the gap between the recognition of the bites and their respective energy contribution [8,13-16].

Strengths

To handle the challenges of big data from wearable devices, new statistical thinking and computational methods are needed. The use of machine learning techniques, able to grab all the available information to solve complex learning tasks such as classification, clustering, and numerical prediction, represent a possible advancement.

This study will address these existing challenges and make the following innovative contributions:

1. Build a detailed and objective picture of eating activity under seminaturalistic conditions, as a reliable and robust basis for the subsequent analytical steps.
2. Use cutting-edge advances in machine learning for big raw data generated by inertial sensors.

3. Implement a prototype algorithm for caloric intake, independent on the wearable device used at the development stage, which will hopefully improve dietary monitoring.

Limitations and Final Remarks

We acknowledge that the whole system is still premature for real-time implementation and that future work will require a broader range of food items, a larger sample size, and a free-living condition. Furthermore, we will need to check the hypothesis that the type of food rather than other participant and food characteristics (eg, cutlery used to eat, anthropometry) is the best proxy of caloric intake. Moreover, we will have to investigate whether the signals recorded by the wearable devices actually hold promise in measuring caloric intake. Nevertheless, this ambitious project has great potential to empower dietary monitoring.

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Conflicts of Interest

None declared.

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Protocol

A Game-Based School Program for Mental Health Literacy and Stigma Regarding Depression (Moving Stories): Protocol for a Randomized Controlled Trial

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Abstract

Background: The prevalence of elevated depressive symptoms among youth in most western societies is high. Yet, most adolescents who are experiencing depressive symptoms do not seek help. Low mental health literacy, high stigma, and low social support have been shown to hinder help-seeking. A small number of interventions has been developed to target mental health literacy and stigma, but few focus on actual help-seeking and first aid behavior. We have developed a game-based school program called Moving Stories that targets mental health literacy, including knowledge and behavior, and stigma among adolescents, in regard to depression specifically.

Objective: Our aim is to describe the protocol for a study that will test the effectiveness of the program Moving Stories in a Dutch adolescent sample. We hypothesize that adolescents who participate in the program Moving Stories will have better mental health literacy and less stigma regarding depression compared to adolescents in the nonintervention control group at posttest and at 3- and 6-months follow-up. We also expect a positive change in actual help-seeking and first aid behavior at 3- and 6-months follow-up.

Methods: Moving Stories has been developed by a professional game design company in collaboration with researchers and relevant stakeholders. The effectiveness of Moving Stories will be tested through a randomized controlled trial with two conditions: Moving Stories versus control. Participants will fill in questionnaires at pretest, posttest, and 3- and 6-months follow-up. Our power analysis showed a required sample size of 180 adolescents.

Results: Four high schools have agreed to participate with a total of 10 classes. A total of 185 adolescents filled in the pretest questionnaire. The last of the follow-up data was collected in December 2018.

Conclusions: If Moving Stories proves to be effective, it could be implemented as a school-based program to target mental health literacy and stigma regarding depression; this could, in turn, improve early help-seeking in adolescents suffering from depression.

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KEYWORDS

depression; help-seeking behavior; helping behavior; health literacy; stigma; video games; adolescence; secondary schools

Introduction

Background

Depression is considered to be one of the leading causes of disability worldwide. A recent World Health Organization report indicated that 4.4% of the world population is suffering from a depressive disorder [1]. Although the prevalence of depressive disorders in youth is lower than in adults [1], the numbers of young people experiencing elevated depressive symptoms are substantial. In a recent large-scale European study, approximately 40% of adolescents were suffering from clinical or subclinical depressive symptoms [2], which put them at increased risk for developing a depressive disorder in adulthood [3,4]. Furthermore, in adolescence, both symptoms of depression as well as a full-blown depressive disorder have been related to academic problems [5,6], social problems [5], physical problems, [5] and suicidal ideation [4]. In view of these long-term negative consequences, it seems important that young people seek the help they need to deal with depressive symptoms.

Even though many young people are experiencing depressive symptoms, over half of them do not seek help [7]. Some of the barriers to help-seeking are low mental health literacy, perceived stigma, and a preference for self-reliance [7,8], while social support and encouragement by others to seek help are related to increased help-seeking [7]. It is important to overcome these barriers and encourage social support, as prolonged time between depression onset and actual treatment leads to a diminished response to treatment and a smaller chance of remission [9]. Considering the high prevalence of depressive symptoms, the negative consequences, and the benefits of seeking help early in the process, it is relevant to target the causes that hinder help-seeking behavior in young people. Consequently, we have developed Moving Stories, a game-based school program that targets both mental health literacy and stigma regarding depression in young adolescents.

Mental Health Literacy and Stigma

Mental health literacy has been defined as “knowledge and beliefs about mental disorders which aid their recognition, management, or prevention” [10]. Mental health literacy does not only refer to knowledge, but also to connected actions [11], not only by those who need help, but, equally important, by the people close to them.

With regard to recognizing a disorder, multiple studies have shown that both adolescents and adults find it difficult to recognize a mental health disorder [11,12]. Compared to adults, adolescents seem to be even less able to identify a disorder like depression [13]. Therefore, especially in adolescents, it is crucial that symptom and disorder recognition improve, as symptom recognition has been linked to choosing appropriate help and treatment [14].

Although increasing people’s ability to recognize a depressive disorder is beneficial for help-seeking behavior, labeling a person as mentally ill has also been linked to stigmatizing attitudes [15]. These attitudes, in turn, have been linked to a diminished amount of appropriate help being offered to peers in need of help [16], possibly counteracting efforts to increase help-seeking. Stigma is also considered to be an important factor as to why people who could benefit from help do not seek help or do not fully participate in treatment [17]. Consequently, this means that in targeting symptom recognition it is also necessary to focus on stigma.

One of the coping strategies that people with mental problems often use is finding social support. Most people view this type of help as potentially beneficial, but it becomes a concern when they turn solely to friends and family instead of seeking professional help [11]. Adolescents prefer seeking help from people they know [18,19] and they believe this help to be beneficial [20]. For adolescents, seeking help only from peers becomes a specific concern, since peers might not be able to provide sufficient or appropriate help [11]. Hence, adolescents could benefit greatly from knowing more about help-seeking options and available treatments. Moreover, teaching adolescents how to help their peers in learning about appropriate first aid for mental health could encourage the seeking of appropriate help among those who need it.

Mental Health Literacy and Stigma Interventions

Although the research on mental health literacy interventions for youth is scarce, the few existing studies show promising results [12]. One example is of a school-based intervention consisting of short educational sessions in the classroom, involving a trainer who has lived experience with a mental disorder [21]. In a sample of 14-16-year-olds from the United Kingdom and Canada, findings showed an increase in mental health literacy after receiving the intervention. A second school-based intervention with lived-experience trainers targets symptom and disorder recognition with information-delivery sessions, videos, and discussions. This intervention proved to be effective in improving symptom and disorder recognition in Australian adolescents between 14 and 18 years of age [22]. A third school-based mental health literacy program consists of 10 hours of class sessions about mood disorders and helping peers, with teachers providing the program. The program was associated with increased mental health literacy and decreased stigma in Australian 13-16-year-olds [23].

More recently, teen Mental Health First Aid was developed [24]: an adolescent version of the well-studied Mental Health First Aid training for adults [25]. A recent meta-analysis demonstrated that the adult training results in a decrease of negative attitudes and an increase of knowledge and supportive behaviors toward others with mental health problems [26]. For the recent adolescent version, a Delphi consensus study was conducted to find key messages to use in the training to help adolescents provide basic mental health first aid to their peers [27]. Based on those findings, a 5-point action plan was developed that serves as the basis for the training. The first two effect studies showed promising results, with mental health

literacy increasing and stigma decreasing in participating adolescents [24,28].

The research on mental health literacy interventions is scarce, but more work has been conducted on the effectiveness of antistigma programs. Most studies on decreasing stigma among youth reveal that education and contact with a person with lived experience—someone who has suffered from a mental health disorder him- or herself—are related to decreases in stigma [29]. A meta-analysis showed that education and contact were equally effective in decreasing stigma [29], while a review showed that personal contact was more important in reducing stigma among young people [30].

Even though there are promising programs for mental health literacy and stigma among youth, there are still few interventions that target actual help-seeking behavior. Most intervention programs focus on enhancing knowledge, but not on enhancing behavioral styles [11]. We have developed a game-based school program called Moving Stories. While most mental health literacy programs consist of didactic sessions, we argue that the nature of video games fits better with our goal of teaching skills alongside increasing knowledge. Already, there are several examples of video games successfully teaching youth health knowledge and skills (eg, in cancer treatment specifically [31] and healthy lifestyles in general [32]) and changing mental health stigma [33]. Games provide the opportunity to practice behavior in a relatively safe, engaging, and virtual environment and to learn by doing [34]. Moreover, players usually receive immediate feedback on their actions in games, encouraging them to continue and learn more [35]. Finally, games are an important part of young people's lives [36], making a game-based intervention relevant for this population.

Objectives

The goal of this paper is to describe the protocol for a study that will test the effectiveness of the program Moving Stories in a Dutch adolescent sample by means of a randomized controlled trial. Our first hypothesis is that adolescents who participate in the Moving Stories program will have better mental health literacy and will endorse fewer stigmatizing attitudes regarding depression than adolescents who do not participate, both directly at posttest and at 3- and 6-months follow-up. Second, we expect a change in help-seeking and first aid behavior. At 3- and 6-months follow-up, we expect that adolescents in the Moving Stories group, compared to the control group, will have sought more help if they were experiencing depressive symptoms or provided increased appropriate first aid if they were in contact with a peer who was experiencing depressive symptoms.

Methods

Design

The effectiveness of Moving Stories will be tested within a randomized controlled trial with two conditions: Moving Stories versus a nonintervention control group (see Figure 1 for the flowchart of the study design). We have chosen not to include a third condition with an alternative program because there is currently no mental health literacy program for young adolescents available in the Netherlands. Classes within a school will be randomized to either condition to avoid skewed distribution of participants over the two conditions due to school effects. The outcomes will be measured by self-report at four assessment points: T1 (pretest, within one week before the start of the program); T2 (posttest, within two weeks after the end of the program); T3 (3-months follow-up); and T4 (6-months follow-up), with the exception of the behavioral outcomes, which will not be assessed during posttest.

Program

Moving Stories is a game-based school program, which consists of three parts: (1) an introduction lesson; (2) a single-player, mobile, 3D video game; and (3) a contact session with someone with lived experience with a depressive disorder. The program targets three components of mental health literacy, specifically regarding depression, namely (1) recognition of when a disorder is developing, (2) knowledge of help-seeking options and treatments available, and (3) first aid skills to support others who are developing a mental disorder or are in a mental health crisis [10]. Moreover, the program aims to decrease stigma around depression among youth. Moving Stories has been developed for high school students and should be offered to an entire class. The program is delivered within one week, making it convenient to incorporate into schools.

During the introductory lesson, adolescents who were in a class together were asked to download the game on their mobile phone. Moving Stories can be downloaded from the Google Play Store or Apple's App Store (iOS). All adolescents in the class received a classroom password to be able to play the game. This password was linked to their class schedule, allowing for joint playing time and feedback moments. The adolescents were then able to watch an introductory video about the game. The video game is about a character, Lisa, who is the player's fictional cousin (see Figure 2). The introductory video talks about who she is and what the relationship is between her and the player. The video also conveys that Lisa has not been feeling well lately. She has lost interest in most things, seems to be somber most of the time, and over the past few days has not gotten out of bed. The player is asked whether they could help her. After the video, the adolescents were told that they would play the game for five days. Each morning, when they would start the game while still at home, they would wake up in Lisa's house and would be able to do five things for her (eg, get her something to drink). Some of those actions would be positive, while others would be negative. After they would choose five actions, they would go to school and their day would start. During the day at set time points, they would get feedback from Lisa about what they did in the game through automated text messages. They would earn points for their actions; together these points would add up to a total *Relationship* score, which would be shown in the menu of the game. That score would illustrate the quality of their relationship to Lisa and at the same time gives the research team an indication of the adolescents' first aid skills through the actions they took to help Lisa in a more targeted and constructive way. The adolescents were also told that they could share the messages with each other and that sharing them might give them more information about the game and more quickly improve their skills in the game. Lastly, they were told that if they had questions or wanted to discuss what

they had seen in the game before the contact session at the end of the intervention, they could go to their school welfare coordinator or school counselor.

The video game has a menu (see Figure 3) with buttons to access the house and Lisa's messages, as well as a meter for the *Relationship* score. The menu also shows which of the five playing days the player is on and includes a button that leads players to an information page within the game. The information page shows the player's personal ID and has a button they can press when they "feel like giving up on life." If the player presses the button they are immediately directed to the 113 Zelfmoordpreventie (Suicide Prevention) website, the Dutch organization for suicide prevention, where they can chat or have a call with a trained volunteer. The 113 Zelfmoordpreventie website helps both adults and youth.

Within the house (see Figure 4), players are able to walk around, examine objects, talk to Lisa, and perform actions. Through interactions with Lisa, we aimed to increase the players' ability to recognize depressive symptoms. There is no limit to walking, examining, or talking; however, players are only able to perform five actions per day, which are all related to good or bad first aid skills [27] and which will increase or decrease the Relationship score with Lisa. Once players perform those five actions, they are asked whether they wanted to go to school or redo the day. Playtime of the game per day is approximately 10-15 minutes. During the day, the entire class receives personal messages at the same time from Lisa, with feedback on their personal actions through text messages. Through the feedback, we aimed to increase players' knowledge of help-seeking options and improve their first aid skills. The feedback moments are mainly scheduled during break times, so the players will have the opportunity to discuss the messages and talk about game strategies.

Figure 1. Flowchart of the study design.

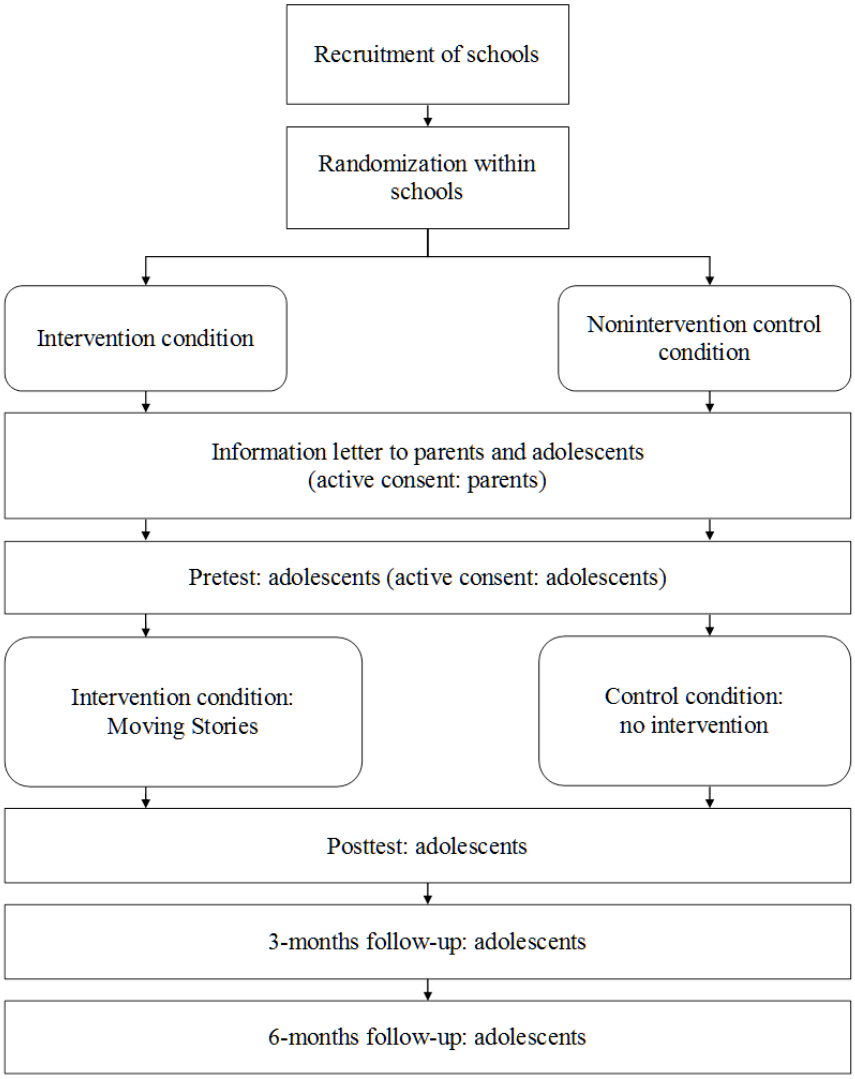
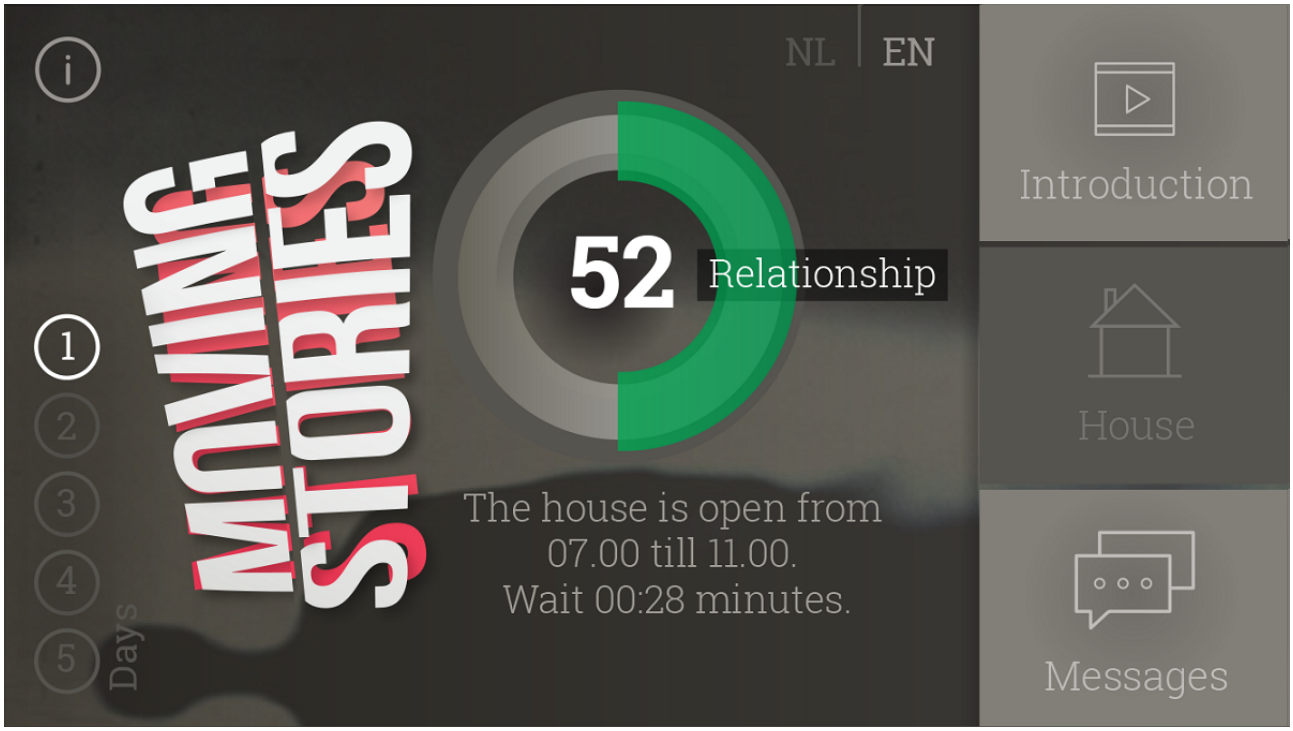


Figure 2. Moving Stories' video game character, Lisa (screenshot; translated to English).

Figure 3. Moving Stories menu (screenshot, translated to English).



The goal of the game is for players to build a relationship with Lisa by showing interest, trying to help her feel a little better, and following up on promises. The end goal of the game is to get an adult involved, after discussing this with Lisa. When the player reaches a *Relationship* score of 50, Lisa gets out of bed. When the player reaches a *Relationship* score of 95, Lisa will be willing to talk to an adult about what is going on. Only when the player discussed this with her, and she mentioned she was willing, does the action of calling an adult get rated positively. After five days of playing, all players see a final scene that takes place a few months into the future. In the scene, Lisa tells the player that she got help and that she is getting better. Based on the final *Relationship* score, Lisa thanks the player for their efforts during the time they were in the house and gives specific

feedback on what the player could have done to further help her.

Figure 4. Lisa's house in Moving Stories (screenshot).

After five days of playing, the program finished with a contact session. In this concluding session, the story of the girl in the game was brought into the real world. A trainer with lived experience with depression led the contact session. All trainers have been trained by the Trimbos Institute in telling their story, guiding a discussion about the game, and translating their story and that of the game to specific first aid skills. In the session, the trainer told their own story and used the experiences of the adolescents in the game to discuss five first aid skills the adolescents could go back to when they want to help a friend who might be suffering from depression. These five skills, or action points, in helping a friend were based on content from the teen Mental Health First Aid training [24] and have been translated into Dutch: (1) Look for warning signs, (2) Ask how they are, (3) Listen without judgment—"without judgement" was added specifically to this program, (4) Help them connect with an adult, and (5) Be a friend. During the contact session, adolescents were allowed to ask questions about the game and about the experience of the trainer. To guide the discussion, the trainer used a PowerPoint presentation with predetermined questions that were related to the content of the game and the five action points. A member of the research team was present to make sure that all questions were discussed.

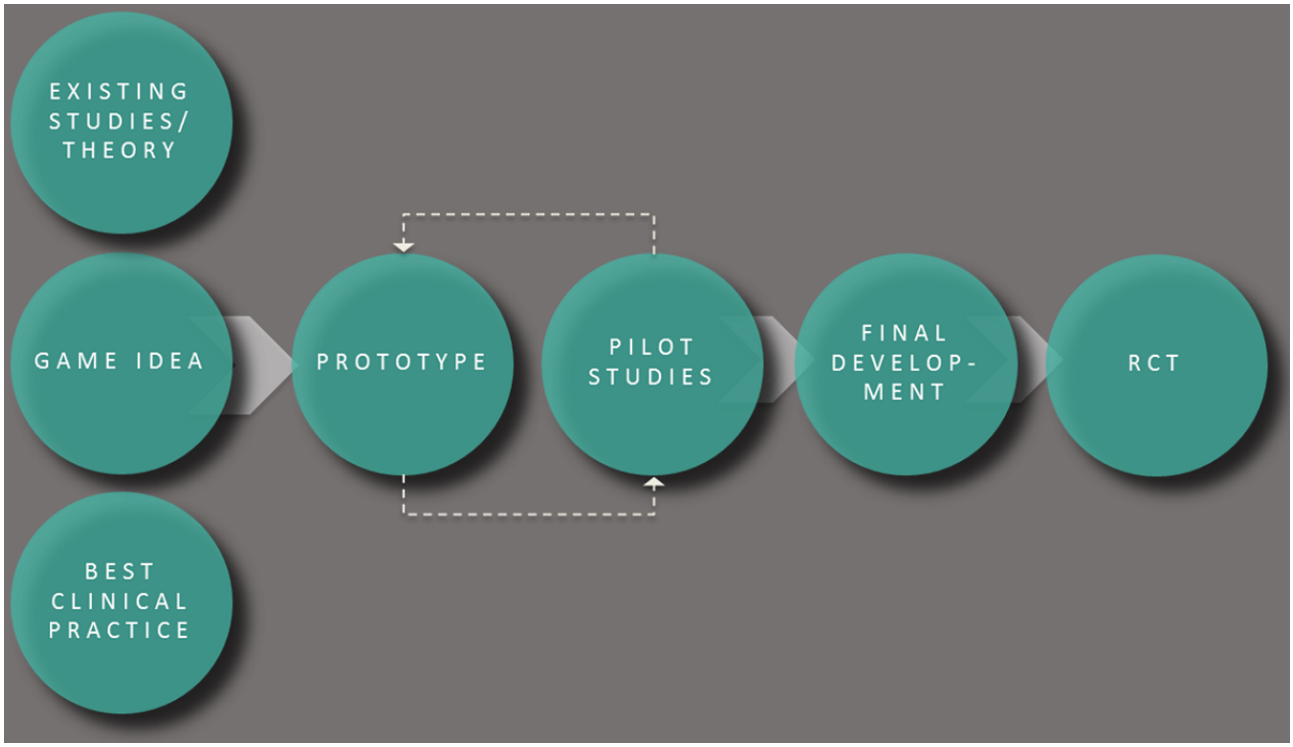
Moving Stories has been developed through a close collaboration between game designers and behavioral scientists using an iterative design process (see Figure 5). This means that multiple prototypes have been tested in pilot studies before the final version was built. All stakeholder groups have been involved during each development phase, including youth, therapists, and teachers. The concept of the game was based on the latest literature and best practice experiences. In total, we ran through five iteration rounds, each with several playtests. Over 200 people played the game before final development.

Procedure

Participants are adolescents in the second year of high school (ie, 12-15 years old). Schools in the Netherlands were approached and asked to participate with at least two second-year classes to allow for within-school randomization. The exclusion criterion was refusal from either the parent or the adolescent to participate.

After schools agreed to participate, the classes were allocated to either the Moving Stories or control condition by an independent researcher using computer-generated random numbers. All parents and adolescents in the participating classes received an information letter via the school with information about the study (see Multimedia Appendix 1). Along with the letter, parents received a consent form, which they had to sign and send back to the researchers in order to give consent for their child's participation. Before adolescents filled in the pretest, they will also had to give written active consent for participation. All questionnaires at all assessment points were Web based and were either filled in at school or at home.

Figure 5. Iterative design process for the development of Moving Stories. RCT: randomized controlled trial.



To verify that Moving Stories does not increase depressive symptoms or suicidal ideation in adolescents, the Child Depression Inventory (CDI) [37,38] was administered. At all assessment points, if adolescents had a score on depressive symptoms in the clinical range and/or suicidal intention (CDI>29 and/or a score of 2 on question 9 of the CDI) [37,38], both the parents and adolescent were contacted by phone by a clinically trained member of the research team to inform them of the result and to give advice on where to seek professional help. We follow standard Dutch guidelines, in which we refer adolescents and their parents to the appropriate professional channels of care, where they will receive an assessment and subsequent intake if necessary. No follow-up of this group will be initiated from the research team itself. This procedure was approved by the Research Ethics Committee and complies with Dutch care guidelines. Adolescents who were contacted were not excluded from participating in the study, since that would increase stigma. During analyses, we will check and, if necessary, control for the possible effects of contacting participants and referring them to care.

To make sure that all adolescents who seek help from teachers during the study receive the help that they need, all teachers were provided with an information booklet developed for this study that includes short practical tips on what they can do to help their students. The primary researcher informed the teachers and other professionals involved at the school about the study and the short practical tips at an information session. In addition, teachers had the opportunity to follow an e-learning program on suicidality and depression in youth. This program, called Mental Health Online [39], aims to improve knowledge and self-confidence in people working with youth and has been found to be effective [40]. For this study, the developers of Mental Health Online have added an information page on depression to the program, since the e-learning program mainly discusses suicidality in youth [41] (in Dutch).

At pretest, adolescents were provided with a participant number by the researcher to fill out the questionnaires. They also received a personal player ID in the game. The data from the questionnaire and the data from the game will be matched through the participant number and personal player ID. Adolescents filled in their names and contact information during the pretest; this information can only be accessed by the primary researchers (AT and MK) and data management team at the Trimbos Institute (Dutch National Institute on Mental Health and Addiction) for the purpose of calling adolescents and their parents in case of clinical depressive symptoms and/or suicidal ideation. Adolescents were reminded, through email or via a phone call, to fill in the questionnaires. Data are stored on a secure server in accordance with European privacy law.

We expected that most adolescents would have had a suitable mobile phone or tablet that can run the video game Moving Stories. If an adolescent did not have a mobile phone or tablet that was suitable for the video game, a mobile phone was provided by the research team for the duration of the program. Adolescents received €12.50 in total for filling in the questionnaires at the four assessment points. Both parents and adolescents were allowed to withdraw their consent at any time during the study without consequences. Ethical approval for this study was provided by the Ethical Committee of the Faculty of Social Sciences at the Radboud University Nijmegen (ECSW2017-2306-526). This study is registered in the Dutch Trial Register (NTR7033).

Measures

Descriptives

Sociodemographic variables include gender, age, ethnicity, and current educational level. We measured prior gaming experience by asking participants if they play video games and, if so, on what platforms and how many hours per week they play video games.

Depressive Symptoms

The CDI [37,38] was used to control for depressive symptoms. The questionnaire consists of 27 items, each with three statements to choose from. Participants were asked to pick the statement that best described how they felt in the previous two weeks. An example of an item's three statements is as follows: *I sometimes feel sad; I often feel sad; I always feel sad*. Each statement corresponds to a score of 0, 1, or 2. Scores are added up to a total score for depressive symptoms. The Dutch version of the CDI has good internal consistency and test-retest reliability [42].

Outcome Measures

Overview

Mental health literacy regarding depression was measured by (1) symptom recognition, (2) first aid intentions, (3) knowledge of first aid, (4) first aid confidence, (5) beliefs about help, and (6) help-seeking intentions. Depression stigma was measured by (1) personal stigma, (2) perceived stigma, and (3) social distance. For an overview of all measures used and the relative assessment points, see Multimedia Appendix 2. All measures that did not have a Dutch version have been translated into Dutch and translated back into English by an independent researcher. Incongruities were discussed and resolved. Cronbach alpha values will be calculated for all measures with more than one item.

Symptom Recognition

Symptom recognition was assessed by using three vignettes with gender-matched descriptions of 15-year-old adolescents with depression, social anxiety, and psychosis, respectively [43]. Participants were asked what might be going on with this person. Responses were open ended. The symptom *irritability* has been added to the depression vignette, since this is considered an important symptom in adolescence [44]. Correct scores in the depression vignette are defined by labeling the person as depressed or by using a word related to depression. Overestimation of depression is defined by labeling the person in the social anxiety and/or psychosis vignette as depressed or by using a word related to depression. For the following items, the vignette of the person with depression was used as an example.

First Aid Confidence

Confidence in providing first aid was measured by asking how confident the participant would be to help the person in the vignette if he or she was their friend: 5-point scale from 1 (not at all confident) to 5 (very confident) [24].

First Aid Intentions

To measure general first aid intentions, participants were asked how much they agree with the statement "If [name] was a friend, I would help him/her": 5-point scale from 1 (totally disagree) to 5 (totally agree). Specific first aid intentions were assessed by asking whether they would perform the mentioned first aid action "if [name] was a friend": 5-point scale from 1 (never) to 5 (certainly). In total, six helpful (eg, "Tell [name] I have noticed something seems wrong and I want to make sure s/he is okay") and six harmful (eg, "Ignore [name] because s/he is being attention-seeking") actions were mentioned [28] and an open-ended option was provided (eg, "I would do something else other than the options mentioned above, namely..."). The scores for the harmful actions will be reverse scored. A total score for first aid intentions per scale will be calculated by summing up the scores for the helpful actions and the reverse-scored harmful actions, with higher scores representing better first aid intentions. Both scales have acceptable-to-good reliability [28].

Beliefs About Help

Beliefs about help were assessed by asking whether the following 10 people would make person's situation in the vignette *better*, *not better*, *not worse*, or *worse*: (1) boyfriend or girlfriend; (2) friend (not related); (3) parent; (4) other relative; (5) psychologist or social worker (outside school); (6) phone helpline; (7) general practitioner; (8) teacher; (9) school welfare coordinator or school counselor; and (10) religious leader (eg, priest, imam, or rabbi). They were also asked who of those 10 would be most helpful. The number of selected adult sources deemed to be helpful (*better*) will be used to calculate beliefs about appropriate help: the *other relative* category will be excluded, since it could include an adult *or* peer [24].

Stigma

Both personal and perceived stigma was measured using the Dutch Depression Stigma Scale [45]. Any mention of the word *depression* was substituted by the situation of the person in the vignette (eg, "[name] is *dangerous*," similar to the procedure in Jorm and Wright [46]). The last two statements in the scale about hiring a person with depression and voting for them if they were a politician were not used because we do not consider those relevant for this age group. The original personal and perceived stigma scales both have acceptable-to-good internal consistency [47]. Social distance was measured with the five items from the Social Distance Scale for youth [46]. The Social Distance Scale for youth has excellent internal consistency [28].

First Aid Behavior

First aid behavior was measured by asking whether the participant has had contact with someone who has experienced a problem similar to that seen in the vignette within the last three months. A problem is defined as when "someone has changed a lot in his/her normal thoughts, feelings, and behavior, which made it hard for him/her to move on with his/her life. The situation did not resolve itself and went on longer than you had expected." If the participant answered *yes* or *maybe*, they were then asked whether they offered the other person their help. If so, or if they are unsure, they were asked what they did out of the 12 actions and the open-ended option mentioned in

the First Aid Intentions section above. First aid behavior will be calculated similar to that of first aid intentions [28].

Help-Seeking Intentions

Help-seeking intentions were measured using the General Help-Seeking Questionnaire (GHSQ) [48], to which we added the options *teacher* and *school welfare coordinator/school counselor* to match all sources of help to the items in the Beliefs About Help section. Average scores for the following three categories will be calculated: (1) general help-seeking intentions, (2) help-seeking intentions using informal sources, and (3) help-seeking intentions using formal sources. Higher scores will indicate higher intentions. The GHSQ has good internal consistency and excellent test-retest reliability [48].

Help-Seeking Behavior

Help-seeking behavior was assessed by asking whether the participants themselves had experienced a problem similar to the situation in the vignette. If they responded with *yes* or *not sure*, they were asked whether someone has helped them with this problem in the last three months and who this person was: multiple options were allowed. We did not distinguish between whether the help was provided to the participant or whether they sought out the help from this person themselves. The same list of people from the Beliefs About Help section and the GHSQ [24,48] was used with the additional response option *Don't know for sure*. If the participant indicated their boyfriend or girlfriend and/or a friend had helped them, they were asked what that person did out of the 12 first aid actions and the open-ended option mentioned in the First Aid Intentions section above [28]. This was done in order to assess the first aid skills in youth surrounding the person who had experienced a problem such as that in the vignette.

Evaluation of Moving Stories

During posttest, participants in the intervention group were asked to evaluate the program Moving Stories across seven items using a 5-point scale from 1 (totally disagree) to 5 (totally agree); for example, "How much do you agree with the following statement? I would like to play the game another time to get a better score." To distinguish between the different components of the program and the study (ie, game, evaluation session, and research), the participants were also asked which of the components they would recommend to a friend if they had the opportunity to participate in the study over the next year.

Contamination Check

To check for possible contamination effects due to the within-school randomization, the participants in the control group were asked at 6-months follow-up whether they had heard of the game Moving Stories and, if so, whether they had played it. If they indicated they had played it, they were asked on what platform they did so.

Sample Size

The sample size was based on the expected difference (Cohen *d*=0.40) between the intervention and control condition for mental health literacy and stigma at 3-months follow-up, based on Perry et al [23]. We performed a power analysis using Stata version 14.2 (StataCorp) [49], assuming baseline-adjusted regression analyses (alpha=.05; beta=.20). Our provisional estimates for the correlations between pre- and posttest and between posttest and 3-months follow-up are .50. A coefficient of variation of .19 (estimated mean cluster size=18; estimated cluster size range=11-25 [50]) and an intracluster correlation coefficient of .02 [23] lead to a design effect of 1.35. Taking into account the design effect, we calculated that we need 3.75 classes per condition to show the expected effect, rounding up to four classes per condition, with 18 adolescents per class. To adjust for a *t* distribution [51], we added one class per condition, resulting in five classes (ie, 90 adolescents) per condition and a total necessary sample size of 180. Since we will perform the analyses according to the intention-to-treat principle, dropout was not taken into account.

Statistical Analyses

Descriptive statistics will be calculated for all variables of interest (eg, knowledge of first aid, stigma, and help-seeking intentions). In order to assess whether randomization results in similar groups, we will examine whether there are differences between the two conditions on relevant covariates (ie, sex, age, educational level, ethnicity, gaming behavior, and depressive symptoms) using *t* tests for the continuous variables and chi-square tests for the categorical variables. Variables that are distributed differently between the two conditions will be entered as control variables in all models testing the effects of the conditions.

We will perform our analyses according to the intention-to-treat principle, meaning we will include all children who filled in the pretest questionnaires in the analyses to test the study hypotheses. We will control for clustered data because children are nested within classes. We will use Mplus version 8 (Muthén & Muthén) [52] for the analyses, since it has special features to deal with missing data. It also allows for analyzing complex data while controlling for clustering. To test whether children in the experimental condition have shown an increase in mental health literacy and a decrease in stigma at 3- and 6-months follow-up, compared to the control condition, regression analyses will be conducted. Both the effect sizes and the confidence intervals will be reported. Open-ended questions will be analyzed exploratively and indicatively where necessary.

Results

As of the writing of this paper, four schools and 10 classes have agreed to participate in this study. At pretest, 185 adolescents and their parents gave consent and filled in the first questionnaires. The last of the follow-up data was collected in December 2018.

Discussion

This paper describes the protocol of the first study that will be used to test the effectiveness of the mental health literacy program Moving Stories, which not only targets knowledge and beliefs, but also aims at training youth in both help-seeking and first aid behavior, specifically regarding depression in youth. This project is unique in its use of an online game to teach

mental health literacy. Moreover, the program has been designed by professional game designers in close collaboration with relevant stakeholders. We used a rigorous experimental design to answer our research questions. Our study adds to the latest literature on mental health literacy, as there is a lack of intervention studies in adolescents.

Since we randomized within schools and between classes, there is a risk of contamination between the classes. However, considering the necessary sample size, randomizing between schools would potentially lead to large school differences and we have estimated the between-class risk of contamination to be lower than the between-school effect. We will check for potential contamination effects at the last measurement point. Another limitation is that we were unable to objectively assess what the adolescents discussed outside the game. We only measured what they did within the game and assessed outcomes through self-report questionnaires; therefore, we will be unable to say anything about the possible effect of these discussions. Lastly, although we asked about provided first aid behavior, we did not include any objective behavioral measures in this study. Conclusions about actual first aid behavior are therefore limited.

If Moving Stories proves to be effective, it could be implemented as a school-based program to target mental health literacy and stigma and, in turn, improve early help-seeking. Combining the program with screening questionnaires on depression could further aid early detection of mental health problems in adolescents.

Acknowledgments

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Authors' Contributions

AT is the primary researcher on this study and is supervised by RCMEE, IG, and MK. AT has also contributed to the development of Moving Stories. EH was the lead designer on the development of Moving Stories. IG and RCMEE had advisory roles in the development of Moving Stories.

Conflicts of Interest

Moving Stories was developed by IJsfontein and the Trimbos Institute in collaboration with the Behavioural Science Institute of the Radboud University Nijmegen and 113 Zelfmoordpreventie.

Multimedia Appendix 1

Information letters for parents and adolescents (translated to English).

[PDF File (Adobe PDF File), 106KB - resprot_v8i3e11255_app1.pdf]

Multimedia Appendix 2

Measured variables and respective assessment points.

[PDF File (Adobe PDF File), 37KB - resprot_v8i3e11255_app2.pdf]

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Abbreviations

CDI: Child Depression Inventory
GHSQ: General Help-Seeking Questionnaire

NWO: Netherlands Organisation for Scientific Research
RCT: randomized controlled trial
SMS: short message service
T1: pretest
T2: posttest
T3: 3-months follow-up
T4: 6-months follow-up

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Protocol

A Self-Regulation–Based eHealth and mHealth Intervention for an Active Lifestyle in Adults With Type 2 Diabetes: Protocol for a Randomized Controlled Trial

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Abstract

Background: Adoption of an active lifestyle plays an important role in the management of type 2 diabetes. Online interventions targeting lifestyle changes in adults with type 2 diabetes have provided mixed results. Previous research highlights the importance of creating theory-based interventions adapted to the population's specific needs. The online intervention "MyPlan 2.0" targets physical activity and sedentary behavior in adults with type 2 diabetes. This intervention is grounded in the self-regulation framework and, by incorporating the feedback of users with type 2 diabetes, iteratively adapted to its target population.

Objective: The aim of this paper is to thoroughly describe "MyPlan 2.0" and the study protocol that will be used to test the effectiveness of this intervention to alter patients' levels of physical activity and sedentary behavior.

Methods: A two-arm superiority randomized controlled trial will be performed. Physical activity and sedentary behavior will be measured using accelerometers and questionnaires. Furthermore, using questionnaires and diaries, patients' stressors and personal determinants for change will be explored in depth. To evaluate the primary outcomes of the intervention, multilevel analyses will be conducted.

Results: The randomized controlled trial started in January 2018. As participants can start at different moments, we aim to finish all testing by July 2019.

Conclusions: This study will increase our understanding about whether and how a theory-based online intervention can help adults with type 2 diabetes increase their level of physical activity and decrease their sedentary time.

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KEYWORDS

protocol; randomized controlled trial; eHealth; mHealth; type 2 diabetes; self-regulation; physical activity; sedentary behaviour; mobile phone

Introduction

Diabetes is associated with various health problems including kidney failure, retinopathy, and cardiovascular disease [1]. By 2035, it is estimated that one in ten adults will have diabetes [1]. This exponential growth of diabetes is largely accounted for by type 2 diabetes, which is responsible for 85%-95% of the disease cases [1]. Adopting an active lifestyle (ie, being

physically active and limiting sedentary behavior) has shown to play an important role in both the prevention and management of type 2 diabetes [2,3]. Consequently, cost-effective approaches that help adults with type 2 diabetes in increasing their physical activity and reducing their sedentary behavior are needed.

Electronic health (eHealth) and mobile health (mHealth) interventions have the potential to reach large populations in a cost-effective way and are effective in promoting an active lifestyle in the general population [4]. Nevertheless, research about the effectiveness of online interventions targeting adults with type 2 diabetes reveals mixed results [5-7]. Based on these findings, several proposals have been formulated to better design and implement eHealth and mHealth interventions for adults with type 2 diabetes. First, interventions should be grounded in and informed by theoretical models [5,7,8]. Research revealed that online programs that are developed using theoretical models result in larger effect sizes [9]. A useful perspective may well be the self-regulation framework, which focuses on both preintentional (such as increasing knowledge) and postintentional (such as action and coping planning) processes of behavior change [10]. This framework describes behavior change as a goal-guidance process starting from personal determinants for change until goal maintenance or, if necessary, disengagement [11]. Second, online interventions should take into account the perspective and needs of the users. This can be accomplished by involving end users during the entire developmental process of the online program [12,13]. Third, developers should address the high levels of attrition that are negatively affecting many online interventions [14]. Combining a website with a reminder system, such as automated emails or text messages, may be one of the ways to reinforce website use [7].

There are many papers discussing the effects of online interventions. Nevertheless, a clear and thorough description of the interventions themselves is often missing. This impedes research, as researchers often start from scratch when creating an intervention. The publication of study protocols that clearly describe the active ingredients and the "dose" of the interventions are therefore needed [5]. This study describes the protocol for a randomized controlled trial examining how a self-regulation–based eHealth and mHealth intervention ("MyPlan 2.0") targeting sedentary behavior and physical activity influences the behavior-change process of adults with type 2 diabetes. The needs of adults with type 2 diabetes were taken into account, as they were actively involved in the development of the program [15,16]. "MyPlan 2.0" consists of a website that motivates users to create, follow, and maintain their own goals for physical activity or sedentary behavior in combination with an optional mobile app offering daily support. The aim of this paper is to describe "MyPlan 2.0" and provide the study protocol that will be used to investigate the website's effectiveness and underlying mechanisms. The items addressed in this protocol paper are based on the 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [17]. Multimedia Appendix 1 presents the completed SPIRIT checklist.

Methods

Ethical Approval

This study was approved by the Committee of Medical Ethics of the Ghent University Hospital (Belgian registration number: B670201732566) and registered as a clinical trial (Clinicaltrials.gov NCT03291171). Written informed consent from each participant will be obtained. Precautions will be taken to ensure participants' privacy during data analysis.

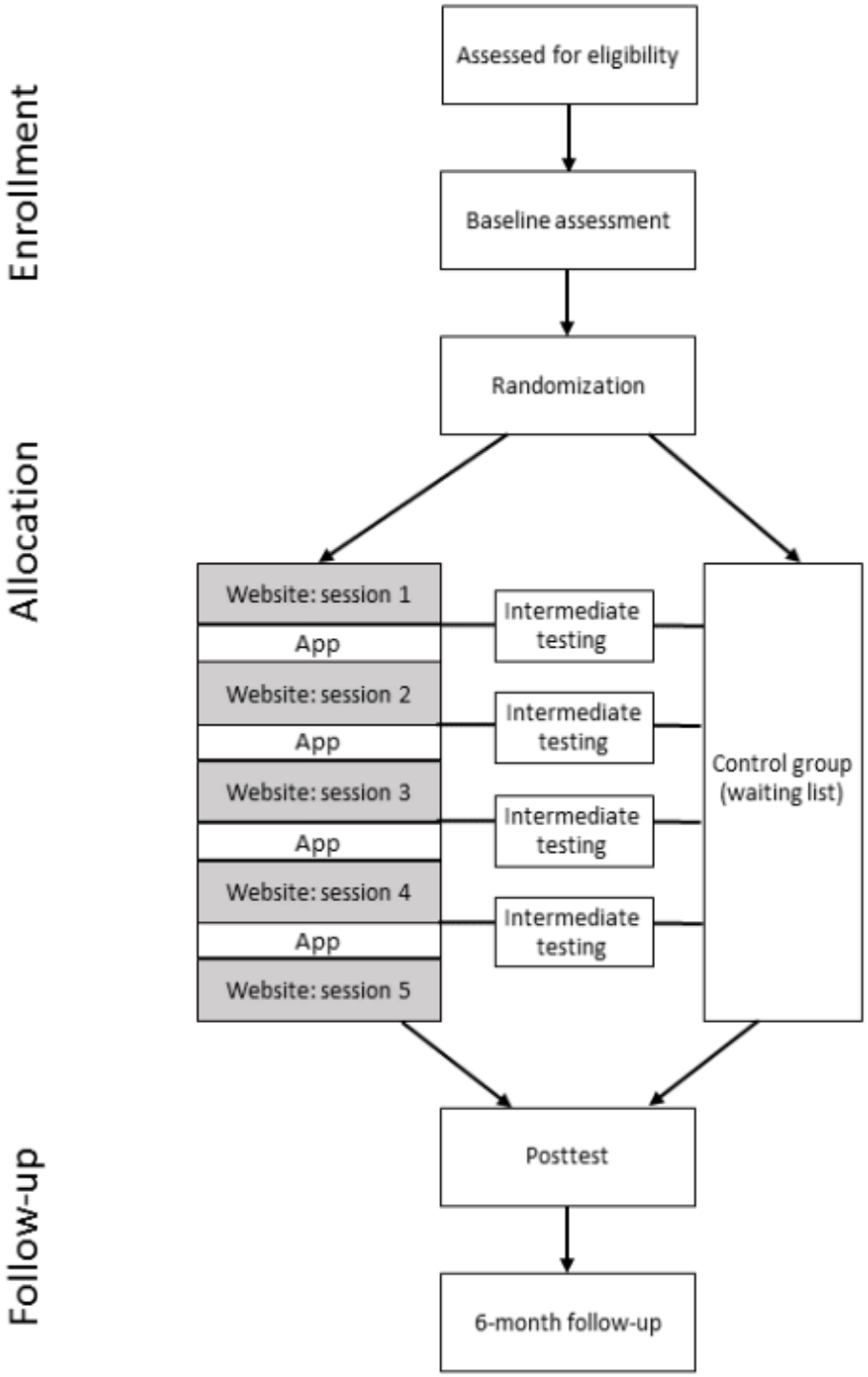
Study Design

A two-arm superiority randomized controlled trial will be performed. The study flow is depicted in Figure 1. Data will be collected during three home visits. During the first home visit, written informed consent will be obtained from the participants, and the participants will be asked whether they would like to increase their physical activity or decrease their sitting time. Participants will then complete questionnaires on physical activity, sedentary behavior, personal determinants for change (eg, self-efficacy), and health-related outcomes. Furthermore, participants' weight and waist circumference will be assessed. Finally, participants from both groups will wear an accelerometer for a period of 10 days and fill out a morning and evening diary on each of these days. The diaries will assess participants' daily goals and possible person-related barriers (ie, fatigue, stress, depressed mood, pain, nausea, and feelings of numbness or tingling in limbs).

After this period, LP will randomly allocate participants to the waiting list control group or the intervention group in a 1:2 allocation ratio by using an automated randomizer [18]. This will be done independent from patients' choice to increase their physical activity or decrease their sitting time. Participants allocated to the intervention group who chose to increase their physical activity will be directed to the website targeting physical activity, whereas participants who chose to decrease their sitting times will be directed to the website targeting sedentary behavior. Participants owning a smartphone will be asked to download the mobile app. The website part of the intervention consists of five consecutive modules (a start module and four follow-up modules) spread over a 5-week period. Each week, participants from both groups will be phoned by a researcher. During these phone calls, questions regarding participants' personal determinants for behavior change (eg, self-efficacy) will be repeated. In doing so, we will achieve the temporal separation needed to investigate causal pathways [19]. Furthermore, the phone calls will be used to check whether patients had hypoglycemia or made changes to their medication.

One week after completing the program (for the intervention group) or 6 weeks after finishing the baseline measures (for the control group), a second home visit will be scheduled during which the posttest will be carried out. In this phase, questions regarding process evaluation will be added to the questionnaires of the intervention group. Finally, 6 months after the baseline test, the intervention group will be visited a third time by the researchers to perform the follow-up test in order to examine whether the potential effects of the intervention are sustainable.

Figure 1. Study flow.



Hypotheses

Our primary hypotheses for this study are as follows: (1) The intervention group allocated to the module "Physical Activity" will show an increase in total physical activity from pre- to posttest compared to no change in the control group. This effect will be sustained in the intervention group from the posttest to the follow-up test. (2) The intervention group allocated to the module "Sedentary Behaviour" will show a decrease in sedentary behavior from pre- to posttest compared to no change in the control group. This effect will be sustained in the intervention group from the posttest to the follow-up test.

Our secondary hypotheses are as follows: (1) Positive changes in physical activity or sedentary behavior will be mediated by increases in the personal determinants self-efficacy, action planning, and coping planning. (2) The intervention group will have more positive health outcomes (ie, a lower weight; smaller waist circumference; and lower levels of fatigue, anxiety, and

depression) from pre to follow-up test. (3) The negative effect of daily stressors (ie, fatigue, stress, depressed mood, pain, nausea, and feelings of numbness or tingling in limbs) on physical activity and sedentary behavior will be smaller in the intervention group from pre- to posttest compared to no change in the control group. This effect will be sustained in the intervention group from posttest to follow-up test.

As moderation analyses for online interventions targeting adults with type 2 diabetes are not usually performed [5], no hypotheses regarding the moderation effects are made. The following factors will be examined as potential moderators: age, sex, education, and chosen behavior (ie, physical activity or sedentary behavior).

Participants

The required sample size was calculated using the software GPower 3.1.9.2 [20]. This program requires the following input: effect size, alpha, power, number of groups, and number of measurements. To our knowledge, there is no meta-analysis documenting the effect sizes of online interventions targeting physical activity or sedentary behavior in adults with type 2 diabetes. As people with type 2 diabetes tend to be overweight and physically inactive, we decided to focus on these characteristics for our effect-size estimation [21]. A meta-analysis by Davies et al (2012) showed that eHealth interventions targeting physical activity levels of overweight or sedentary adults reached effect sizes of 0.37 [22]. Most of the studies included in the meta-analysis used questionnaires rather than accelerometers to measure participants' level of physical activity. Assuming an effect size of 0.37, alpha of .05, beta of .90, two groups (intervention group and control group), and three measurements (pretest, posttest, and follow-up test), the *a priori* power analysis suggests a sample size of 96 (64 participants in the intervention group and 32 in the control group).

Therefore, 96 participants with type 2 diabetes will be recruited via the Ghent University Hospital, the Sint-Lucas General Hospital (Ghent), the Maria Middelares General Hospital (Ghent), and the Damiaan General Hospital (Ostend). To be eligible for participation, participants should have type 2 diabetes, have been diagnosed for at least 1 month, be 18 years or older, speak Dutch, be computer literate, have internet access, and not have participated in previous studies on "MyPlan 2.0." Participants receiving concomitant care and interventions will not be excluded. Potential participants with type 2 diabetes will be recruited via the endocrinologists of the collaborating hospitals. The endocrinologists will check whether visiting patients meet the inclusion criteria, provide eligible patients with a flyer, and ask these patients if the researchers are allowed to contact them. If the patient agrees, the researchers will receive the patient's contact details. The recruitment procedures will continue until the proposed number of participants is reached. Except during the pretest, neither the participants nor the researchers assessing the outcome variables will be blinded.

Description of the Intervention

"MyPlan 2.0" is an eHealth and mHealth intervention targeting physical activity and sedentary behavior. The program is based on "MyPlan 1.0," a self-regulation-based eHealth intervention (ie, a website) originally designed to be used by general practitioners in order to increase the levels of physical activity and the intake of fruit and vegetables in the general population [23]. Although "MyPlan 1.0" was shown to be effective, the high levels of attrition indicated that there was room for improvement [24-27]. Moreover, the general practitioners indicated that the program should also be made available to people with type 2 diabetes, as health self-regulation is of great importance in this population [28]. For "MyPlan 2.0," we decided to focus on physical activity and sedentary behavior. Two studies were performed to guide the adaptations to the program. First, user and website characteristics related to attrition were explored [29]. Second, think-aloud interviews were performed with 20 adults with type 2 diabetes and 20 adults from the general population [15]. We instructed users to verbalize their thoughts while using "MyPlan 1.0." Based on the findings of both studies, a new version—"MyPlan 2.0 version T2D"—was developed. Using semistructured interviews with 21 adults with type 2 diabetes who had completed "MyPlan 2.0," this version was further adapted to users with type 2 diabetes [16].

"MyPlan 2.0" consists of a website and a mobile app. The website, created using LifeGuide [30], is the basis of the intervention and has five consecutive parts. The first time a user logs into the website, (s)he can choose whether (s)he would like to be more physically active or less sedentary. The further structure of the website is independent of the chosen health behavior. First, in order to provide tailored feedback and personalized information (eg, the age and sex of the persons in the success stories are tailored to the user's age and sex), all users answer questions assessing demographic information. Subsequently, users have the option to take a quiz regarding the benefits of the selected health behavior. Next, users fill in a questionnaire to assess their current levels of physical activity or sedentary behavior and receive feedback regarding the time they spend being physically active or sitting. Thereafter, users create a specific plan for increasing their physical activity (eg, "On Monday morning I will walk 10 minutes in the neighbourhood") or decreasing their sedentary behavior (eg, "I will stand when talking on the phone"). Users will then state possible barriers for the selected goal, search for solutions, and decide how they will monitor their goal. Offered choices are a calendar, a booklet, the mobile app, etc. Next, users will see an overview of their goals, barriers, and solutions and how they will monitor their behavior change: This is called the action plan. Finally, users will be offered additional information about how they can receive social support from their environment.

The intervention lasts for 5 weeks. Each week, the users receive an email to go back to the website to evaluate and adapt their goal based on the successes and failures of the past week. In these follow-up sessions (four in total), users can actively reflect on their behavioral change. Each follow-up session has the same structure. First, users see the goal(s) they have set the week before and are asked whether they reached their goal. Feedback based on success or failure is given. Second, users choose to keep or adapt their goal. Third, users think about possible barriers that might come up in the following week and search

for solutions. Fourth, users see an overview of their (new) goal, barriers, and solutions. Fifth, users can read additional tips and tricks to be more physically active or less sedentary. Table 1 gives an overview of the behavior change techniques that are covered by the website. The techniques are labelled according to the taxonomy of behavior change techniques compiled by Michie and colleagues [31].

The mobile app offers daily support during the entire behavior change process. Through the app, users can review their goals, monitor their progression, search for possible coping techniques, and take quizzes regarding physical activity or sedentary behavior. By visiting the website, completing quizzes, and monitoring their behavior change, users can collect points in the mobile app. This gaming element was added to increase engagement with the intervention. The techniques implemented in the mobile app can be found in Table 2. The techniques are labelled according to the taxonomy of behavior change techniques compiled by Michie and colleagues [31]. Multimedia Appendix 2 presents screenshots from the website and the mobile app.

Measurement instruments

Questionnaires

Demographic Variables

Participants' age, sex, height, civil status, education, profession, and the time since diagnosis will be assessed using a questionnaire in the pretest.

Physical Activity and Sedentary Behavior

The Dutch version of the long International Physical Activity Questionnaire (IPAQ-L) [32] and the Longitudinal Aging Study Amsterdam (LASA) sedentary behavior questionnaire [33] will be used to assess the context-specific physical activity and sedentary behavior. The interview version of the IPAQ-L and the LASA questionnaires will be conducted, as previous research showed that participants tend to overreport their levels of physical activity when using self-administered questionnaires [34]. This will be done during each of the three testing waves.

Health Outcomes

Participants' feelings of depression, anxiety, and fatigue will be assessed during each testing wave using scales of the Patient-Reported Outcomes Measurement Information System [35]. Feelings of depression and anxiety will be measured via the Dutch version of the depression short-form scale (version 1.0) and anxiety short-form scale (version 1.0), both of which contain six items with five answer options: "never," "seldom," "sometimes," "often," and "always." Participants' fatigue will be measured using the subscale "fatigue" of the Dutch version of the 29-profile scale (version 2.01). The subscale contains four items with five answer options: "not at all," "a bit," "somewhat," "to a fairly high degree," and "to a high degree."

Personal Determinants

Personal determinants for behavior change (ie, self-efficacy, risk perceptions, outcome expectations, motivation, intention, action planning, coping planning, and self-monitoring) will be measured in both groups during each testing wave and the weekly phone calls. These determinants will be assessed using multiple items (minimum three items per determinant) that were selected by presenting a large number of items measuring Health Action Process Approach (HAPA) determinants to 11 experts in the self-regulation framework. All experts indicated whether each item measured the presented HAPA determinant and how sure they were of their answer [36]. Based on these responses, discriminant content validity was assessed using the method described by Johnston et al [36], and the best scoring items were selected. Each item has 10 answer options, ranging from "completely disagree" to "completely agree."

Accelerometry

Participants' sedentary time and total, moderate-to-vigorous, and light physical activity will be assessed for a period of 10 days during each of the three testing waves using ActiGraph accelerometers (model GT3X+; Pensacola, FL), which have been shown to be reliable and valid [37-40].

Anthropometry

Anthropometry will be carried out on each of the three testing waves (ie, during each home visit). The visiting researcher will assess participants' weight using a Seca weighing scale (model 813; Benson Avenue, CA), whereas waist circumference will be measured at the lowest rib margin and the iliac crest at the midaxillary line using Seca measuring tape.

Diary

Mental and Physical Well-Being

Each morning and evening, participants will rate the extent of fatigue, stress, depressed mood, pain, nausea, and feelings of numbness or tingling in the limbs experienced by using a 10-point scale, ranging from "absolutely not" to "very much."

Action Planning

Each morning, participants will report their planned actions for that day by indicating which type of goals they planned (eg, social activities, work, and physical activity). Each evening, participants will report the level to which they reached their listed goals by using a 10-point scale, ranging from "did not work out" to "worked out very well." An overview of the measures and the time points during which they will be assessed is shown in Table 3.

Table 1. Overview of the self-regulation techniques implemented in the website.

Self-regulation technique	Implementation mode
Providing information on the consequences of behavior, in general	During session 1, users have the option of taking a quiz. The quiz contains questions regarding the benefits of the chosen health behavior (ie, increasing physical activity or reducing sedentary behavior). Each answer is followed by a clear explanation.
Exploring social support	During session 1, users can read more information about how they can obtain social support from their partner, friends, family, or colleagues.
Providing feedback on performance	During session 1, users complete a short questionnaire regarding their current levels of physical activity or sedentary behavior. Thereafter, they can see for how much time they are physically active or sedentary and in which domains (eg, transport or leisure time).
Action planning	In each session, users have the option to create their own goals to increase their physical activity or decrease their sedentary behavior. By answering different questions, the goals are made as specific as possible (eg, "On Monday and Wednesday morning I will walk 10 minutes in the neighbourhood").
Barrier identification/problem solving	In each session, users are prompted to think about possible barriers regarding their plans and search for potential solutions (eg, "I might forget my plan to take a walk in the evening, so I will stick a note on the fridge").
Prompting self-monitoring of behavior	In each session, the website encourages users to monitor their behavior change and presents options to do so.
Prompting review of behavioral goals	During each follow-up session, users are asked to review the extent to which the goals set in the previous session were achieved.

Table 2. Overview of the self-regulation techniques implemented in the mobile app.

Self-regulation technique	Implementation mode
Providing information on the consequences of behavior, in general	Users have the option to take several quizzes on the benefits of the chosen health behavior (ie, increasing physical activity or reducing sedentary behavior).
Prompting self-monitoring of behavior	Every evening, users receive a notification to fill in whether they were more active today than they used to be before. The entries of each week are shown in a graph visible to the user.
Action planning	Users can review their goals and make adaptations, if necessary. In the mornings of days during which users should live up to their goal, a notification is sent to remind them about the goal.
Barrier identification/problem solving	Users can see an overview of common barriers and solutions for these barriers.

Cognitive interviews, usually performed in small samples [41], were used to assure the comprehensibility of the diary and questionnaire assessing personal determinants for behavioral change [42,43]. We purposively selected participants aged ≥50 years, because the prevalence of type 2 diabetes peaks in older age [1]. The participants were instructed to read and complete the diary and questionnaire. For each item, the interviewer (LP) asked the participant whether (s)he considered the item to be difficult, how (s)he came to an answer, and which time period (s)he took into account when providing an answer. Based on the results of these interviews, adaptations to the items were made. The mean (SD) age of the participants was 58.3 (6.5) years (range, 52-67 years). Demographic information of the participants is provided in Table 4.

Data Quality Assurance

The data-collection process will be guided and monitored by the researchers. As this study is part of a postgraduate doctoral degree project, no specific data trial steering or data monitoring committee was assigned. However, the study progress will be discussed monthly with the research team. Only accelerometer data from participants who had 4 valid days including 1 weekend day ("valid" defined as ≥10 hours of wear time) will be included in the analysis [44]. Furthermore, responses to the IPAQ-L and LASA questionnaires will be checked for plausibility. For the IPAQ, we will use the method described by Dubuy et al [45] to truncate the data. For the LASA questionnaire, we will truncate the data to a maximum total score of 16 hours a day [46].

Statistical Analysis

Statistical analysis will be performed after completing the data-collection phase. No interim analysis will be executed. Descriptive statistics and independent samples *t* tests will be carried out to explore and identify potential differences between the intervention and the waiting-list control group. To evaluate the primary outcomes of the intervention, three-level (hospital, patient, and time) analyses will be conducted. Intention-to-treat analyses will be performed. As the drop-out rate is usually high in eHealth research [14], it is likely that a per protocol analysis will not be feasible. Furthermore, participants of the intervention group will only be included in the analysis if they complete four of five sessions on the website. Moderating effects will be identified via interaction terms (including the possible moderator). For the secondary outcomes, mediating effects will be investigated using structural equation modelling. Changes in health outcomes and the effect of daily stressors on patients' activity levels will be assessed using multilevel analysis. Data analysts will not be blinded to participants' group allocation.

Table 3. Overview of the measures.

Measures	Baseline	Intermediate test	Posttest	Follow-up test
Demographic information using the general questionnaire	✓			
Physical activity and sedentary behavior				
Accelerometer	✓		✓	✓
IPAQ-L[a]	✓		✓	✓
LASA[b] sedentary behavior questionnaire	✓		✓	✓
Health outcomes				
Weight	✓		✓	✓
Waist circumference	✓		✓	✓
PROMIS[c] fatigue	✓		✓	✓
PROMIS depression	✓		✓	✓
PROMIS anxiety	✓		✓	✓
Personal determinants - single items	✓	✓	✓	✓
Daily stressors and goals				
Fatigue	✓		✓	✓
Stress	✓		✓	✓
Feelings of depression	✓		✓	✓
Pain	✓		✓	✓
Nausea	✓		✓	✓
Numbness/tingling in limbs	✓		✓	✓
Goals	✓		✓	✓
Evaluation of goals	✓		✓	✓

[a]IPAQ-L: long International Physical Activity Questionnaire.

[b]LASA: Longitudinal Aging Study Amsterdam.

[c]PROMIS: Patient-Reported Outcomes Measurement Information System.

Table 4. Demographic information of the participants from the cognitive interviews (N=4).

Demographics	N
Women	3
Level of education	
Primary school	1
Secondary education	1
College	2
Diagnosed with type 2 diabetes	2

Process Evaluation

Contextual Factors

Individuals live in certain contexts that inevitably shape their lifestyle. As the design of the environment plays an important role in developing and maintaining an active way of living [47], patients' perception of the environment will be examined during the pretest. This will be done via the short version of the Assessing Levels of Physical Activity questionnaire, which has shown to be valid and reliable [48]. Furthermore, we will check for physical conditions that may have hindered the participant from being active. This will be examined during the posttest and the follow-up tests using the question, "In the past six weeks, were there physical factors (e.g. sickness or injury) making it hard for you to be physically active?" In case the participants give a positive answer, they will be asked to describe the physical factor.

Textbox 1. Overview of the questions assessing participants' satisfaction with the website and the mobile app.

Satisfaction with the website (scale: 1 - very poor to 10 - outstanding):

1. Overall, to what extent did you like the website of 'MyPlan 2.0'?
2. To what extent did you like the quiz?
3. To what extent did you like the questionnaire and the accompanying feedback?
4. To what extent did you like the action planning module?
5. To what extent did you like the coping planning module?
6. To what extent did you like the tips and tricks section?
7. To what extent did you like the feedback in the follow-up sessions?

Satisfaction with the mobile app (scale: 1 - very poor to 10 - outstanding):

1. Overall, to what extent did you like the mobile application of 'MyPlan 2.0'?
2. To what extent did you like the quizzes?
3. To what extent did you like the monitoring module?
4. To what extent did you like the action planning module?
5. To what extent did you like the coping planning module?
6. To what extent did you like the points collection module?

Satisfaction with "MyPlan 2.0" as a whole (scale: 1 - not at all to 5 - very much):

1. Was the information and support delivered by 'MyPlan 2.0' comprehensible ?
2. Was the information and support delivered by 'MyPlan 2.0' useful?
3. Was the information and support delivered by 'MyPlan 2.0' personally relevant to you?
4. Was the information and support delivered by 'MyPlan 2.0' motivating?
5. Did you enjoy using 'MyPlan 2.0'?

Usage of the Website and the Mobile App

LifeGuide allows researchers to monitor website usage and time spent on the website. Participants from the intervention group who do not return to the website after receiving the reminder email will be contacted by phone by one of the researchers. The time point and number of these calls will be monitored for each participant.

Satisfaction With the Website and the Mobile App

Users' satisfaction with both the website and the mobile app will be assessed using questionnaires during the posttest and by analyzing the usage data. Textbox 1 gives an overview of the questionnaire items and response categories. The questions are based on items used in other studies examining the appreciation of online interventions [49,50]. Participants who did not use the mobile app will not receive the questions regarding appreciation of the mobile app. Time spent on the website and the number of optional pages visited will be assessed by analyzing the website usage data.

Dropout

To gain insight into participants' reasons for attrition, several questions will be asked in case participants decide to quit using the program. Textbox 2 gives an overview of the questions and their accompanying scale. These questions are created by the research team based on a viewpoint article regarding attrition in eHealth by Eysenbach [14].

Textbox 2. Overview of the questions about participants' reasons for attrition. Scale for all questions was 1 (not at all) to 5 (very much), except question number 17 (response options: yes/no).

1. 'MyPlan 2.0' lived up to my expectations.
2. The website of 'MyPlan 2.0' is userfriendly.
3. The mobile application of 'MyPlan 2.0' is userfriendly.
4. My diabetes educator reacted positively regarding my participation in 'MyPlan 2.0'.
5. My GP reacted positively regarding my participation in 'MyPlan 2.0'.
6. My friends and family reacted positively regarding my participation in 'MyPlan 2.0'.
7. 'MyPlan 2.0' helped me to be more physically active/to sit less.
8. The personal contact with the researchers of 'MyPlan 2.0' were an additional reason for me to participate.
9. Going through 'MyPlan 2.0' took a lot of my time.
10. Filling out the questionnaires took a lot of my time.
11. I did not like wearing the accelerometer.
12. I did not like being weighed and measured.
13. I doubted to participate in this study.
14. While taking part in the study drastic changes in my life occurred (e.g. death of a family member, had a (grand)child, new job, etc.).
15. I can work well with a computer.
16. When I have computer problems, I can rely on others to help me.
17. I also took part in other programmes targeting a healthy way of living.

Informed Consent

All participants will be required to provide written informed consent before starting the study (ie, during the first home visit). Each participant will be informed about the design of the study, its purpose, confidentiality of data, and the fact that (s)he has the right to leave the study at any time without stating any reason.

Adverse Effects

Adverse effects are defined as negative outcomes related to participation in the study. Possible adverse effects in this study might be injury or severe hypoglycemia resulting from increased physical activity. The occurrence of adverse effects will be recorded and evaluated for both the intervention and control groups.

Data Storage

All data will be stored on a password-protected computer and central disk space. Data from the website will additionally be stored on password-encrypted servers. Only persons who are part of the research team will have access to the data. Multimedia Appendix 3 presents the data-management plan.

Incentives

To encourage participants to fill out their diaries, draw lots will be given based on the number of questions answered. The intervention group and the waiting-list control group will have equal chances to win prizes (ie, gift vouchers of popular supermarkets).

Results

Development of the website and the mobile app is complete. The randomized controlled trial started in January 2018. As participants can start the study at different times, we aim to complete all testing by July 2019. Important protocol modifications will be reported on Clinicaltrials.gov. The results of the study will be communicated via publications. For these publications, the American Psychological Association guidelines for authorship eligibility will be followed.

Discussion

Overview

Adopting an active lifestyle is key in the management of type 2 diabetes [3]. As the prevalence of adults with type 2 diabetes is increasing [1], self-management interventions that can be applied to large groups are welcomed. Online interventions have the possibility to reach many users at the same time and have shown to be effective in altering health behaviors, especially when they are theory based [4,9]. "MyPlan 2.0" is a theory-based website and mobile app for motivating and supporting adults with type 2 diabetes to be more physically active and less sedentary.

Study Implications

This study will test the effectiveness of "MyPlan 2.0" for each phase of the behavior change process using a randomized controlled trial. More specifically, this trial will investigate whether the program can increase patients' physical activity and decrease their sitting time. Furthermore, we will determine whether these potential changes are mediated by alterations in

personal determinants for change and result in positive health outcomes. Through the diaries, we will gain more insight into patients' daily struggles to adopt an active way of living. Finally, potential differences based on participants' characteristics will be explored. Consequently, the implications of this study will contribute to the literature of both the theoretical and practical domain of eHealth and mHealth, targeting self-management in adults with type 2 diabetes.

This study design has several limitations. First, as the resources for this study are limited, we will not be able to collect a large sample size. Consequently, it might be more difficult to identify statistically significant intervention effects. This issue highlights the importance of preventing dropout from the intervention. Dropout will be prevented by sending reminders to participants who are not logging in for follow-up sessions on the website via emails and phone calls. Second, considering the important role of creating a feeling of "goal-ownership" in self-regulation theory, participants can freely choose between the components increasing physical activity and decreasing sedentary behavior. We can therefore not ensure that the two components will have the same number of users. As a result, it might be more difficult to detect an effect for sedentary behavior if a large group selects physical activity as their target behavior and vice versa. As the structure of the intervention and the implemented behavior change techniques are exactly the same for both target behaviors, we decided to perform the analysis with one, rather than two, intervention groups. However, the selected behavior will be added as a moderator to the analysis. Third, in order to test our hypotheses, participants will need to fill out many questionnaires. This might cause higher levels of attrition. Fourth, participants are called weekly by the researchers to check for hypoglycemia or alterations in medication and to assess participants' personal determinants for change via an interview. Due to these weekly phone calls, participants might show higher levels of engagement with the intervention than they normally would. However, as we will also implement these weekly calls in the control group, we believe that the calls will have a limited impact on the intervention effects. Finally, as the researcher who will analyze the data will also be involved in the data-collection process, blinding of the data analyst is not possible. To account for this issue, a strict protocol has been developed for processing and analyzing the data.

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Conflicts of Interest

None declared.

Authors' Contributions

LP, MV, IB, and GC designed the project. LD and SS provided additional input for the study design. LP wrote the original draft. GC, MV, IB, and LD edited the manuscript and provided feedback. All authors read and approved the final manuscript.

Multimedia Appendix 1

Completed SPIRIT checklist. SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.

[PDF File (Adobe PDF File), 182KB - resprot_v8i3e12413_app1.pdf]

Multimedia Appendix 2

Screenshots from the website and the mobile app.

[PDF File (Adobe PDF File), 693KB - resprot_v8i3e12413_app2.pdf]

Multimedia Appendix 3

Data management file.

[PDF File (Adobe PDF File), 450KB - resprot_v8i3e12413_app3.pdf]

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Abbreviations

eHealth: electronic health
HAPA: Health Action Process Approach
IPAQ-L: long International Physical Activity Questionnaire
LASA: Longitudinal Aging Study Amsterdam
mHealth: mobile health
PROMIS: Patient-Reported Outcomes Measurement Information System
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Mobile Phone–Based Smoking-Cessation Intervention for Patients Undergoing Elective Surgery: Protocol for a Randomized Controlled Trial

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Abstract

Background: Several large studies have shown that the risk of cardiovascular, respiratory, and wound-healing complications (including death) within 30 days of surgery is greater for smokers than for nonsmokers. However, there is evidence that even short-term perioperative smoking cessation may reduce postoperative morbidity. Over the past few years, it has become more evident that short message service (SMS)–based interventions can help individuals quit smoking.

Objective: The overall aim of this project is to fill the knowledge gap on whether an SMS-based smoking-cessation intervention can be effective in helping patients stop smoking perioperatively. The aim of this trial is to evaluate the effectiveness of an SMS-based intervention on smoking behavior of patients undergoing elective surgery.

Methods: A two-arm parallel-group randomized controlled trial will be conducted at 20 surgical departments in southeast Sweden. Smokers undergoing elective surgery who own a mobile phone will be included. Power calculations indicate that it will be necessary to randomize 434 participants. One group will be given access to a novel 12-week SMS program, which includes daily SMS messages with behavior change–enforcing text content and hyperlinks to interactive modules, while the other group will not be given access to the intervention. Both groups will have access to the surgical departments' current routine for smoking cessation prior to surgery. Primary outcome measures, prolonged abstinence, and point prevalence of smoking cessation will be measured through questionnaires at 3, 6, and 12 months after randomization. Logistic regression models adjusted using baseline characteristics will be explored to identify potential effects of the intervention.

Results: Recruitment started in late October 2018 and is expected to last for a maximum of 30 months. The first results are expected to be available approximately 3 months after the final date of recruitment.

Conclusions: Owing to the structural problems and scarcity of time and resources, patients at most Swedish surgical departments are simply instructed to quit smoking, and perhaps, referred to a primary health care clinic. An SMS-based smoking-cessation aid can be effective in helping individuals quit smoking and is a very simple and time-efficient tool for surgical departments to use.

Trial Registration: ISRCTN Registry ISRCTN33869008; http://www.isrctn.com/ISRCTN33869008

International Registered Report Identifier (IRRID): PRR1-10.2196/12511

(JMIR Res Protoc 2019;8(3):e12511) doi:10.2196/12511

KEYWORDS

smoking cessation; mobile phone–based interventions; SMS; mHealth interventions

Introduction

Background and Rationale

Smoking is responsible for more than 60 diseases and is the single most influential preventable factor for disease and premature mortality [1]. In Sweden, tobacco is associated with 9.6% of the total disease burden [2]. Around 6400 people die every year in Sweden due to smoking. The previously recorded decline in the number of smokers in Sweden has started to level out, and in 2016, the proportion of smokers among both women and men was 9% [3]. Among individuals aged 45-64 years, the proportion of daily smokers was higher than that for any other age group—13% for women and 9% for men. Including occasional smokers, these proportions increase to 16% for women and 13% for men [3].

Studies show that approximately 65% of all smokers want to quit, and approximately 50% make at least one quit attempt each year, but only 10% seek or gain access to evidence-based supportive measures [4]. In addition to the addictive nature of smoking, the cost of treatment and time commitment make cessation a challenge [5,6].

Over 70 years ago, The Lancet published an article describing increased surgical complications after operation for patients who were smokers [7]. Since then, several large studies have shown that the risk of cardiovascular, respiratory, and wound-healing complications (including death) within 30 days of surgery is greater for smokers than for nonsmokers [8,9]. However, there is evidence that even short-term perioperative smoking cessation may reduce postoperative morbidity [5,10].

The rationale behind smoking cessation before surgery is that the short-term harmful effects of carbon monoxide and nicotine in the blood disappear 24-48 hours after smoking cessation. The harmful effects of carbon monoxide are mediated by a reduction in the availability of oxygen to the tissues by 3%-12% and associated with an increased risk of cardiac arrhythmias [10]. Nicotine stimulates the surgical stress response and increases the blood pressure, pulse rate, and systemic vascular resistance, thereby increasing the workload of the heart [10]. As anesthesia and surgery cause an increased strain on cardiac and circulatory functions, an existing oxygen imbalance can be worsened in patients who smoke, potentially resulting in hypoxemia in vital organs. Smoking also induces mucus production, which might impede the clearance of mucus, leading to an increased risk of postoperative pulmonary infections in combination with a reduced immune function associated with smoking [11].

The optimal timing and intensity of smoking cessation before surgery to reduce postoperative pulmonary complications remain unclear, but the period before a planned surgery might still be seen as a window of opportunity for smoking interventions [8,10,12]. A multicenter randomized control trial where smoking cessation was instituted after operation for acute fracture showed a decreased risk of postoperative complications in the intervention group, indicating that even cessation after surgery can be beneficial [13]. In contrast, findings reported in a Cochrane review [10], based on indirect comparisons and evidence from two small trials, showed that interventions beginning 4-8 weeks before surgery and including weekly counseling were most likely to have a significant impact on complications and long-term smoking cessation.

Previous Research and Findings

Over the past few years, it has become more evident that short message service (SMS)–based interventions can help individuals quit smoking. In a Cochrane review from 2016 [14], it was indicated that long-term quit rates increased by 67% among those who were given access to SMS-based smoking-cessation interventions compared to those who were not. These findings were supported by a second meta-analysis conducted the same year, which found that abstinence increased by 63% with the use of SMS-based interventions [15].

Our research group has previously investigated the use of an SMS-based intervention (NEXit) for smoking cessation among university students in Sweden [16-18]. The intervention was evaluated using a two-arm, parallel-group randomized controlled trial including 1590 participants between the ages of 21 and 30 years. With respect to 8-week prolonged abstinence, a statistically significant difference was found between the intervention group (25.9%) and control group (14.6%). Differences in the 4-week point prevalence between the groups were also statistically significant (20.6% versus 14.2%). The intervention has now been adapted to a younger age group and is currently in trial among high-school students in Sweden [19].

There is, however, no research in Sweden or elsewhere on the use of SMS-based interventions for smoking cessation prior to surgery. Given the success of the approach in other contexts and the importance of smoking cessation prior to surgery, it is valuable to determine if such an approach could work in this context.

Aims and Hypotheses

There is strong evidence that short-term smoking cessation before surgery can reduce postoperative complications and morbidity. There are, however, several structural problems in the Swedish health care system concerning the organization of smoking cessation for patients waiting for surgery. The overall aim of this project is to fill the knowledge gap on whether an SMS-based smoking-cessation intervention can be effective in helping patients stop smoking preoperatively. This trial protocol includes a two-arm parallel-group randomized controlled trial that aims to evaluate the effectiveness of the SMS-based intervention on smoking behavior as a tool in addition to the current routine treatment and to measure potential mediators of the intervention on smoking cessation.

There are two hypotheses in this study: (1) Smoking outcome measures will differ between the two groups at 3, 6, and 12 months after randomization. The 3-month period will be the primary time point. (2) Importance of smoking cessation and self-efficacy will mediate the effects of the intervention on smoking outcomes at 3 months. The same measures at 3 months will mediate the effect of the intervention at 6 months (and 6 months on 12 months).

Methods

Intervention Content

Rationale

Previous cessation interventions have not been able to establish clear evidence of which components or techniques are most essential to include for smoking cessation [20-22]. In the absence of a clear theory as the basis of the intervention, the content of the text messages in the proposed intervention was based on our previous smoking-cessation research concerning university students, key elements from other internet- and SMS-based interventions, official manuals about smoking cessation, and books from cessation experts [14,16-18,23-32]. The length of the intervention of 12 weeks was set to conform with previous interventions, recommendations, and our own previous experience [23,26,28,31-37].

The messages were developed with the intention to encourage participants to quit smoking. The messages included information about the consequences of smoking, how to quit and stay smoke free, tasks to perform (such as getting rid of ashtrays and cigarettes), coping strategies to deal with cravings, motivational messages, and how to avoid smoking triggers. Content that specifically focused on the benefits of smoking cessation prior to the trial was added. One of the initial messages also contains a hyperlink to a video where a surgeon gives a motivational speech and explains why it is important to quit smoking prior to surgery.

Intervention

The proposed intervention consists of 130 messages that are sent via SMS to the participant's mobile phone over a 12-week period. Two to four messages will be sent per day during the first few weeks, which will be reduced to two per day during the middle part of the intervention and further reduced to one message per day during the latter part of the intervention. Some of the messages include hyperlinks that take the participants to interactive modules that they should engage with. There are a total of nine such modules, and throughout the intervention period, participants will be reminded of their responses to modules they have completed in the past.

Briefly, the nine interactive modules that users engage with throughout the intervention are as follows:

1. A set of tips and tasks, of which participants choose five that suit them.
2. A set of reasons to quit smoking, of which the participants choose five (or enter their own reason).
3. A series of questions that result in a plan for how to deal with certain situations in which the temptation to smoke is increased, such as "When I have had my dinner, I will have a piece of fruit" or "While I am waiting for the bus, I will listen to music."
4. A set of information boxes that relate to withdrawal symptoms.
5. A set of tips that participants choose, or enter on their own, on what to do when craving cigarettes.
6. A set of information boxes with information about what happens to the human body after smoking cessation.
7. A set of information boxes with information about good habits that can replace the smoking habit.
8. A series of questions that lead to suggestions of physical activities that the participant might want to try in order to improve his/her health further and relieve abstinence.
9. A pros and cons list created by the participant for smoking cessation.

In summary, the intervention is based on previous research and expert knowledge and has been designed to suit the specific context of the current situation of the participant—a situation in which they must quit smoking preoperatively.

Design

To investigate the effect of the intervention, a randomized controlled trial (trial registration: ISRCTN33869008) will be conducted at 20 surgical departments in southeast Sweden. The trial will follow a two-arm single-blind parallel-group design. Figures 1 and 2 offer an overview of the design in the form of a SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) figure and CONSORT (Consolidated Standards of Reporting Trials) flowchart, respectively. The trial began in October 2018.

Intervention and Control Settings

One group will be given access to the novel intervention, while the other group will not be given access to the intervention. Both groups will have access to the surgical departments' current routine for smoking cessation prior to surgery. The current routine varies slightly among departments, but generally consists of referring individuals to either the national quit-smoking helpline or their local primary health care provider. None of the participating departments' supply any additional cessation help.

Recruitment

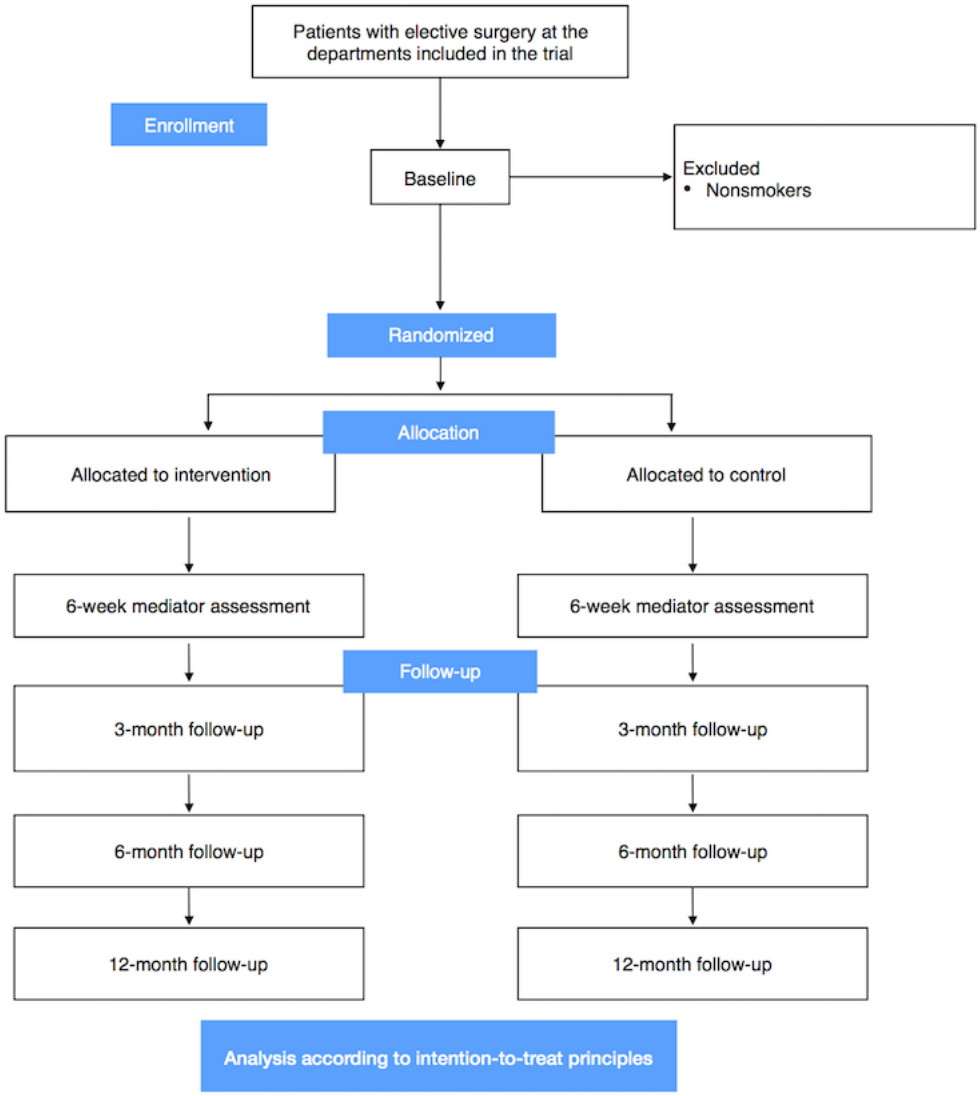
The study will be advertised through printed material provided to patients when they meet with a nurse or operation planner prior to surgery. During this meeting, the nurse or operation planner will emphasize on the importance of smoking cessation prior to surgery and hand out the printed material about the trial. Patients will also be informed about other support they can receive for smoking cessation.

Patients who want more information about the study will have to send an SMS message with a specific code to a dedicated phone number. In response, they will receive a message containing a hyperlink to a webpage that contains more information about the study. On the webpage, participants who wish to partake in the study will complete the informed consent form, following which a baseline questionnaire will be presented to them. Participants will be randomized once the baseline questionnaire has been completed.

Figure 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.

		STUDY PERIOD					
	Enrollment	Allocation	Post-allocation				Close-out
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4	t_x
ENROLLMENT:							
Informed consent	X						
Eligibility screen	X						
Allocation		X					
ALLOCATIONS:							
Intervention		X	←	—	→		
Control		X	←	—	→		
ASSESSMENTS:							
Baseline questionnaire	X						
Mediator questionnaire				X			
Follow-up questionnaire					X	X	X

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flowchart.



Recruitment will be continuous for a minimum of 12 months and a maximum of 30 months. After the initial 12 months, the recruitment period will be extended in 6-month periods until a sufficient number of participants have been recruited according to power calculations (to a maximum of the 30 months).

This protocol was approved by the ethical review board in Linköping (DNR 2018/316-31).

Eligibility

Smokers undergoing elective surgery who own a mobile phone will be included in the study. No age restrictions will be applied. Patients will be excluded if they inform the operation planners that they do not smoke or if they report that they smoke zero cigarettes when filling out the baseline questionnaire.

Randomization

Randomization will be fully computerized, not employ any strata or blocks, and not be possible to subvert because all subsequent study processes are fully automated. The trial is single blind, as participants will be aware of group allocation. Since the randomization procedure is automated, group allocation will not be disclosed to individuals responsible for the research project (researchers and surgical staff).

Follow-Up

Six weeks after randomization, mediating factors will be assessed through a questionnaire. At 3, 6, and 12 months after randomization, smoking-cessation outcomes and mediating factors will be assessed through questionnaires. In all cases, hyperlinks to the questionnaires will be sent to participants' mobile phones via an SMS. Two reminders will be sent, after which phone calls will be made to collect the primary outcome measures only. A maximum of five phone calls will be made to each participant at each follow-up stage.

Measures

All questions asked at baseline and subsequent follow-ups can be found in Multimedia Appendix 1.

Hypothesis 1:

- Primary outcome measures: Prolonged abstinence and point prevalence of smoking abstinence.
- Secondary outcome measures: Seven-day point prevalence of smoking abstinence, mean number of quit attempts since participation in the trial, number of uses of other smoking-cessation services since joining the trial, and number of cigarettes smoked weekly (if still smoking).

Hypothesis 2:

- Mediation measures: Importance and self-efficacy of quitting and staying smoke free.

Prolonged abstinence is defined according to the Russell standard definition [38], applying the usual threshold of not smoking more than 5 cigarettes in the past 8 weeks (thus allowing for a 4-week grace period). The 8-week period is then adjusted to 5 and 11 months at 6- and 12-months of follow-up, respectively. Point prevalence of smoking abstinence is defined as not smoking any cigarette in the past 4 weeks, which aims to capture delayed effects of the intervention, as suggested by the Society for Research on Nicotine and Tobacco [39]. Importance and self-efficacy will be investigated by two questions (Multimedia Appendix 1) rated on a scale of 1 to 10.

Statistical Analysis

Methods

All analyses will be performed under the intention-to-treat principle, where all randomized individuals will be included. Missing outcome data will initially be handled using complete-case analysis, which assumes that data are missing at random. If data are systematically missing, it may be possible that early responders differ from late responders, and in extension, that late responders are more similar to nonresponders. We will therefore explore the plausibility of the missing-at-random assumption by regressing the primary outcomes on the number of follow-up attempts needed before a response was recorded. To further explore the missing-at-random assumption, attrition will be investigated among study groups by comparing baseline characteristics between those who did and those who did not respond at follow-up. A sensitivity analysis that includes imputed values for missing outcome data (using multiple imputation by chained equations) will also be performed. Data will be graphically examined for outliers or data input errors, and sensitivity analyses will be performed while excluding any erroneous data points.

Hypothesis 1

Primary outcome measures and 7-day point prevalence of smoking abstinence will be analyzed using logistic regression. Negative binomial regression will be used to analyze the number of quit attempts, other smoking cessation services used, and cigarettes smoked weekly. Both unadjusted and adjusted models (primary) will be investigated. The following baseline characteristics will be adjusted for all models: gender, age, years of smoking, mean number of cigarettes smoked weekly, use of snuff, Fagerströms Nicotine Dependence Scale [40], importance, and self-efficacy.

Effect-modification analyses will be performed for the two primary outcomes. The following potential effect modifiers measured at baseline will be explored: gender, age, years of smoking, mean number of cigarettes smoked weekly, use of snuff, Fagerström Nicotine Dependence Scale, importance, and self-efficacy. Each effect-modification analysis will be performed by comparing adjusted logistic regression models excluding and including the interaction parameter using the likelihood ratio test.

For all models, coefficients of interest will be assessed for statistical significance using a null hypothesis testing approach, where tests will be two-tailed at the .05 significance level with 95% CIs. Alongside the null hypothesis tests, posterior distributions using a Bayesian approach will be calculated for each coefficient [41]. Both significance tests and posterior distributions will create a basis for scientific inference.

Hypothesis 2

Mediators will be explored using a causal inference framework [42], where Monte Carlo methods are relied upon for inference.

This allows for any type of model (linear and nonlinear) to be used to represent the relationships between the group allocation, mediating variable, and the outcome. Three models will be created for each outcome measure, two of which investigate the mediating factors on their own and a third that incorporates both mediators at once. If any baseline characteristics are found to moderate the effect in the primary analysis, additional mediator models will be created to include these characteristics as moderators.

Exploratory Analyses

As part of the primary investigator's precision health initiative, we aim to include predictive modeling of the intervention. Traditionally, trials contrast the mean difference between two groups, but do not address individual variability. Intuitively, we know that some individuals will respond well to an intervention, others might not, and some might further be harmed by it. We aim to predict how individuals will respond to an intervention using only individual baseline characteristics. Therefore, we will measure characteristics at baseline related to the behavior-change theory, in particular, importance and self-efficacy, as well as conventional baseline characteristics (age, gender, etc). These characteristics will then be used to inform statistical models that predict individual outcomes.

Predictive analysis requires a radically different approach of assessing a model's performance, as explaining and predicting are two different tasks [43]. We will use a Bayesian approach using shrinkage priors [44,45], which allows us to include all characteristics measured at baseline and learn which ones should be included in the predictive model from the data. The result is a model that can tell individuals how likely it is that the intervention has a positive effect on them specifically, rather than quoting the group mean difference.

Power Calculation

A previous study that explored the effect of an SMS-based smoking-cessation intervention for Swedish university students found that 25.9% in the intervention group had not smoked more than 5 cigarettes in the past 8 weeks compared to 14.6% in the control group [16]. This is comparable to a Cohen *d* value of 0.3, which can be interpreted as a small-to-medium effect. In general, this is in line with what we should expect from brief digital lifestyle interventions. In order to identify a statistically significant difference between the two groups, under the expected Cohen *d* value of 0.3, we will need to recruit 192 patients per group (at 0.8 power and .05 significance level). Assuming a 10% loss to follow-up, the final sample size required is 434 patients.

With 20 surgical departments recruiting participants over 12 months, we would require each department to recruit an average of 1.8 participants each month. If necessary, the recruitment period of 30 months will require 0.7 recruited participants on an average per month per department. We believe that this is feasible, given the commitment from the departments.

Results

At the time of submission of this protocol, recruitment had not yet started. Recruitment started in late October 2018 and is expected to last for a maximum of 30 months. The first results are expected to be available approximately 3 months after the final date of recruitment.

Discussion

The project within which this trial is contained is focused on perioperative smoking cessation, mainly with a focus on reducing postoperative complications. However, more generally, smoking is responsible for approximately 9.6% of the total disease burden in Sweden, and the annual number of new younger smokers is between 16,000 and 20,000 [2,6]. Approximately 9% of the general population of Sweden comprises daily smokers [3]. Globally, smoking is the most important preventable cause of ill health and death, where for every death related to smoking, more than 20 additional individuals suffer from at least one serious smoking-related illness [1]. Thus, any opportunity presented to help individuals to quit smoking should be taken advantage of.

Surgical departments in Sweden are obligated to inform patients about complications related to smoking and surgery, but should also offer help to quit smoking. However, structural problems and scarcity of time and resources lead to patients simply being instructed to quit, and perhaps, referred to a primary health care clinic. Some surgical departments have staff dedicated to helping patients quit smoking, but not many departments can offer this resource. An SMS-based smoking-cessation aid can be effective in helping individuals quit smoking and is a very simple and time-efficient tool for surgical departments to use. Health care professionals only need to inform patients about a phone number, and patients can sign up by sending a single SMS message.

This trial will collect data on the effectiveness of the intervention and further the growing evidence on SMS-based interventions for smoking cessation. This will help decide whether the intervention should be made generally available for all surgical departments in Sweden. Furthermore, the participation of several departments in the trial will give us a unique opportunity to identify key barriers in current practice and adapt the sign-up procedure to reach as many patients as possible and disrupt current routines as little as possible. These insights will lay the foundation for future implementation of research projects. If the intervention is found to be effective, it might have a substantial impact on not only the number of postoperative complications but also the disease burden in Sweden caused by smoking, in general.

A limitation of this study is that is that it does not include cessation of smoke-free tobacco (such as snuff). To our knowledge, no studies have thus far identified an association between smoke-free tobacco and postoperative complications. Thus, the benefits of an intervention targeting smoke-free tobacco will have to be evaluated in a separate trial. Another limitation is the use of nonbiochemical verification at follow-up. However, the Society for Research on Nicotine and Tobacco recommends that in population-based studies with limited face-to-face contact, it is neither required nor desirable to use biochemical verification [39]. Finally, this trial has been designed to power the statistical analyses of two primary

outcome measures; thus, analyses of secondary outcome measures and mediation measures should be regarded as preliminary and exploratory work.

Acknowledgments

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Conflicts of Interest

MB and PB own a company that develops eHealth interventions and systems for the general public, health professionals, and other privately owned companies.

Multimedia Appendix 1

Questionnaires.

[PDF File (Adobe PDF File), 216KB - resprot_v8i3e12511_app1.pdf]

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Abbreviations

SMS: short message service
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
CONSORT: Consolidated Standards of Reporting Trials

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Protocol

A Smartphone Game to Prevent HIV Among Young Africans: Protocol for a Randomized Pilot Study of a Mobile Intervention

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Abstract

Background: Young people aged under 25 years make up an increasing proportion of the population in emerging economies such as Kenya, where half of new adult HIV infections are among 15- to 24-year olds. Interventions targeting this age group have the potential to avert HIV infections among an increasingly large at-risk population. Interactive communication technologies offer a promising platform for reaching young people in engaging ways.

Objective: *Tumaini* is a narrative-based smartphone game designed to help young Africans protect themselves from HIV. The objective of this study was to pilot test the game, focusing on the data needed to inform a future randomized controlled efficacy trial, including assessments of study feasibility and safety.

Methods: The study took place in Kisumu Town, western Kenya, in spring 2017. The game-based intervention was pilot tested for 16 days with a sample of 60 preadolescents aged 11 to 14 years. Participant recruitment was initiated through schools. Participants were randomly assigned to the control or intervention arms of the study. One parent for each of the intervention arm participants was also recruited (n=30). The intervention arm participants were provided with smartphones on which *Tumaini* was loaded so that they could play the game at home. Youth completed behavioral surveys at baseline, posttest, and 6-week follow-up. The intervention arm participants provided quantitative feedback on their experience of the game-based intervention at posttest. They and their parents further participated in postintervention focus group discussions. Feasibility-related study metrics were collected on recruitment, enrollment, attrition, safety of participants, and return of phones.

Results: Recruitment and enrollment of the 60 preadolescents and parents were successfully completed within 18 days. No participants were lost to follow-up: all youth completed all 3 waves of the survey and 27 intervention arm youth and 22 parents and caregivers participated in the focus groups. No safety concerns were reported. All phones were returned after the intervention period; none were damaged or lost. All intervention arm participants initiated gameplay, recording a mean exposure time just under 27 hours.

Conclusions: Findings indicate that it is feasible and safe to test a smartphone-based HIV prevention intervention for very young adolescents in urban and peri-urban sub-Saharan Africa by initiating recruitment in schools and temporarily providing youth participants with smartphones on which the game is loaded. A randomized controlled trial powered to assess the efficacy of the game-based intervention is being designed to be carried out in the same geographic area as the pilot, using similar methods.

Trial Registration: ClinicalTrials.gov NCT03054051; https://clinicaltrials.gov/ct2/show/NCT03054051 (Archived by WebCite at http://www.webcitation.org/6wjwpX8Bg.)

International Registered Report Identifier (IRRID): DERR1-10.2196/11209

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KEYWORDS

HIV; youth; sub-Saharan Africa; Kenya; serious game; narrative; mobile phone; pilot test; randomized controlled trial; mhealth; prevention; smartphone

Introduction

In 2016, 1.8 million people around the world became infected with HIV, adding to the more than 35 million already living with the virus. More than 2 in every 5 infections occur in southern and eastern Africa. Youth aged 15 to 24 years continue to account for a large proportion of the population becoming infected, and young women are especially at risk [1]. Due to demographic shifts, adolescents make up an increasingly large proportion of the population in emerging economies, with 60% of the population in sub-Saharan Africa currently under 25 years [2,3]. It is projected that globally, under current conditions, an additional 3.5 million adolescents will become HIV-positive by 2030 [4].

Kenya and neighboring Tanzania and Uganda account for 21% of all HIV infections among 15- to 19-year olds in sub-Saharan Africa [5]. In Kenya, youth infections continue to increase. In 2015, young people aged 15 to 24 years accounted for over half of all new adult infections, with young women outnumbering young men 2:1 [6].

There is growing recognition that programs specifically targeting young people are critical to reducing the burden of HIV among adolescents and the population in general [7,8]. To maximize the impact of these interventions on infection rates, it is important to reach young people before they engage in behaviors that put them at risk for HIV. In addition, a strong foundation of accurate knowledge, positive attitudes and perceived social norms, healthy behavioral intentions, parent-child communication, and behavioral skills and related self-efficacy to avoid or reduce risk can help young people protect their health once they reach sexual debut and beyond [9-14]. Mobile technology can be leveraged to address these needs [15].

Increasingly accessible mobile technologies offer a promising platform for delivering interactive health promotion interventions that reach youth in new and engaging ways. In Kenya, 90% of the population has access to a mobile phone [16], and smartphone use is on the rise, as handsets become more accessible and affordable [17]. Increasing engagement with smart technologies affords young people growing opportunities to learn and practice skills where they are, when they want, and as often as they need. These technologies have the potential to deliver important information and skills training in highly interactive ways at lower cost and greater reach than is possible with group-based prevention interventions; however, further research is needed to determine the extent to which they are able to deliver on this promise [18]. In addition, it is possible for the intervention to be delivered with near-perfect fidelity, allowing only for intended, programmed, and user-driven customization [19,20].

The growing interest in mobile health (mHealth) and the recognition of its potential has led to the development of a range of interventions tackling a variety of health issues, including sexual and reproductive health. In particular, there is increasing recognition that serious electronic games, where the primary purpose is not entertainment [21], can deliver content in intrinsically motivating ways, blending entertainment with key content and skills training. Even more importantly, by giving players the opportunity to inhabit and navigate new situations, such interventions offer an especially exciting avenue for cognitive rehearsal and experiential skills building.

Although there is a growing evidence base for the efficacy of mHealth among adolescents [22], many mHealth interventions, including those targeting behavior change around sexual and reproductive health and developed for use in low-income countries, have thus far been delivered via feature phone, or nonsmartphone, platforms, for example, 2-way messaging interventions [23,24]. A smartphone-based mode of delivery provides access to more interactive and engaging interventions, including serious games. Internet connectivity, either via Wi-Fi or a data plan, can allow users to find, download, and update intervention materials as needed. It also makes it possible for new content and messages to be pushed to users and for user activity and progress to be monitored remotely. In addition, the large storage capacity of smartphones provides space for a large complex program that allows for significant interaction. The traditionally larger screen also provides a more attractive learning environment. These features make smartphones a particularly appealing delivery platform for game-based interventions, without the user cost and accessibility challenges of a computer-based or tablet-based program.

Smartphones are a relatively new, though promising [25,26], platform for delivering theory-driven health promotion interventions. Thus, few such interventions have been efficacy tested, particularly those focusing on sexual and reproductive health, and aimed at adolescents in low-resource settings. If we are to ensure that those at risk have access to the best skills-building and informational content available, we must thoroughly test and evaluate promising new approaches by tailoring proven research methods to the needs of these new platforms and interventions.

This paper describes the protocol for the pilot study of a narrative-based smartphone game called *Tumaini* in Kisumu, western Kenya. This study was carried out in collaboration with the Kenya Medical Research Institute (KEMRI). Its objective was to pilot test the game-based intervention, focusing on data needed for a larger efficacy trial, including assessments of study feasibility and safety, where feasibility is defined as successful recruitment, enrollment, and retention of a cohort of 11- to 14-year olds and safety is defined as absence of negative outcomes from participation in the study. The purpose of this paper is to present our protocol, as well as the study's feasibility and safety findings, with a view to guiding the development of

other smartphone-based mHealth intervention studies aimed at school-aged populations in low-resource settings.

Methods

Overview

This study was a pilot randomized controlled trial (RCT) conducted with 60 male and female preadolescents aged 11 to 14 years, in the East, West, and Central administrative locations of Kisumu Town, Kisumu County, Kenya. Participants were identified via school-initiated recruitment and randomized to 1 of the 2 study arms. Adolescents in the control arm received standard of care (no intervention beyond any existing sex education from family, school, and peers); intervention arm participants played *Tumaini*, an interactive, narrative-based electronic game, which had been loaded on study-provided, low-cost Android smartphones. The intervention period lasted 16 days. Participants in both arms completed baseline, postintervention, and follow-up surveys. Intervention arm adolescents and their parents also participated in postintervention focus group discussions (FGDs). Primary outcomes for this study focused on the feasibility and safety of the study. Secondary outcomes included acceptability of the game and behavioral mediators of sexual initiation and condom use, reported elsewhere [27].

Description of the Intervention

Tumaini (Multimedia Appendix 1) is a theoretically grounded, narrative-based game for inexpensive Android smartphones developed in collaboration with a US commercial game developer, Realtime Associates, and with input both from US-based and Kenyan specialists in adolescent sexual health and from Kenyan preadolescents and their parents. It is designed to increase age and condom use at first sex by increasing knowledge about sexual health and HIV, building risk-avoidance and risk-reduction skills and related self-efficacy, challenging HIV stigma and harmful gender norms and attitudes, fostering future orientation, goal-setting, and planning, and promoting dialogue with adult mentors. *Tumaini* uses interactive narrative to promote problem-solving, cognitive and behavioral rehearsal, observational learning, and immersion.

Tumaini's design draws on social behavioral theory, including Social Cognitive Theory [28] and the Theory of Possible Selves [29], Entertainment-Education literature [30], games for health literature [31-34], and existing evidence-based HIV prevention interventions aimed at youth [35-39]. Game design and scripting also drew on extensive research on a vast sample of HIV-themed narratives written by young Africans [40-42]. Preadolescents and parents in Kisumu provided input via FGDs. The game is in English and includes an audio track featuring Kenyan voice talent.

The mobile intervention is made up of 3 intersecting components: (1) a choose-your-own-adventure game, where players role-play 6 diverse characters, making choices for them that determine the course of their lives, (2) a set of mini games that reinforce knowledge and skills development, and (3) *My Story*, in which players create an avatar of themselves, set personal goals, and relate the game narrative to their own lives. *Tumaini* comprises approximately 12 hours of discrete gameplay and is designed to be replayed so that players can observe the outcomes of different decisions.

Trial Registration, Ethics, Consent, and Institutional Board Approval

The study was approved by the Institutional Review Boards of Emory University (IRB00081150) and KEMRI (KEMRI/SERU/CGHR/019/3100). The study was also registered on ClinicalTrials.gov (NCT03054051).

Eligibility

Preadolescents eligible to enroll had to meet 4 criteria: (1) be aged 11 to 14 years at the time of recruitment, (2) reside in Kisumu Town, (3) not attend a boarding school, and (4) demonstrate a Grade 3 to 4 English proficiency on the Flesch-Kincaid scale, assessed via a brief screening exercise. This level of English literacy was not expected to act as a barrier to recruitment, as primary school education (ages 6 to 14 years) has been free and compulsory in Kenya since 2003, and all subjects are taught in English from Standard 4 (age 10 years and above) onward. Boarding school students were ineligible as they do not return home on weekends during the school term and would thus have been unavailable for the follow-up surveys and postintervention FGDs. Only 1 child per family was eligible to enroll. Any preadolescent or parent in a family previously engaged in formative research or review of the game or study documents was ineligible.

Parents were eligible to participate in postintervention focus groups if they had a child enrolled in the study.

Smartphone ownership was not a requirement for eligibility as phones were provided to intervention arm participants. This strategy sought to minimize socioeconomic bias in the sample. It also ensured consistency of smartphone technology.

Incentives

Participants were not offered incentives for this study. They were reimbursed US $5 for their time and transportation costs for each study visit.

Recruitment

The KEMRI study lead contacted county Ministry of Education officials for permission to initiate recruitment of participants through schools in the Kisumu East, Central, and West subcounties. In dialogue with the Emory team, the KEMRI team randomly sampled 11 schools for recruitment from a list of all primary day schools within those locations, stratified to ensure representation of both private and public schools, and all eligible geographic zones. The head teachers of the selected schools were invited to an informational meeting and given a brief overview of the study. After securing the head teachers' agreement to initiate recruitment at their institutions, the head teachers selected 6 schools, 2 from each subcounty, by simple random pick from a bowl.

At each selected school, informational letters were given to a random sample of 24 pupils in grades 5, 6, 7, and 8 in each school, with 6 pupils randomly selected from each grade. These letters described the study and invited parents/caregivers

(*parents*) to attend an informational meeting. Additional letters were distributed in 1 of the schools to increase yield.

A total of 7 meetings were held with parents, during which study staff described the nature of the study and answered questions from attendees. In responding to these questions, study staff were able to draw on prepared frequently asked questions (FAQs) documents compiled based on the points raised by parents who had participated in previously conducted FGDs, described below. The recruitment meetings invited parents to volunteer for participation. Study staff individually screened interested attendees for eligibility using a standard form and collected contact information with a view to scheduling enrollment visits. Parents uninterested in enrolling completed a brief questionnaire, identifying reasons for nonparticipation.

Enrollment

Enrollment took place at the home of potential participants so that they could be easily located in the event of attrition. If a family was not willing to meet at home, an alternative location was chosen. Study staff provided a brief review of the project, answered any remaining questions, and rescreened both parents and preadolescents for eligibility before securing parental consent, followed by child assent. Consent was only required from 1 parent; however, approval of both parents was sought where possible. If more than 1 child in the household was eligible, staff randomly selected 1 for enrollment by drawing a name from a bowl.

In total, 60 parent-child dyads were enrolled, balancing child participants by sex and making efforts to ensure that participation was evenly distributed across the 11- to 14-year age range. This was achieved through stratified sampling of parent/child dyads by age, school, and gender of the child, employing random numbers. Any ineligible or nonconsenting/assenting family was replaced from the pool of other potential participants, taking care to select from the same school where possible and keeping the preadolescents' age and sex balanced across the whole sample. Parents were informed that if their child was randomly assigned to the intervention group, they would themselves be enrolled and invited to participate in a postintervention focus group. Consents, assents, refusals, and ineligibilities were tracked by study staff at each visit (Figure 1).

Study Metrics

The primary outcomes of this pilot are measures of study feasibility (recruitment modalities, time to enroll target number of participants, reasons for non-enrollment, participant retention, tracking of study phones, and safety of participants with phones). Participants' willingness to play the game and the game's usability, appeal, understandability, relevance, and value are addressed in a separate publication.

The metrics used to assess study feasibility were collected via Excel-based records, assembled by the KEMRI team. These were compiled from paper-based screening forms used during recruitment meetings and consent/assent procedures.

The metrics for game-related primary outcomes were collected via a short multiple-choice assessment of the game experience by the intervention arm participants administered at posttest and by FGDs with them and their parents between posttest and follow-up. In addition, in-game data collection automatically tracked time-stamped user interaction with the interface, allowing for calculations of exposure. Although the data focusing on participants' safety are presented here, findings related to other study metrics will be reported separately.

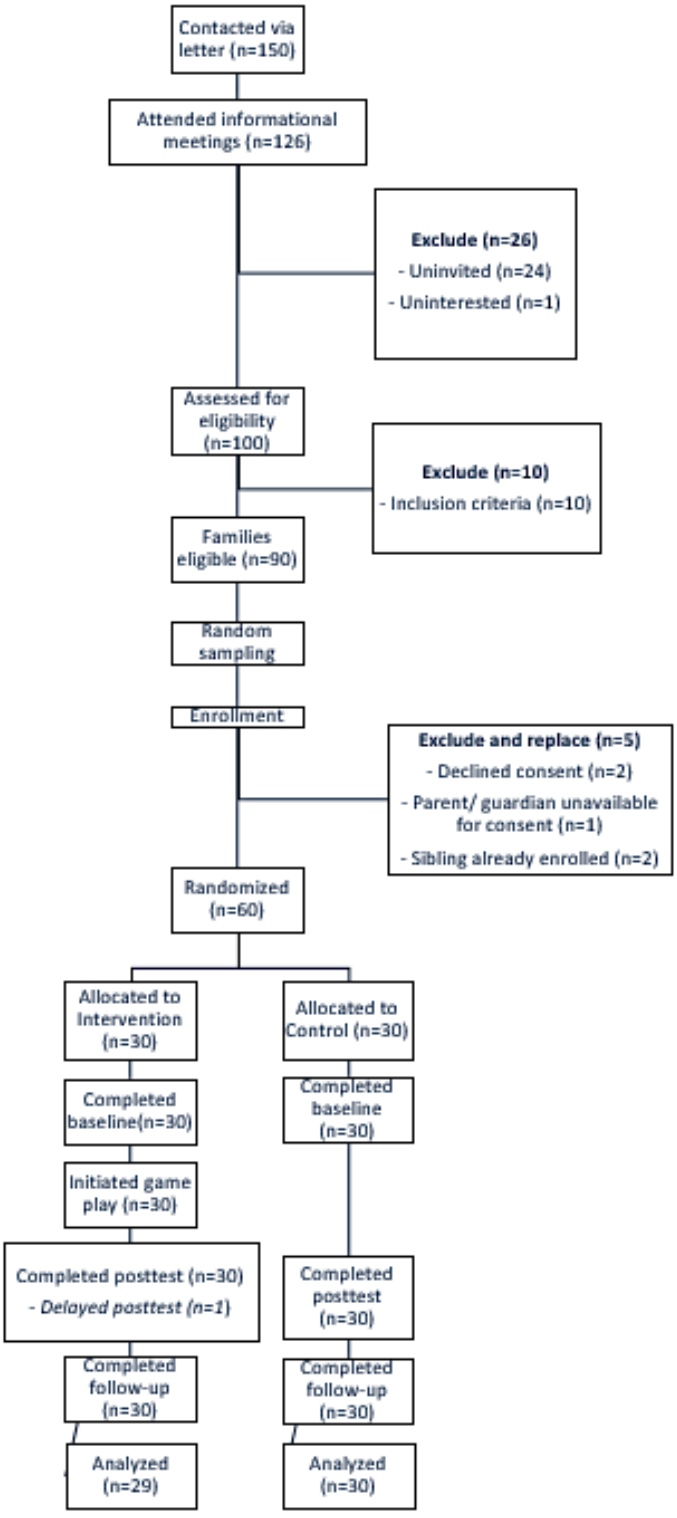
Data related to secondary (behavioral) outcomes were collected using a survey administered at baseline (T1), immediately following the 16-day intervention (T2), and 6 weeks post intervention (T3). Both this and the game experience survey were implemented via Audio Computer-Assisted Self-Interview software (ACASI, Tufts University) using headphones to ensure participants' privacy. Outcome data for behavioral mediators are reported elsewhere [27].

Survey Instrument

The behavioral survey instrument assessed mediators associated with age at onset of sexual activity and condom use at first sex, including knowledge, self-efficacy, risk assessment, perceived social norms, attitudes, behavioral intentions, future orientation, and parent-child dialogue. Thematic domains included puberty, sex, relationships, peer pressure, condom use, HIV, sexually transmitted infections, pregnancy, and alcohol and drugs. These formed the study's secondary outcomes. We drew individual measures from existing instruments, adapted them for age, linguistic, and cultural appropriateness and consistency of formatting, and we supplemented them with additional measures where necessary. We prioritized existing measures that had been previously used with sub-Saharan African youth populations [38,43-49]. These formed the study's secondary outcomes. We drew individual measures from existing instruments, prioritizing those previously used with sub-Saharan African youth populations [38, 43-49]. The chosen items were adapted for age, linguistic, and cultural appropriateness [15] and consistency of formatting, and supplemented with additional measures where necessary. In the interest of age appropriateness, we also included hypothetical risk scenarios presented as vignettes [50] that contextualized situational risk assessment, behavioral intention, and self-efficacy. The demographic section of the survey assessing the socioeconomic status was based on Demographic and Health Survey question and response options, reframed to be more meaningful to the young participants [51].

The draft English survey was translated into Dholuo and back translated into English, and subsequently presented to parents to ensure the items would be acceptable to them. Parents participating in these focus groups were also presented with information about the study, and they contributed questions they would want answered if they were considering enrolling their child. Parents' questions were used as the basis for the FAQ document and informational materials used during recruitment.

Figure 1. Consolidated Standards of Reporting Trials flow diagram.



Based on feedback received from parents and schools, it was decided that the survey would be delivered solely in English rather than in Dholuo or Kiswahili or with multiple language options. Adding proficiency in Dholuo or Kiswahili as an eligibility criterion would likely have biased our participant sample. Dholuo is not spoken by all Kisumu area residents and Kiswahili, although a national language, was not more consistently understood than English among our participant demographic. As English proficiency was already an eligibility criterion as the intervention was in English, having an English-language survey was not expected to limit the participant pool.

We conducted cognitive assessments of a full draft of the English-language instrument with preadolescents to ensure face validity. Feedback was integrated into the survey between rounds, with each subsequent round. The final survey was programmed into ACASI via the Questionnaire Development System and piloted with 10 preadolescents.

Staff Training and Informational Materials

The research team had access to a phone loaded with *Tumaini* ahead of the start of recruitment, enabling them to become familiar with the intervention. Recruitment and data collection staff were trained on the game design, study goals, recruitment, enrollment, eligibility screening, and data collection modalities before recruitment and enrollment activities. Staff questions were collected during training and referred to the study leads for clarification. All research team members involved in qualitative data collection had previous experience, including training provided before formative research. This was supplemented with study-specific instructions before all focus groups, to ensure that the specific goals of each round of discussions during survey testing and postintervention FGDs were clear. Additional notes on moderation were provided where needed after review of the discussion transcripts.

Ahead of recruitment and enrollment meetings, informational handouts were developed by the study teams based on parental comments during FGDs and staff questions during training. These were provided to the recruitment and enrollment staff, enabling them to respond to attendee questions and concerns in a uniform way and accurately represent the goals of the study across all meetings. Areas of focus included a review of the consent materials, details of study visits, randomized study arm assignments, and any concerns about the phone, game content, and the logistics of gameplay.

Randomization

Participants were allocated a study identification number (study ID). A deidentified participant list, including study ID, sex, school, and age, was transmitted to a blinded member of the Emory team, uninvolved with recruitment. From this list, a simple coin toss was used to assign participants to either study arm in a 1:1 ratio, blocking by school and sex.

Study Procedures

The first study visit, intervention, and second study visit took place during the April 2017 school holiday in Kenya. During the first study visit, at the KEMRI offices, study aims were reviewed, consent and assent procedures were revisited, and the baseline behavioral survey was administered to preadolescents. Participants were given a study card with their assigned study ID for future visits. Upon completion of the survey, the participants were informed to which study arm they had been randomized. Due to the nature of the study, it was not possible for the participants or study team to be blinded. The control arm received standard of care, namely no additional intervention beyond any existing sex education from family, school, and peers.

Intervention Arm

The intervention arm participants attended a group introductory session after learning their random assignment. Although participants had not known the results of randomization until after the baseline was completed, study staff scheduled each participant's study visit time slot to ensure that intervention arm participants would all be present on the same day for these sessions. The session covered phone safety, phone and game interface, and instructions about playing the game at least one hour a day for the duration of the 16-day study. Parents of intervention participants were given a short briefing about similar topics, and they were provided with study staff contact information in case a phone- or intervention-related issue arose. These parents were later consented as participants before their participation in postintervention focus groups.

All intervention arm participants were provided with a phone kit containing the study phone, a charger, and a pair of earbuds, to maximize player immersion and ensure that they could have privacy if so desired. Study staff logged phone IDs and phone assignments by participants' study IDs for future data linkage. The study team had additional phone kits including handsets loaded with *Tumaini* to ensure continued participant activity in the event of a loss, theft, or phone malfunction. Any replacements issued to participants were logged in the participant data management system.

Phone Setup

All 30 study phones and 5 additional backup phones were set to local time and current date. All subscriber identification module (SIM) cards were removed and phones fully charged. The game was installed; all other features and apps were blocked using a parental monitoring and control app. This app, enabled and disabled via a passcode, was set to block calling (in the event an active SIM card was inserted), Wi-Fi, and data access, in addition to other apps. These restrictions were set not only to address parents' concerns that their children might use the phone for other purposes but also to make keeping the phones less attractive to study participants. This was important to ensure that gameplay data could be downloaded from each handset, that ownership of the phone did not act as a disproportionate or coercive incentive, and that all copies of *Tumaini* were collected at the end of the pilot study to ensure equipoise for a future efficacy trial. A simple pattern-based passcode was programmed into all the phones to increase participants' sense of ownership of the phone and to discourage siblings' and friends' unauthorized access. A visual passcode was chosen as being easier to recall than one that was number- or letter-based. All study phones were identified with a unique ID number visible on the outside of the phone and inside the phone case and linked to the participants' study identifiers in the participant management database. The game was programmed to record the individual phone ID as part of the game's log file, allowing linkage of gameplay data to individual participants for subsequent analysis.

Before handing out the phones to participants, a daily alarm was set to remind participants to play. The timing was chosen to be as minimally disruptive to the family's life as possible, with particular consideration to the timing of the study over the Easter weekend.

Postintervention Procedures

The intervention period lasted 16 days, the maximum length possible during the school holiday period. All 60 participants were contacted by phone to schedule the postintervention visit. Study visit time slots were allocated by study arm as for the baseline visit. All participants took a survey identical to that administered at baseline with the exception that its demographics

section was shortened. Intervention arm participants also responded to additional questions about their gameplay experience. The study staff logged the return of phone kits by intervention arm participants and turned off all phones.

The data manager downloaded the gameplay log file from each phone. To allow correct identification and analysis of participants' data, participants were asked to identify the creator of each profile present in the log file: themselves, a parent (mother or father), a sibling (older or younger, male or female), a friend (male or female), or someone else.

The follow-up survey, identical to the posttest survey, was administered 6 weeks after the posttest.

Postintervention Focus Groups

Intervention arm preadolescents and their parents participated in FGDs between the postintervention and follow-up surveys. In all, 4 sex- and age-stratified preadolescent groups were held (11-12-year-old females, 11-12-year-old males, 13-14-year-old females, and 13-14-year-old males). Moreover, 4 parent FGDs were held, stratified by the age of their child. All FGDs focused on the appeal of the game, its content, the value of the content and delivery mode, and communication with others about the game. In addition, youth were asked about the appeal of specific components of the game: narrative, characters, mini games, goal-setting component, prizes; their parents were asked for comments on possible future studies. The focus groups took place in a combination of English, Kiswahili, and Dholuo, and were recorded and then transcribed in English.

Data Analysis

All ACASI data were downloaded from the individual computers by the study staff and saved to a password-protected server in text format. The data manager compiled a master dataset from all 60 entries at each wave of the survey, using Warehouse Manager, a standard data management system used for ACASI. All entries were identified only by participants' study IDs. All quantitative analyses of data relating to primary and secondary outcomes were carried out using SAS analysis software, version 9.4, using intent-to-treat analysis.

Descriptive statistics of participant characteristics were calculated. Scores from individual survey items with objectively correct or incorrect answers were combined into composite scores by theoretical construct and thematic domain, as well as for the survey overall. Composite scores weighted each question equally on a 0 to 1 scale, with 1 being the *correct* response (eg, high self-efficacy, correct knowledge).

Participants' change in scores on individual items as well as composite measures between baseline (T1) and posttest (T2), and between T1 and follow-up (T3) were calculated and mean changes (T1 to T2, and T1 to T3) compared across study conditions using 2-tailed 2-sample *t* tests with alpha=.05.

Intervention arm quantitative feedback on the game experience was also imported into SAS and descriptive statistics were calculated and stratified by sex and age group.

Focus group transcripts were loaded into MAXQDA 12 qualitative analysis software (Verbi GmbH). They were coded for themes that emerged inductively from the transcripts (eg, family dynamics) and for deductive themes, based on the discussion guide.

Results

Recruitment and enrollment were carried out between March 20, 2017 and April 7, 2017. A total of 7 informational meetings were held for parents, with 126 attendees screened for interest and eligibility (Figure 1). Consent and assent procedures were completed in 3 days. One participant who had consented but would not be able to complete all study visits was replaced from the pool of available eligible participants. Participants were age- and sex-balanced. All 60 participants who completed the baseline assessment also completed the other 2 surveys. One intervention arm participant completed the posttest several days late and was excluded from posttest (T2) analyses. All intervention arm participants initiated gameplay. In addition, 27 intervention arm participants and 22 of their parents participated in the focus groups. All study phones were returned; there was no loss or theft of, or damage to, the handsets. A few participants reached out to the study team for troubleshooting help; all concerns were successfully addressed and no phones needed replacing. Phone IDs enabled study staff to accurately link gameplay data to participants' study IDs.

Participant demographics are presented in Table 1. There were no significant differences across the 2 study arms. Smartphone access and experience were slightly higher in the intervention arm, with only 3 reporting no one in their household having a smartphone and 22 having previously used one. Intervention arm parents participating in the FGDs were mostly female (n=25); only 5 fathers or other male guardians participated.

No safety concerns were reported by parents or participants. All but 1 participant (n=29, 97%) said he or she felt *very safe* while in possession of the phone. The remaining participant indicated he felt "a little safe"—the middle anchor of the Likert scale. During FGDs, parents confirmed that they had not had concerns about their children's personal safety. In particular, in 3 FGDs, parents attributed their lack of worry to the fact that "it was not a phone that was being used for communication, it was only the game," (parent of a 11-12-year old).

Preliminary analysis of gameplay log files indicated that across all the profiles participants identified as their own they played, on average, just under 27 hours over the 16 days of the pilot study. Review of log files showed unexpected date and time changes occurring during gameplay. Although the time and date had been set accurately by the study staff, 18 logs (of 30) showed the date and time resetting to their defaults at least once during the study period. These changes affected neither the game's ability to log player activity nor the ability of data analysts to assess gameplay duration. In addition, parents in 2 FGDs noted that the alarm seemed to ring at inconvenient moments, such as at night or when the child was not nearby to silence it. It seems likely that the changes in time, date, and alarm schedule were linked to phone batteries being removed to attempt to install a SIM card or to charge the battery externally. With the high level of engagement with the game, the alarm reminder is likely unnecessary for a future study.

Table 1. Participant demographics at baseline.

Characteristics	Intervention (n=30)	Control (n=30)	Total (N=60)
Sex, n (%)			
Female	14 (47)	16 (53)	30 (50)
Male	16 (53)	14 (47)	30 (50)
Age (years), mean (SD)	12.8 (1)	12.6 (1)	12.7 (1)
Religion, n (%)			
Catholic	14 (47)	14 (47)	28 (47)
Protestant/Anglican	8 (27)	2 (6)	10 (17)
Muslim	2 (7)	4 (13)	6 (10)
Seventh Day Adventist	4 (13)	4 (13)	8 (13)
Other	2 (7)	6 (20)	8 (13)
Living situation, n (%)			
Both parents	22 (73)	20 (67)	42 (70)
One parent	6 (20)	5 (17)	11 (18)
Housing type, n (%)			
Permanent	8 (27)	13 (43)	21 (35)
Semipermanent	11 (37)	6 (20)	17 (28)
Temporary	9 (30)	6 (20)	15 (25)
Iron sheets	2 (7)	4 (13)	6 (10)
Smartphone ownership, check all that apply, n (%)			
Parent	21 (70)	15 (50)	36 (60)
Self	2 (7)	1 (3)	3 (5)
Sibling	11 (37)	5 (17)	16 (27)
Other adult	4 (13)	1 (3)	5 (8)
No one	3 (10)	8 (27)	11 (18)
Have used a smartphone before baseline, n (%)	22 (73)	19 (63)	41 (68)

Additional results related to acceptability and to the study's secondary (behavioral) outcomes were analyzed, and these are reported in separate [27] and forthcoming publications.

Discussion

Principal Findings

This manuscript describes the pilot study of a smartphone-based HIV prevention intervention for preadolescents in Kenya. Theoretically grounded mobile interventions, particularly those delivered via smartphone, have the potential to engage young people and effect behavior change without requiring a large cadre of project staff to deliver, maintain, and update the content. In particular, well-designed smartphone-based interactive games can provide opportunities to learn, practice, and strengthen crucial health-protective skills in a safe space.

This pilot study shows the feasibility of a trial of a smartphone intervention in which the game is delivered on study-provided phones that were subsequently collected. Although smartphone ownership is increasing and handsets have become more affordable, ownership does still skew toward the wealthier [52]. If smartphone ownership or access had been an eligibility criterion, the sample would have been biased toward a higher socioeconomic status, an important factor in the team's decision to provide smartphones to study participants. Projected increases in smartphone ownership over time (by 2025, mobile phone penetration is expected to reach 52% in sub-Saharan Africa as a whole, up from 44% in 2017, with 67% of connections expected to be via smartphone) [17] will support roll out of the game-based intervention, should it prove efficacious. At 80% of the adult population, Kenya mobile phone ownership is higher than that of sub-Saharan Africa as a whole [53]. It is also expected that if the game is rolled out, it is likely to be accessed on a parent's or older sibling's phone rather than on an adolescent's own device. In the meantime, this model of intervention delivery offers an important and feasible means to reduce sociodemographic bias and ensure consistency of technology when testing smartphone-based mHealth interventions.

This pilot study explored recruitment initiated through schools, made possible by securing approval from the local Ministry of Education before contacting school officials. By engaging the

Ministry of Education early in the study process, the team was able to address any potential concerns and secure buy-in, crucial to carrying out research activities with a youth population. In addition, the study team engaged parents throughout the study, including providing informational sessions to assess their interests in participating and to answer questions before study activities. We believe this helped to establish transparency with parents and increase their willingness to participate and encourage their children to remain in the study, contributing to rapid enrollment and a lack of attrition. These recruitment and engagement strategies could be scaled up successfully for a future larger-scale randomized trial of this and similar interventions. Zero loss to follow-up and a lack of safety concerns support the feasibility of this type of study and its potential for scale-up.

Future Directions

A future efficacy trial is likely to take the form of a multiyear RCT, with repeated behavioral measures supplemented with collection of a herpes simplex virus 2 (HSV-2) biomarker. HSV-2 is relatively prevalent and, as such, has been used in conjunction with self-reported sexual behavior in other studies of interventions aimed at reducing HIV infection among young people in sub-Saharan Africa [54]. Additional protocols for disclosing test results and linking to care will need to be developed in line with Kenyan guidelines for HIV testing [55].

The larger sample necessitated by the proposed efficacy trial will require an expanded recruitment strategy from a larger pool of primary schools. There are over 200 primary education establishments in the Central, East, and West Kisumu subcounties; therefore, this is not expected to limit our ability to recruit the necessary pool of participants, even without expanding the recruitment area.

In view of the increased sample size, we will consider shifting survey delivery to a mobile platform, such as Open Data Kit on phones or tablets. This would allow faster survey implementation via simultaneous delivery at multiple sites across Kisumu without losing the audio component of ACASI (important to maximize comprehension).

Limitations

Due to the length of the school holiday period during which the trial took place, the intervention period was limited to 16 days and follow-up activities took place over 6 weeks. During a full-scale efficacy trial, the expected exposure to *Tumaini* will be more extensive and will allow for a more thorough assessment of player engagement and game use over time. This assessment will also allow us to determine any potential associations between length of exposure and outcomes and thereby estimate a minimum recommended exposure time. The game was designed with a minimum exposure time of 10 to 12 hours in mind; this corresponds to the approximate duration of a group-based intervention. If study results indicate that wider distribution of the intervention is warranted, no external limit to play time would be placed on users.

Although this study did not experience any attrition, we acknowledge that this may be related to the short duration of the intervention period and its follow-up assessments and that a longer, multiyear efficacy study is likely to lead to some loss to follow-up (KEMRI studies indicate that typical attrition is 15% over the course of a multiyear study). The KEMRI team has a strong track record of retaining participants during longitudinal studies, including through intermittent contact with participants between study visits and repeated contact ahead of visit scheduling.

Conclusions

The findings of this pilot indicate that it is feasible to safely test a game-based HIV prevention intervention delivered via smartphone, with effective recruitment and no issues of loss to follow-up or of study-provided smartphones. These methods will inform the development of a larger RCT of the *Tumaini* game-based intervention. This study provided intervention arm participants with low-cost smartphones on which the game was preloaded. If this intervention were to prove efficacious, it is anticipated that increases in smartphone ownership would support rollout at scale. The approach tested here has the potential to guide the development of other smartphone-based mHealth intervention studies aimed at school-aged populations in low-resource settings.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Sample Tumaini graphics.

[PDF File (Adobe PDF File), 149KB - resprot_v8i3e11209_app1.pdf]

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Abbreviations

ACASI: Audio Computer-Assisted Self-Interview
FAQ: frequently asked question
FGD: focus group discussion
HSV-2: herpes simplex virus 2
ID: identification
KEMRI: Kenya Medical Research Institute
mHealth: mobile health
RCT: randomized controlled trial
SIM: subscriber identification module

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Protocol

A Brief Web-Based Nutrition Intervention for Young Adult University Students: Development and Evaluation Protocol Using the PRECEDE-PROCEED Model

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Abstract

Background: Young adults are a priority population for nutrition interventions because of the high prevalence of unhealthy eating behaviors, high risk of weight gain, and the importance of this life stage for developing lifelong eating behaviors. Innovative intervention strategies are needed to reach and engage young adults, whereas more detailed reporting of intervention development and testing would facilitate progress in this challenging research area.

Objective: This paper describes the development of the EATS (Eating Advice To Students) intervention, a targeted, brief Web-based nutrition intervention for young adult (17 to 35 years) university students, and describes the pilot randomized controlled trial (RCT) to assess intervention feasibility.

Methods: EATS was developed using the PRECEDE-PROCEED model. The development involved a cross-sectional survey of university students' eating behaviors and determinants, a systematic review of brief nutrition interventions, and consultation with a project steering committee. EATS was developed as a website with 4 components: (1) brief screening quiz with personalized feedback, (2) provision of information, tips, and strategies for each target eating behavior (consumption of vegetables, fruit, discretionary foods, and breakfast) and 2 guided exercises to facilitate behavior change, (3) goal setting, and (4) creating strategies. A pilot RCT with students from the University of Newcastle, Australia, was conducted from February to July 2018. The students were randomized to EATS or a brief Web-based alcohol intervention (attention control). The process evaluation included intervention acceptability (Web-based survey postintervention completion) and objective usage data (collected in real time). Efficacy data (Web-based survey at baseline and 3 months) included diet quality, consumption of target food groups (eg, fruits and vegetables), alcohol intake, self-efficacy to perform target eating behaviors, and well-being.

Results: Collection of the 3-month follow-up data was completed in July 2018.

Conclusions: EATS presents an innovative solution to many of the difficulties faced in targeting young adults to improve their eating behaviors. Given the strong methodological approach undertaken, this study provides a significant contribution to advance this research area.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12618000118202; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374365&isReview=true (Archived by WebCite at http://www.webcitation.org/765o5fVwa)

International Registered Report Identifier (IRRID): DERR1-10.2196/11992

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KEYWORDS

eHealth; young adults; universities; students; diet

Introduction

Background

Young adults (17 to 35 years) are a priority population for nutrition interventions because of their high prevalence of unhealthy eating behaviors [1,2], high risk of weight gain [3,4], and the importance of this life stage for developing lifelong eating behaviors [5]. However, reaching and engaging young adults in health behavior change interventions, including nutrition interventions, is challenging [6,7]. Reaching and engaging young adults may be challenging because of factors such as transient living arrangements and perceptions such as seeing health behavior interventions as irrelevant to their life stage, and giving their health a low priority compared with other time commitments [8,9]. The need for interventions targeted to young adults to address poor health behaviors among this group has been recognized, and therefore, this area of research is now gaining momentum [10-12]. For example, in a recent review of lifestyle interventions aiming to prevent weight gain in young adults, 19 of the 30 included studies had a nutrition component and dietary outcomes [12]. However, there is still further research to be done, with higher quality and detail in reporting [13].

One avenue for further exploration is targeting young adults through the university setting [14]. This is because the number of individuals across the globe enrolling in universities is increasing, with many in the young adult age category. For example, upward of 20 million students are enrolled in universities in the United States and Europe [15,16], with 40% of those in the United States aged 18 to 24 years [15]. In Australia, approximately 60% of the 1.5 million university students are aged between 18 and 24 years [17]. Furthermore, university initiatives to promote optimal health are gaining traction internationally as the utility of this setting to support health promotion interventions because of its existing infrastructure (eg, technology, facilities, and expert researchers and health professionals within the university staff) is increasingly recognized [18]. Furthermore, young adults may be more amenable to intervention and behavior change while immersed in the university learning environment [19], as well as being in a formative stage for developing lifestyle behaviors [14,20].

Developing appealing and engaging interventions also requires cognizance of the many factors individuals face in this life stage because of their impact on behavior and behavior change, for example, changes in employment, tertiary study, and family and social life, as well as development in terms of self-identity and self-efficacy. One of the key barriers to healthy eating for young adults is lack of time [9], and with this in mind, exploring intervention approaches that cater to this (ie, brief interventions) could be worthwhile. On this note, it has been acknowledged that the use of community-based participatory research models to guide intervention development can contribute to more engaging and effective health behavior interventions [8,21]. In the current context, the university setting provides an ideal platform for participatory research.

Objectives

This paper describes the development and evaluation plan for a targeted, brief Web-based nutrition intervention for young adult (17-35 years) university students using the PRECEDE-PROCEED model.

Methods

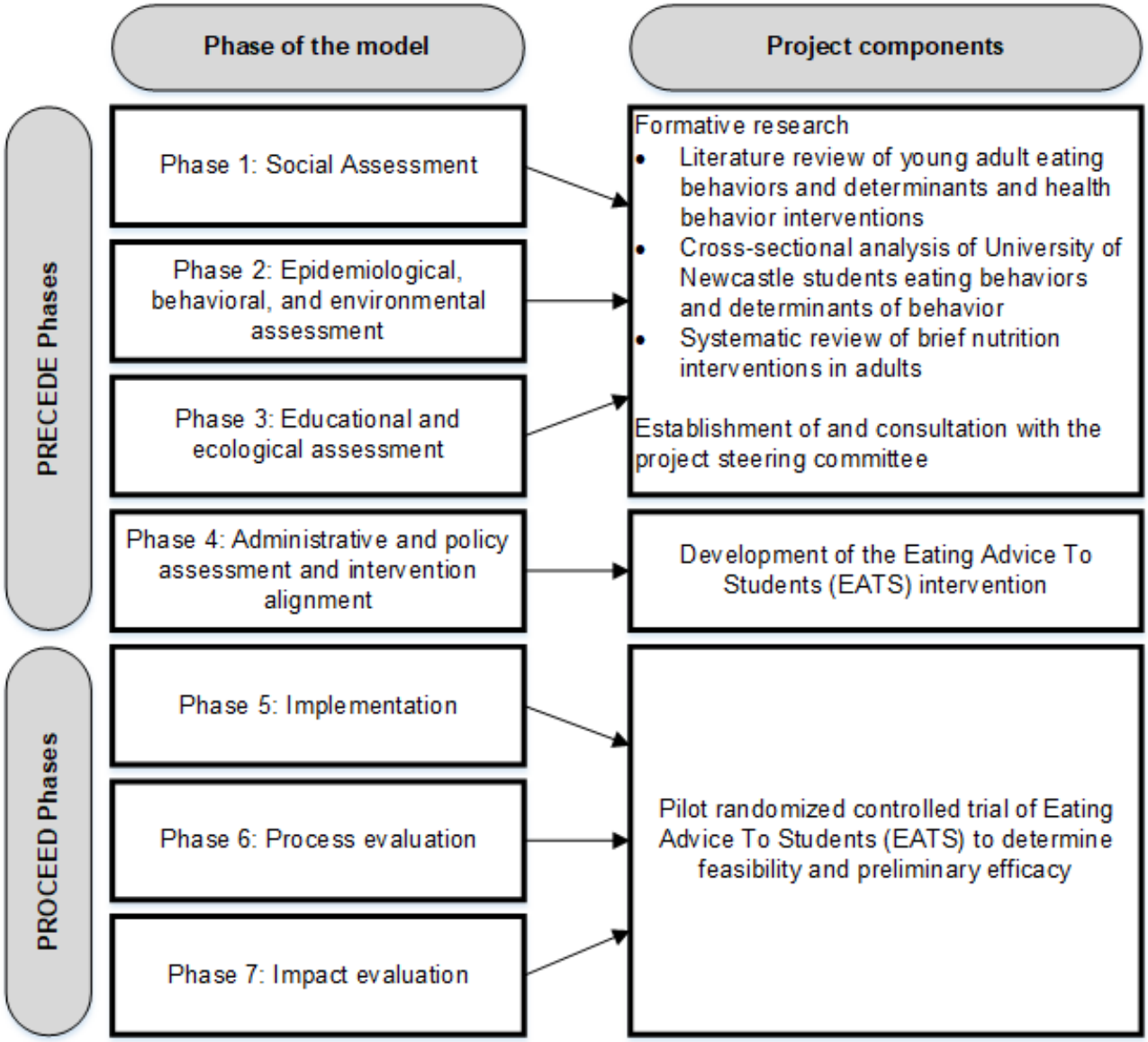
Overview

The PRECEDE-PROCEED planning model developed by Green et al [22] was used as the basis for the development and evaluation of the Eating Advice To Students (EATS) intervention. This model is an ecological approach to health promotion, and it has been used extensively in previous applications of health promotion interventions, including in young adults and university students [8,23]. The model comprises 8 phases, which can be broadly categorized into planning (PRECEDE, phases 1-4) and evaluation (PROCEED, phases 5-8) [24]. An overview of the PRECEDE-PROCEED model and a description of how each component of this project relates to the model is provided in Figure 1 and outlined below. As this is a pilot study, outcome evaluation (phase 8) was not assessed.

Phase 1: Social Assessment

To develop an intervention that is acceptable and appropriate, the focus of phase 1 was to develop an understanding of the target population, specifically the University of Newcastle (UON) student population, and to explore its demographics, social norms, and health problems [22]. A literature review was undertaken and a steering committee, including members of the target population and key staff in the university setting, was formed. The literature review highlighted the difficulty in reaching and engaging young adults to change their lifestyle behaviors [13]. It was also highlighted that undertaking university study is a key experience for many young adults [15,16] and that unhealthy eating behaviors are also characteristic of young adults who attend university [25,26]. It was based on these findings that the target population was further refined to include young adult (17 to 35 years) university students. The steering committee was also formed during this phase, with its role being to guide intervention development, assist in piloting the intervention, and to have ongoing involvement in ensuring translation into University Health Promotion. The steering committee includes key staff members (eg, from University Health Promotion, Student Residences, and Student Communications and Marketing) and a diverse group of students representing undergraduate and postgraduate, health and nonhealth degree background, international and domestic, and male and female.

Figure 1. Overview of development and evaluation of the Eating Advice To Students (EATS) intervention for young adult university students, by phase of the PRECEDE-PROCEED model.



Phase 2: Epidemiological, Behavioral, and Environmental Assessment

Phase 2 was focused on developing a logic model of the health problem, linking the health problem to environmental and behavioral determinants [22]. During this phase, the goal was to identify the priority eating behaviors and determinants to be targeted and addressed in the intervention. To achieve this, the literature was reviewed and a cross-sectional analysis of the data from the UON Student Healthy Lifestyle Survey (SHLS) 2016 was conducted. From the literature, it was identified that students typically have low consumption of nutrient-rich foods, particularly fruits and vegetables [27], and high consumption of energy-dense, nutrient-poor foods, especially takeaway foods and confectionary [28,29]. In addition, the major determinants influencing eating behaviors were found to be environmental factors such as living situation, social environment, financial status, as well as personal factors such as age and gender [30-34]. Gaps in the evidence base included that there are few studies among university students that explore a broad range of eating behaviors and the associations among them, as well as a broad range of determinants. Furthermore, there is a distinct lack of studies of this nature in Australian students. The cross-sectional analysis of the SHLS included 4383 students (70.59% [3094/4383] female; mean age 25.5 (SD 9.3) years, and 92.01% [4033/4383] domestic students). Eating behaviors were assessed using short diet questions relating to consumption of fruits, vegetables, breads, cereals, red meat, a range of discretionary (ie, energy-dense and nutrient-poor) food categories (eg, confectionary, processed meat products, and hot chips, wedges or fried potatoes), and breakfast [35]. The priority eating behaviors identified were fruits (45.74% [2005/4383] consuming <2 servings per day), vegetables (91.31% [4002/4383] consuming <5 servings per day), discretionary foods (eg, 68.67% [3010/4383] consuming confectionary 1-2 times per week or more; 54.55% [2391/4383] consuming hot chips, wedges or fried potatoes 1-2 times per week or more), and breakfast (41.75% [1830/4383] not consuming daily). The key determinants identified were living situation, gender, and faculty of study, with females, students living in their own home

or on-campus, and students enrolled in the Faculty of Health and Medicine found to have healthier eating behaviors overall [36].

Phase 3: Educational and Ecological Assessment

Phase 3 builds on the logic model from phase 2 by exploring the predisposing, reinforcing, and enabling factors influencing behavior [22]. To explore these, the literature was reviewed, a systematic review was conducted to evaluate the effectiveness of a potentially applicable intervention approach, and the steering committee was consulted for input. From the literature review, key predisposing factors for healthy eating were desirability for improved health outcomes, weight management, and attractiveness, whereas the main deterrent was lack of motivation [9,37-39]. The key reinforcing factors were having positive social support and social influence [9,37-39]. Enabling factors, that is, conditions facilitating or preventing healthy eating, were in terms of having the time, facilities or skills to prepare healthy foods, the relative low cost and high availability of unhealthy food options, and social expectations to consume unhealthy foods in certain situations [9,37-39]. With time being a major barrier to healthy eating and to participation in health behavior interventions, the potential efficacy of a brief intervention was explored. To add precedent, brief interventions have been found to be effective in reducing alcohol intake among young adults and university students [20,40]. As the second step within this phase, a systematic review was conducted with the aim of evaluating the effectiveness of brief (ie, single session) nutrition interventions in adults and to identify behavior change techniques (BCTs) associated with effective interventions [41]. The review specifically included studies in all adults (ie, ≥18 years) rather than young adults so as not to limit the number of included studies and the scope of the review. This is because no systematic reviews had been conducted assessing brief or single-session nutrition interventions. The participant characteristics of the included studies suggest it is appropriate to translate the findings to the young adult population, for example, 20 of the 45 included studies had a participant mean age between 18 and 35 years, although the majority of these were not targeted to a young adult population. It was found that brief interventions, particularly those that were tailored and instructional, can improve dietary behaviors in the shorter term. BCTs identified as effective were incorporated in the development of EATS. Finally, a summary of the findings and proposed intervention content from all formative research undertaken in phases 1 to 3 was presented to the steering committee members and a meeting was held to discuss and gather their feedback.

Phase 4: Administrative and Policy Assessment and Intervention Alignment

Phase 4 focuses on determining the program and intervention components required to effect the desired behavior changes, with respect to the determinants of behavior identified in the previous phases and with consideration to the organizational, policy, and administrative resources available [22]. This phase requires the inclusion of behavior change theories to support the translation of the knowledge gained from previous phases, that is, the causes and determinants of behavior, into the behavior change the intervention aims to achieve. During this phase, (1) the EATS intervention was developed, including the program logo and recruitment materials as shown in Figures 2 and 3 and (2) both EATS and all design materials were pretested and evaluated with the steering committee.

Figure 2. Sample recruitment poster used to recruit young adult university students to the Eating Advice To Students (EATS) brief Web-based nutrition intervention pilot randomized controlled trial.

Figure 3. Sample Facebook post used to recruit young adult university students to the Eating Advice To Students (EATS) brief Web-based nutrition intervention pilot randomized controlled trial.

Development of Eating Advice To Students

EATS was developed based on the findings from the previous phases as well as by drawing on the social cognitive theory (SCT) [42], the theory of planned behavior (TPB) [43], best practice guidelines (ie, the Australian Dietary Guidelines) [44], and the experience and expertise of the research team. The SCT and TPB were chosen as their constructs reflect key factors influencing behavior and behavior change in the target group, such as social environment and social norms, and because of their previous applications in efficacious health behavior interventions in young adults [8,45,46]. EATS was developed as a brief or single-use intervention. The goal of EATS is to facilitate improvement in overall diet quality, including targeting 4 specific eating behaviors: consumption of fruits, vegetables, discretionary foods (ie, foods that are not necessary for a healthy diet as they are energy-dense and high in saturated fat, added sugars, added salt or alcohol, and low in fiber such as confectionary, hot chips, and sugar-sweetened beverages) [44], and breakfast. The intervention involves password-protected access to the EATS website with instructions to access on a single occasion. The website includes 4 components: (1) a brief screening quiz providing personalized feedback on eating behaviors and barriers to healthy eating; (2) provision of information, tips, and strategies for each target behavior and 2 guided exercises to facilitate behavior change; (3) goal setting; and (4) creating strategies. For the goal setting and creating strategies components, participants could select goals and strategies from the examples provided, write their own using the instructions provided, or both. The website directs participants to complete the components in that order, with participants specifically encouraged to complete components 2 to 4 for those eating behaviors identified in component 1 as being outside the dietary guidelines. The website also provides links and resources for further information, for example, a cookbook with cheap and healthy recipe ideas. The estimated completion time for the intervention is approximately 25 min depending on the number of components completed and resources accessed, with components 1, 3, and 4 estimated to take up to 5 min each and component 2 estimated to take up to 10 min. The key determinants identified from the previous phases were incorporated in the intervention content, for example, different living situations were considered in the examples and advice provided in terms of facilities available for food storage and preparation, lack of time was considered in terms of providing quick and easy meal ideas, and age and gender were considered in the visual design of the website. The intervention components were mapped to BCTs based on the 93-item Behavior Change Taxonomy v1 by Michie et al [47] and SCT and TPB constructs [42,43], as detailed in Table 1. Behavior change theories and BCTs have been used in combination as the theory provides the basis to explain behavior change, whereas the BCTs are the specific, practical components used to change behavior [48].

Table 1. Behavior change techniques and theory constructs applied in the Eating Advice To Students (EATS) brief Web-based nutrition intervention, by intervention component.

Intervention component	Behavior change techniques	Behavior change theory constructs
Screening quiz with personalized feedback on eating behaviors and barriers to healthy eating	Feedback on behavior, social support (emotional), information about health consequences, credible source, restructuring the social environment, identification of self as role model, and framing/reframing	TPB[a]: Attitude (eg, participants advised to reframe their thinking around achieving a balanced diet); SCT[b]: Knowledge (eg, providing information on Australian Dietary Guidelines)
Information, tips, and strategies for each target behavior	Instruction on how to perform the behavior, information about health consequences, information about social and environmental consequences, salience of consequences, demonstration of the behavior, social comparison, credible source, framing/reframing, restructuring the physical environment, restructuring the social environment, and avoidance/reducing exposure to cues for the behavior	SCT: Outcome expectancies (eg, providing information on health risks and benefits)
Goal setting	Goal setting (behavior), information about antecedents, instruction on how to perform the behavior, prompts/cues, restructuring the physical environment, restructuring the social environment, avoidance/reducing exposure to cues for the behavior, and focus on past success	SCT: Goals (participants instructed in setting goals and plans to achieve them); TPB: Perceived behavioral control and SCT: Perceived self-efficacy (eg, participants encouraged to focus on past successful behavior when setting goals/plans)
Creating strategies	Problem solving, action planning, information about antecedents, instruction on how to perform the behavior, prompts/cues, behavioral practice/rehearsal, behavior substitution, habit formation, habit reversal, restructuring the physical environment, restructuring the social environment, avoidance/reducing exposure to cues for the behavior, and mental rehearsal of successful performance	TPB: Perceived behavioral control and SCT: Perceived facilitators and impediments (eg, participants encouraged to plan for situations where achieving healthy eating is difficult)

[a]TPB: theory of planned behavior.

[b]SCT: social cognitive theory.

The UON Student Communications and Marketing team was engaged to develop a logo for EATS and recruitment materials including a poster, digital signage, and social media posts (Facebook and Twitter). Sample recruitment materials are shown in Figures 2 and 3. Key points included in the brief, based on the findings from the previous phases, were to ensure the materials were targeted toward 17 to 35 year old young adults, equally appealing to both genders, and emphasizing particular characteristics of EATS, for example, brief and Web-based.

Pretesting

The project steering committee was consulted to pretest and provide feedback on the beta version of the EATS intervention, including content and functionality, and to evaluate and provide feedback on the logo and recruitment materials. The feedback and suggestions were incorporated into the final versions of both.

Phases 5 to 7: Implementation, Process, and Impact Evaluation

Phase 5, implementation, involves finalizing the implementation and evaluation plans and support of program delivery before implementing the program. Phase 6, process evaluation, assesses program acceptability and usage, as well as recruitment and retention (primary outcomes). Phase 7, impact evaluation, assesses change in behavior or determinants of behavior [22]. Diet quality is a primary outcome, whereas all others are secondary outcomes. The plans for process and impact evaluation are outlined below.

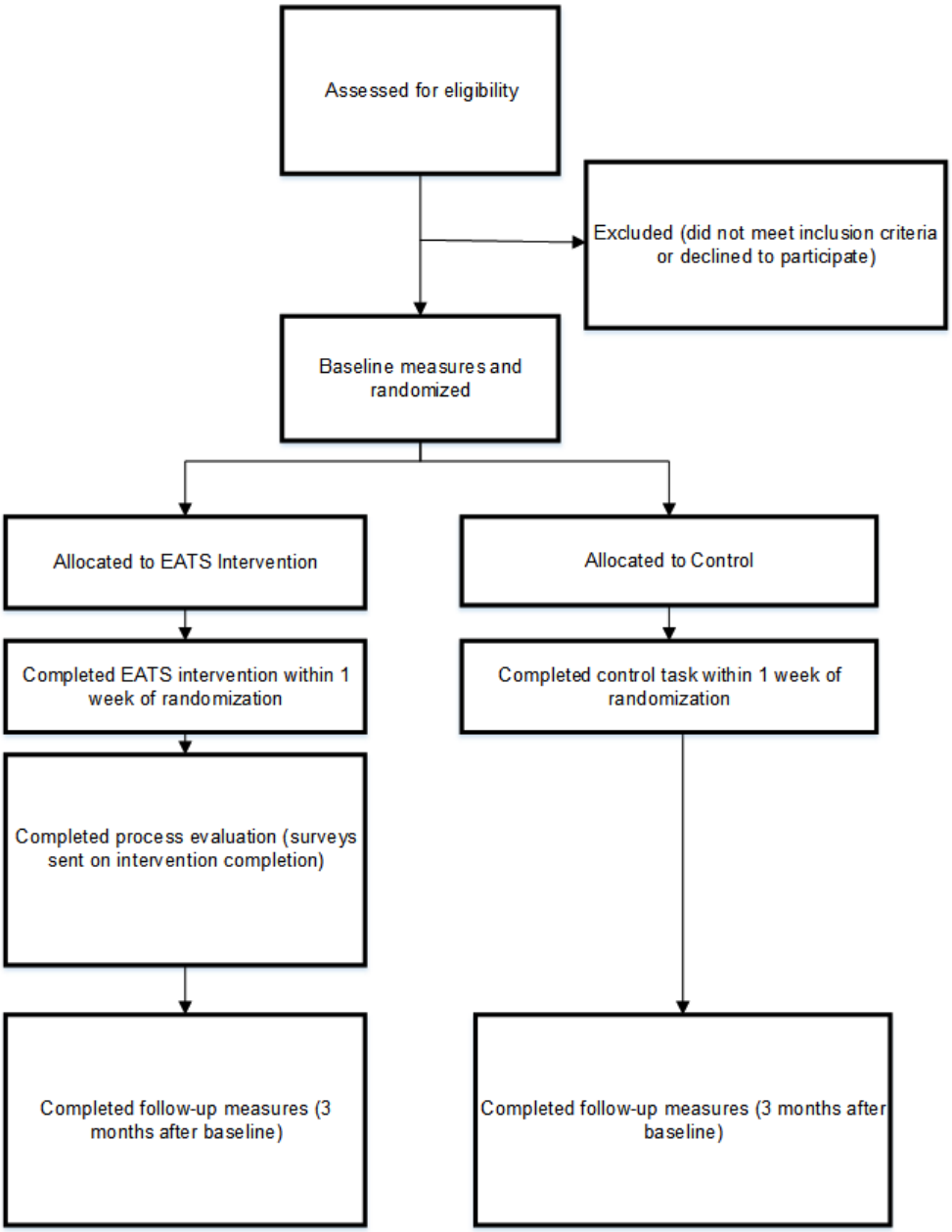
Study Design

The EATS intervention was evaluated in a pilot randomized controlled trial (RCT) with participants randomly allocated to the EATS intervention or attention control group from February to March 2018 and followed up from May to July 2018. Measures were collected at baseline and 3 months after baseline, with the exception of program acceptability (measured post intervention completion) and intervention usage (measured in real time). A diagram of the study timeline and flow is presented in Figure 4. Ethics approval was obtained from the UON Human Research Ethics Committee (H-2017-0404), and the trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000118202p).

Objectives and Hypotheses

The aim was to evaluate the feasibility of a brief (one-time use) Web-based nutrition intervention for young adult (17 to 35 years) university students, including process evaluation (phase 6), program acceptability and demand (usability, appropriateness, and usage) and the intervention's ability to recruit and retain the target group and impact evaluation (phase 7), the intervention's impact on eating behaviors 3 months later compared with an attention control group who completed a brief Web-based alcohol intervention. It was hypothesized that EATS would have high acceptability among young adult university students. It was also hypothesized that young adult university students who completed EATS would have greater improvements in eating behaviors 3 months later compared with those who completed the control intervention.

Figure 4. Diagrammatic summary of study timelines and flow of the Eating Advice To Students (EATS) brief Web-based nutrition intervention pilot randomized controlled trial.



Participants and Recruitment

Students aged 17 to 35 years from the UON, Australia, were recruited for the pilot study. Exclusion criteria included having a medical condition requiring a prescribed diet (eg, diabetes). The participants were recruited via posts on the University social media pages (Facebook and Twitter) and posters and digital signage displayed across University campuses. The recruitment was also supported by the project steering committee that further promoted the study via personal networks within the university. Participants were reimbursed for their time, including a gift voucher to the value of Aus $10 after completing baseline measures and a second gift voucher to the value of Aus $10 after completing follow-up measures. All measures, including baseline, follow-up, and process evaluation, were collected via Web-based surveys conducted using Qualtrics Survey Platform (Qualtrics).

Sample Size

As this is a pilot study, a formal sample size calculation was not performed. The total sample size was set at 126 (ie, 63 per group). This would exceed the median sample size of 30.5 among nondrug trials in a review of the methods and conduct of pilot and feasibility trials [49], ideally allowing for more diversity within the sample in terms of sociodemographics and student-related characteristics, and this was also based on the time available for recruitment to allow the study to be conducted within the university semester (5 weeks), as well as study funding. As males are often underrepresented in health behavior research, a lower limit of 30% of the target sample size being male was set, which would exceed the proportion of males typically achieved in previous intervention studies among this target group [7]. To maximize the number of male participants enrolled, interested females were waitlisted once the proportion of females reached 70% of the target sample size. As the

proportion of 30% male participants was unable to be reached, female participants were invited from the waitlist until the recruitment period was complete.

Randomization

Randomization was conducted by an external statistician. Allocation was stratified by gender (female; male and other gender identity). Allocation sequences within strata were generated by a statistical software program, using permuted block randomization with random block sizes of 2 and 4.

Control Group

Attention control group participants completed Thrive, a brief Web-based intervention designed for university students with a focus on alcohol intake [50]. Thrive provides feedback on their current alcohol intake and related risk, as well as links to further resources for support. The control group participants also received access to the EATS intervention after completing follow-up measures.

Measures

Process Evaluation Measures

Program Acceptability

Program acceptability, including satisfaction, usability, and appropriateness, was evaluated using a process evaluation survey developed for the study. Participants were asked to rate each of the components (quiz, goal setting, and creating strategies) as well as the website overall on a 5-point Likert scale from strongly agree (5) to strongly disagree (1) for usefulness, relevance, usability, and ability to motivate. Participants also rated their overall satisfaction with the EATS intervention, from very satisfied (5) to very unsatisfied (1); whether the intervention met their expectations, from strongly agree (5) to strongly disagree (1); and their opinion on the length of the intervention, from too much time (5) to too little time (1). The participants were also asked a series of open-ended questions relating to their likes and dislikes and suggestions for improvement for each of the intervention components and the intervention overall, as well as reasons for not visiting Web pages or using intervention components where relevant.

Intervention Usage

Intervention usage was objectively tracked using Google Analytics (Google LLC) and through the Qualtrics Survey Platform (Qualtrics). This included device used, website visit duration, number of pages viewed, and links accessed, including whether participants accessed the quiz, goal setting, and creating strategies components. For the goal setting and creating strategies components, the number of goals and strategies set was also recorded.

Recruitment and Retention

The number of individuals enquiring, screened for eligibility, consenting, randomized, completing the intervention, completing process evaluation, and completing follow-up were recorded.

Impact Evaluation Measures

Diet Quality

Dietary intake was assessed using the validated Australian Eating Survey Food Frequency Questionnaire (AES FFQ) [51], a self-administered 120-item semi quantitative FFQ, with participants being asked to report usual intake over the previous 3 months. Diet quality—Australian Recommended Food Score (ARFS)—was derived from FFQ responses. ARFS is calculated using a subset of 70 items from the AES FFQ relating to intake of fruits, vegetables, meat and flesh foods, nonmeat and flesh protein foods, breads and cereals, dairy foods, and water and spreads and sauces [52]. The ARFS is a summation of points scored for each item, with most items scoring 1 point for a consumption frequency of greater than or equal to once per week, and the total score ranging from 0 to 73 points. A higher ARFS reflects higher diet quality, including greater variety, more optimal nutrient intakes, and closer alignment with the Australian Dietary Guidelines [44].

Dietary Intake Related to the Target Eating Behaviors

Intake of fruits, vegetables, discretionary foods, and breakfast were determined from the AES FFQ. This included grams per day and the ARFS subscale for fruits and vegetables, percentage of daily energy intake for discretionary foods, and days per week for breakfast *(Never, 1-2 days, 3-4 days, 5 or more days).*

Alcohol Intake

Alcohol intake was assessed using 2 items from the New South Wales Adult Population Health Survey [35], including frequency of alcohol consumption and number of standard drinks usually consumed per drinking occasion.

Self-Efficacy for Performing Target Eating Behaviors

Self-efficacy for performing the target eating behaviors was assessed using questions derived from the Project EAT II Survey for Young Adults [53]. The participants were asked to rate their level of confidence on a scale of Not at all confident (1) to Very confident (4) for each behavior, for example, Eat at least 2 serves of fruit each day.

Quality of Life

Quality of life was assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire short form [54]. The participants were asked to rate their satisfaction over the previous week on a scale of very good (5) to very poor (1) for each of the 14 items, for example, physical health.

Well-Being

Well-being was assessed using the World Health Organization-Five Well-being Index [55]. The participants were asked to rate how they were feeling over the previous 2 weeks on a scale of all of the time (5) to at no time (0) for each of the 5 statements, for example, I have felt cheerful and in good spirits.

Measures of Potential Contamination

Included in the follow-up survey were 3 items that assessed what, if anything, the participants had used to help them change their eating behavior as a means of assessing potential contamination of intervention effects. These included whether

participants had made changes to their eating behavior over the previous 3 months *(Yes or No)*, and, if yes, an open-response item asking participants to describe the changes; and included a multiple-choice question asking participants to indicate what they had used to help them change behavior, for example, EATS, other research study, program—for example, Lite n' Easy or Weight Watchers—and other.

Data Analysis Plan

Data will be analyzed using Stata software version 14.1 (StataCorp LLC). Process evaluation data will be reported as means and SDs for quantitative questions, for example, scoring of individual program components such as usefulness of the goal-setting feature, and open question responses, such as suggested improvements for EATS, will be compiled and described qualitatively. Intervention usage will be assessed via analysis of usage metrics, including the time spent completing individual components and number of times the links were accessed, to allow comparison with other electronic health (eHealth) research studies. Impact evaluation, that is, to determine the efficacy of the EATS program compared with the control, will be determined using an intention-to-treat approach. All the results for all the participants who enter the study will be included in the analyses. Analyses will assess the difference between the intervention and control groups for the change from baseline to 3 months for all outcomes. Each study effect will be tested as the group by time interaction using a linear mixed model where time will be treated as a repeated measure. The effect sizes and 95% CIs will be reported for each outcome measure. A sensitivity analysis will be conducted to explore the impact of missing data on the primary impact evaluation measure (diet quality).

Results

The pilot RCT has now been completed; the collection of the 3-month follow-up data was completed on July 12, 2018. Data analysis is currently being conducted.

Discussion

Principal Findings

This project used the PRECEDE-PROCEED model to develop a brief Web-based nutrition intervention for young adult university students and plan the evaluation. Nutrition interventions are needed in this target group because of the high rates of unhealthy eating behaviors and the known impacts of this on health and well-being and long-term chronic disease risk [56]. The difficulty is in engaging young adults because of the transitional nature of this life stage and the many factors influencing their health behaviors [9].

The pilot RCT will evaluate whether EATS is deemed acceptable and appropriate by young adult university students and whether it can improve diet quality over a 3-month follow-up period. The process evaluation will provide important feedback from the target population on the appropriateness of the mode of delivery, intervention duration, and individual intervention components. This will be utilized to update and modify the intervention, whereas the intervention usage data will be compared with other eHealth studies to assess participant engagement. Utilizing the university setting, as well as the eHealth mode of intervention delivery, shows promise as a means of effectively targeting and engaging young adults [14,57]. In addition, the development of EATS as a brief intervention draws on the precedence of successful brief interventions to reduce alcohol use among university students [20]. Therefore, the combination of a strong methodological approach to intervention development, the use of a setting with the potential for wide reach among young adults, and the use of an intervention approach with demonstrated efficacy suggest that the EATS intervention may be successful.

Implications

If the evaluation results are positive, the potential implications will be significant in terms of translation and addressing the important health problem of poor diet among young adult university students. The long-term goal of this project is translation into University Health Promotion, that is, to implement EATS as a readily available program for all UON students, facilitated by the University Health Promotion staff. The key strategy to achieve this is the engagement of the steering committee, including key stakeholders to assist in translation. Furthermore, the chosen mode of delivery (ie, automated website) minimizes the ongoing resources required for program delivery. This paper adds to this evidence base and provides a detailed example for future researchers and health professionals working with this group and setting. If successful, there is also the potential that the intervention could be transferable to other universities nationally or internationally.

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Conflicts of Interest

None declared.

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Abbreviations

AES FFQ: Australian Eating Survey Food Frequency Questionnaire
ARFS: Australian Recommended Food Score
BCT: behavior change technique
EATS: Eating Advice To Students
eHealth: electronic health
RCT: randomized controlled trial
SCT: social cognitive theory
SHLS: Student Healthy Lifestyle Survey
TPB: theory of planned behavior
UON: University of Newcastle

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Protocol

Screening Depression and Related Conditions via Text Messaging Versus Interview Assessment: Protocol for a Randomized Study

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Abstract

Background: Depression is an often underdiagnosed and, therefore, untreated comorbidity for low-income, racially or ethnically diverse patients with a chronic illness such as diabetes. Recent updates from the US Preventive Services Task Force guidelines in 2016 recommend depression screening for every adult but does not suggest the mode of assessment. Short message service (SMS) text messaging is an inexpensive, private, and scalable approach to provide depression screening and monitoring; it can also alleviate many barriers, such as transportation, childcare, and clinical visit time faced by the low-income population, in receiving a diagnosis of depression. Current evidence is inconsistent in comparing technology-mediated assessment versus interviewer (INTW) assessment in collecting sensitive health information, as some studies suggest that technology encourages self-disclosure while the other studies show the opposite effect.

Objective: The proposed study will test the use of SMS text messaging to assess depression and its related conditions, including functional disability, pain, and anxiety, in low-income, culturally diverse, safety-net primary care populations with diabetes. The study will examine the concordance between SMS text message and interviewer assessments and evaluate test-retest reliability.

Methods: The proposed study will adopt a randomized design with 200 patients assigned to four study groups: SMS/INTW, INTW/SMS, SMS/SMS, and INTW/INTW. The first two groups will be used to examine the concordance between SMS text message and interviewer assessments. The third and fourth groups will be used to evaluate test-retest reliability. Participants of the study will be recruited from the participants of the prior Diabetes-Depression Care-management Adoption Trial, a large comparative effectiveness research trial in collaboration with the Los Angeles County Department of Health Services. Test-retest reliability and concordance between SMS text message and interviewer assessments will be evaluated by the interclass correlation coefficient and the kappa statistic. Missing data patterns will be explored to understand whether participants are willing to self-disclose information related to depression in SMS text message assessments.

Results: Recruitment of participants was conducted from June 2017 to November 2017. A total of 206 participants were enrolled: 52 (25.2%) in SMS/INTW, 53 (25.7%) in SMS/SMS, 49 (23.8%) in INTW/SMS, and 52 (25.2%) in INTW/INTW. The average age of the participants was 57.1 years (SD 9.2). A total of 57.8% (119/206) of participants were female, 93.2% (192/206) were Latino, and 77.7% (160/206) chose Spanish as their preferred language. Analysis of the SMS text message assessment shows the cost of distributing the 16 questions is about US $0.50 per person per assessment. Full results of the study will be reported elsewhere.

Conclusions: This study is anticipated to establish the feasibility of using SMS text messaging to assess depression and its related conditions in low-income, culturally diverse, safety-net primary care populations with diabetes. We also expect to generate

knowledge about whether patients in the targeted population are willing to reply and self-disclose sensitive information about depression and its related conditions through SMS text message assessments.

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KEYWORDS

depression; diabetes; comorbidity; screening; primary care; health information technology; information and communication technology; text messaging; patient-reported outcome measures

Introduction

Depression is an underdiagnosed comorbidity for those with chronic illness [1] that impairs functional status and worsens outcomes, including morbidity, mortality, and health care costs [2-5]. Diabetes doubles the risk of depression relative to the general population [6,7], but as high as 50% of comorbid depression in patients with diabetes is undiagnosed and thus untreated [1]. Low-income, ethnically diverse patients with chronic illnesses are exposed to even higher risk of depression [7-9]. Hispanics have a higher prevalence of diabetes compared with non-Hispanic whites [10] and are less likely to meet hemoglobin A1c and cholesterol goals [11]. Hispanics are less than half as likely as non-Hispanic whites to receive any depression care, including guideline-level depression care [12].

Depression screening is an effective approach to reduce the rate of undiagnosed depression and thus provides timely treatment for patients [13]. As growing evidence suggests the benefits from depression screening are significant and the harms are minimal, the US Preventive Services Task Force updated its guidelines in 2016 that, for the first time in history, recommend providing screening of depression for every adult [13].

Still, significant barriers exist in adopting depression screening among low-income, ethnically diverse patients with chronic illness. This patient population often prefers safety-net primary care over specialty psychiatric care to seek mental health care. However, safety-net primary care providers often find themselves lacking the time and resources to address mental health issues on top of managing other medical conditions like diabetes [14-17]. Concurrently, minority patients are less likely to voluntarily report depressive symptoms, may view depression as a moral weakness or character flaw (ie, not an illness), and may be more likely to ascribe symptoms of depression to a physical illness [18]. Therefore, low-income, predominantly minority patients in safety-net care systems often miss out on screening and diagnosis for depression [15,19].

The proposed study will test the use of short message service (SMS) text messaging to assess depression and its related conditions, including functional disability, pain, and anxiety, in low-income, ethnically and racially diverse safety-net primary care populations. Text messaging is a highly prevalent and global phenomenon; among the 4 billion mobile phones in use, 3.05 billion, or 75%, are SMS enabled [20]. In the United States, texting among adult mobile phone users is higher among Hispanics and Latinos (83%) than among non-Hispanic whites (70%) [21]. SMS text messaging is also inexpensive, private, and can be scaled to large populations [20,21]. Thus, SMS text messaging could be an ideal approach for conducting depression screening and monitoring in underserved, ethnically and racially diverse populations.

The proposed study will test the use of SMS text messaging, in both English and Spanish, to administer the 8-item Patient Health Questionnaire (PHQ-8) assessment for depression. The Patient Health Questionnaire (PHQ) is a well-validated and widely used depression assessment tool in primary care and the general population [22-24]. Prior studies have shown that the PHQ can be reliably carried out over the telephone by interviewers [25]. However, to the best or our knowledge, no prior studies have evaluated the assessment of the PHQ using SMS text messaging in a safety-net primary care population. In addition, this is the first study to test SMS text messaging assessment for highly comorbid conditions of depression, including anxiety [26], functional disability [8], and pain [27].

Methods

Overall Design

The proposed study aims to recruit 200 patients randomly assigned to one of the four study groups: SMS/interviewer (INTW), INTW/SMS, SMS/SMS, or INTW/INTW. The first two groups will be used to examine the concordance between SMS and interviewer assessments for depression and its related comorbid conditions, including anxiety, functional disability, and pain. The third and fourth groups will be used to evaluate test-retest reliability. Depression assessment will be carried out using the PHQ-8, a widely used depression assessment tool in primary care and general populations [28]. The first two questions of the PHQ-8 are often used for brief assessment of depression and are known as the 2-item PHQ (PHQ-2) [28]. Anxiety will be assessed using the 2-item Generalized Anxiety Disorder scale (GAD-2) [29]. Functional disability will be assessed using the 3-item Sheehan Disability Scale (SDS) [30]. Pain will be assessed by the presence of chronic pain, pain level, and pain interference. Validity of interviewer assessments for the PHQ, SDS, and GAD-2 have been established in prior studies [25,28-30]. By completing the specific aim of this study, we expect to generate data and results that could be used to examine the validity and reliability of SMS text messaging assessment for depression and its related conditions in a safety-net primary care population with diabetes.

Recruitment

Participants of this study will be recruited from the group of participants from the prior Diabetes-Depression Care-management Adoption Trial (DCAT), a large, US

Department of Health and Human Services-funded translational study conducted from 2010 to 2013 [15,31-37]. These patients will be chosen from the DCAT because of the prior contacts and rapport built during the DCAT so that this study can fit within the short timeline of the funding requirements. The DCAT was a comparative effectiveness research trial with three study arms in collaboration with eight safety-net primary care clinics of the Los Angeles County Department of Health Services, the second-largest safety-net system in the United States. The DCAT tested an automatic telephone depression-monitoring system to facilitate collaborative depression care in patients with type 2 diabetes. A bilingual recruiter and interviewer from the DCAT will join the proposed study and will contact the participants in the DCAT technology-facilitated care (TC) group for recruitment. Participants in the DCAT TC group received regular depression monitoring every 3 or 6 months over automatic telephone calls during the DCAT. For those who agree to participate, a random number generator will be used to randomize the patients into one of the four study groups. Participants assigned to the INTW/SMS and INTW/INTW groups will receive assessments over the telephone immediately after they agree to participate. Participants assigned to the SMS/INTW and SMS/SMS groups will be notified that an SMS text message assessment will be sent to them within 48 hours.

Sample Size Determination

Unfortunately, there is no consensus in methods to determine the sample size a priori for studying concordance, validity, and reliability [38,39]. Well-received published studies that evaluated the PHQ and SDS in primary care with interviewer assessment typically had a sample size that ranged from 100 to over 3000 [22-23,25,30]. A widely cited study that evaluated the concordance and test-retest reliability of interviewer assessments carried out over the telephone versus in person for the PHQ had a sample size about 350 [25]. Based on the sample size of previous studies, we suggest that a sample size of 200 would be appropriate, given the limit of our funding, while we acknowledge that a sample size over 1000 would be ideal to produce more reliable results. This study will aim to recruit and study 50 patients in each of the four study groups. As mentioned above, we will first recruit patients from the DCAT TC group (N=442), since these patients are more familiar with technology-mediated assessment for the PHQ. If the number of participants recruited from the TC group is smaller than the targeted sample size (ie, 50 in each of the four study groups), patients will be recruited from the other two study arms in the DCAT, namely the usual care group (N=484) and the supported care group (N=480).

Design of the Text Messaging Assessment

The SMS text messaging assessment will include 16 questions, delivered in the order of the GAD-2, the PHQ-8, the SDS, and pain assessments (see Table 1). The 16 questions will be sent one at a time. After the participant answers a question by texting back the one number that best describes their feelings, the next message will be sent. The questions are numbered as “1 of 16, 2 of 16...” for participants to track their progress. Since SMS text messaging only supports the delivery of plain text, we use the asterisk sign (ie, *) to highlight the important part of a text message. A sample SMS text messaging assessment question is shown in Figure 1. The SMS text messaging assessment is available in both English and Spanish and implemented using the Qualtrics SMS Distribution module [40].

Randomization and Data Collection Plan

The randomization and data collection plan is diagramed in Figure 2. After screening for eligibility and obtaining verbal consent to participate, participants will be randomized to one of the four study groups: SMS/INTW, INTW/SMS, SMS/SMS, or INTW/INTW. For all participants, measures on the following characteristics will be collected by a bilingual (ie, English and Spanish) interviewer:

1. Demographics: age, gender, race and ethnicity, language, marital status, education, and insurance.
2. Personality: Ten Item Personality Measure (TIPI) of the Big Five Personality [41].
3. Cognitive diathesis to depression: 9-item Dysfunctional Attitudes Scale (DAS) Short Form [42].
4. Depression stigma: Depression Stigma Scale (DSS) [43].
5. Mobile phone, Internet, and social media use.
6. Depression history and treatment.

The above participant characteristics will be measured because evidence has suggested that demographics such as gender, personality dimensions such as extraversion, dysfunctional attitudes that exist in individuals with depression, and technology use can influence self-disclosure of sensitive health information [44-46]. Measuring these characteristics is critical for determining the generalizability of the proposed study.

Following the collection of characteristics, participants in the SMS/INTW group will first receive the SMS text message assessment within 48 hours. Within 7 days following the SMS text message assessment, the interviewer will contact the participant over the telephone to repeat the same assessment. Participants in the INTW/SMS group will first answer the interviewer assessment over the telephone; they will then reply to the SMS text message assessment within a 7-day period. Participants in the SMS/SMS and INTW/INTW groups will receive two SMS text messages and two interviewer assessments, respectively, within a 7-day period. The choice of interval between the two assessments (ie, 7 days) is based on a prior study that compares interviewer assessment carried out over the telephone versus in-person assessment of depression [25]. A shorter interval is likely to increase the likelihood of repeating the answer from the first assessment in the subsequent one, while a longer interval will increase the probability of change in real severity of depression.

Table 1. Text messages and their response options for assessing depression and related conditions. Asterisks highlight the important part of the text message.

Module and text message	Response options
2-item Generalized Anxiety Disorder scale	
1 of 16. Over the last 2 weeks, how often have you been bothered by *feeling nervous, anxious, or on edge?*	1: Not at all; 2: Several days; 3: More than half the days; 4: Nearly every day; 5: Don't know; 6: Refuse to answer
2 of 16. Over the last 2 weeks, how often have you been bothered by *not being able to stop or control worrying?*	1: Not at all; 2: Several days; 3: More than half the days; 4: Nearly every day; 5: Don't know; 6: Refuse to answer
8-item Patient Health Questionnaire	
3 of 16. Over the last 2 weeks, how often have you been bothered by *little interest or pleasure in doing things?*	1: Not at all; 2: Several days; 3: More than half the days; 4: Nearly every day; 5: Don't know; 6: Refuse to answer
4 of 16. Over the last 2 weeks, how often have you been bothered by *feeling down, depressed, or hopeless?*	1: Not at all; 2: Several days; 3: More than half the days; 4: Nearly every day; 5: Don't know; 6: Refuse to answer
5 of 16. Over the last 2 weeks, how often have you been bothered by *trouble falling or staying asleep, or sleeping too much?*	1: Not at all; 2: Several days; 3: More than half the days; 4: Nearly every day; 5: Don't know; 6: Refuse to answer
6 of 16. Over the last 2 weeks, how often have you been bothered by *feeling tired or having little energy?*	1: Not at all; 2: Several days; 3: More than half the days; 4: Nearly every day; 5: Don't know; 6: Refuse to answer
7 of 16. Over the last 2 weeks, how often have you been bothered by *poor appetite or overeating?*	1: Not at all; 2: Several days; 3: More than half the days; 4: Nearly every day; 5: Don't know; 6: Refuse to answer
8 of 16. Over the last 2 weeks, how often have you been bothered by *feeling bad about yourself, or that you are a failure, or have let yourself or your family down?*	1: Not at all; 2: Several days; 3: More than half the days; 4: Nearly every day; 5: Don't know; 6: Refuse to answer
9 of 16. Over the last 2 weeks, how often have you been bothered by *trouble concentrating on things, such as reading the newspaper or watching television?*	1: Not at all; 2: Several days; 3: More than half the days; 4: Nearly every day; 5: Don't know; 6: Refuse to answer
10 of 16. Over the last 2 weeks, how often have you been bothered by *moving or speaking so slowly that other people could have noticed, or the opposite—being so restless that you have been moving around a lot more than usual?*	1: Not at all; 2: Several days; 3: More than half the days; 4: Nearly every day; 5: Don't know; 6: Refuse to answer
3-item Sheehan Disability Scale	
11 of 16. On a scale from 0-10, to what extent has your health interfered with your *work*, including school work and housework, in the past month (0: Not at all; 10: Extremely)?	Score from 0-10, where 0 means *Not at all* and 10 means *Extremely*
12 of 16. On a scale from 0-10, to what extent has your health interfered with your *family life* in the past month (0: Not at all; 10: Extremely)?	Score from 0-10, where 0 means *Not at all* and 10 means *Extremely*
13 of 16. On a scale from 0-10, to what extent has your health interfered with your *social life* or relationships with others outside your family in the past month (0: Not at all; 10: Extremely)?	Score from 0-10, where 0 means *Not at all* and 10 means *Extremely*
Pain	
14 of 16. Have you had pain that has been present most of the time for 6 months or more during the past year?	1: Yes; 2: No; 3: Don't know
15 of 16. During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework?	1: Not at all; 2: A little bit; 3: Moderately; 4: Quite a bit; 5: Extremely; 6: Don't know
16 of 16. Please rate your pain by telling us the one number that best describes your pain at its WORST in the last 24 hours (0: No pain; 10: Pain as bad as you can imagine).	Score from 0-10, where 0 means *No pain* and 10 means *Pain as bad as you can imagine*

Figure 1. A sample text message for assessing depression and its related conditions. The asterisks highlight the important part of the message.

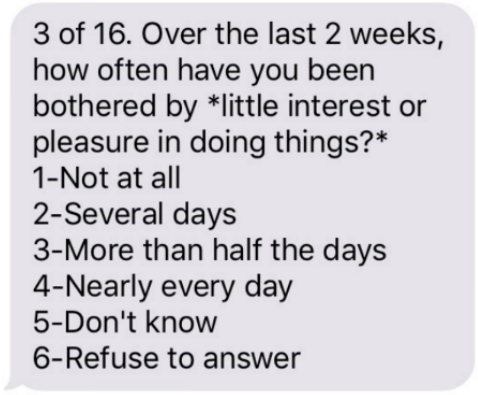
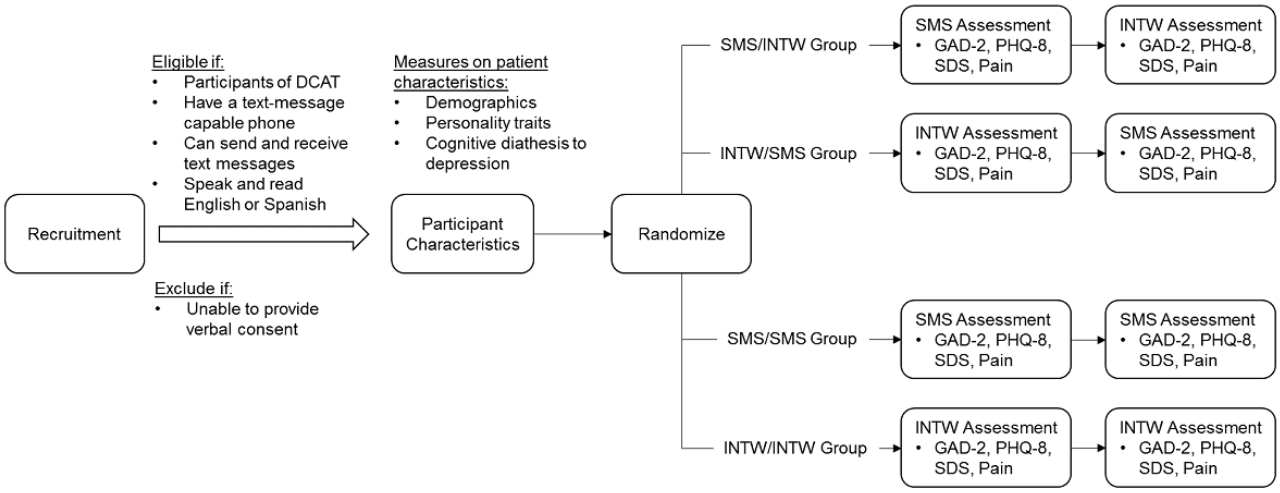


Figure 2. Randomization and data collection plan. DCAT: Diabetes-Depression Care-management Adoption Trial; GAD-2: 2-item Generalized Anxiety Disorder scale; INTW: interviewer; PHQ-8: 8-item Patient Health Questionnaire; SDS: 3-item Sheehan Disability Scale; SMS: short message service.



Patient Safety Plan

If patients report a PHQ-8 score of 8 or higher in any one of the assessments, at the end of the assessment week, a text message will be sent to suggest that they speak to their clinician. Although the chance is small, participants may express thoughts about being better off dead, hurting him/herself, or other suicidal ideation at some point during the telephone recruitment or interview. If this occurs, the recruiter or interviewer will say, "I am not a clinician and I am not qualified to evaluate these thoughts and feelings in detail, but it is important that you get proper medical attention and I would encourage you to discuss these thoughts and feelings with a medical or mental health professional."

Statistical Analysis

Concordance between SMS text message and interview assessments will be measured by the intraclass correlation coefficient (ICC) and the kappa statistic. ICC measures the consistency or reproducibility of SMS text message and INTW assessments. We will calculate both the consistency and absolute agreement measures of ICC. The kappa statistic measures interrater agreement for categorical items. We will use different threshold levels to compute kappa, including PHQ-2 ≥3 and PHQ-8 ≥8, two threshold levels that were suggested to classify major depression [22,28]. We will also compute paired *t* tests to investigate differences in mean scores between SMS text message and interviewer assessments. ICC and kappa will be computed using the "icc" and "kappa2" functions in the R package "irr" (The R Foundation). Paired *t* tests will be performed by the R function "t.test." Test-retest reliability of the SMS text message and interviewer assessments will also be measured by ICC. Finally, internal consistency will be measured by Cronbach alpha, which will be computed using the "alpha" function in the R package "psych."

Since information such as depression and functional disability is sensitive health information, it is critical to understand whether participants are willing to self-disclose such information in an SMS text message assessment. We will calculate the proportion of missing data and explore whether the data are missing at random or is likely to follow some patterns, using descriptive and visualization tools provided by the R packages "mice" and "VIM." We will also perform multiple imputation on the data and compare the concordance and reliability measures on original and imputed data [47].

Results

This study was funded by the Research Council of the Suzanne Dworak-Peck School of Social Work at the University of Southern California and was approved by the University of

Southern California Institutional Review Board. Recruitment of participants was conducted from June 2017 to November 2017. A total of 769 call attempts were made. Among those attempts, 490 (63.7%) were unsuccessful for the following reasons: phone number disconnected (196/490, 40.0%); left voicemail, but participant did not return call (176/490, 35.9%); wrong number (73/490, 14.9%); no one picked up the phone (28/490, 5.7%); or other reasons (53/490, 10.8%). Of the 769 call attempts, 279 (36.3%) patients were successfully contacted and assessed for eligibility. Of the 279 patients that were contacted, 73 (26.2%) were excluded for the following reasons: does not have or know how to use cell phone and/or text message (44/73, 60%) or declined to participate (29/73, 40%). The recruitment led to the enrollment of 206 participants: 52 (25.2%) in SMS/INTW, 53 (25.7%) in SMS/SMS, 49 (23.8%) in INTW/SMS, and 52 (25.2%) in INTW/INTW. The average age of the participants was 57.1 years (SD 9.2). A total of 57.8% (119/206) of the participants were female, 93.2% (192/206) were Latino, and 77.7% (160/206) chose Spanish as their preferred language. Analysis of the SMS text message assessment shows the cost of distributing the 16 questions was about US $0.50 per person per assessment, which includes all 16 questions. Full results of the study will be reported elsewhere.

Discussion

This paper proposed a study with a randomized design to analyze SMS text message assessment, in both English and Spanish, for depression and its related conditions in a safety-net primary care population. The US Preventive Services Task Force recommends depression screening for all adults but does not mention the mode of screening [13]. Existing research has tested the PHQ for depression screening using paper-based self-reported assessment [48-50], in-person interviewer assessment [25,51], and telephone interviewer assessment [15,25]. To the best of our knowledge, there is no published paper about how widely each of those assessment modes are used in practice. The DCAT study was conducted in the Los Angeles County Department of Health Services, which carries out depression screening using the PHQ by in-person interviewer assessment. Compared to other assessment modes, SMS text message assessment is inexpensive, private, and scalable in large populations. Such advantages of SMS text message assessment are particularly beneficial for our targeted population in this study (ie, low-income, racially and ethnically diverse, safety-net patients with diabetes). These patients often face more significant individual and systemic barriers to receive timely depression assessment and treatment. Thus, the proposed SMS text message approach, if successful, could be a beneficial addition to primary care for these patients by providing proactive and timely depression assessment.

The proposed study will generate data and results that fill in the gap of current evidence in technology-mediated assessment for sensitive health information such as depressive symptoms. Current evidence on the effect of technology on self-disclosing such information is inconsistent. Some studies suggest that technology-mediated assessment such as SMS text messaging can create an idealized perception of the interviewer and reduce social desirability bias [52]. As a result, technology-mediated assessment can encourage disclosure of sensitive health information [53,54]. In contrast, there is also evidence suggesting technology-mediated assessment discourages disclosure of sensitive information, since the distance and private space created by technology may discourage patients to seek help [55].

The proposed study has a few limitations. First, the sample size is relatively small due to the limit of our funding. Second, the study participants' experience built in the prior DCAT study may make those participants more familiar with technology-mediated assessment than average people in the targeted study population. Nevertheless, the 4-year interval between the DCAT study, conducted from 2010 to 2013, and this study, conducted in 2017, is long enough that it is likely to decrease the potential influences of DCAT assessment. Finally, the study participants are predominantly Latino, which may limit the generalizability of the study results to other safety-net primary care populations, especially those with a majority of African American patients.

The anticipated outcome of this study is to establish feasibility of using SMS text messaging to assess depression and its related conditions. Specifically, we aim to gather data and results for concordance and test-retest reliability of SMS text message and interviewer assessments in low-income, racially and ethnically diverse populations with diabetes. We also expect to generate preliminary knowledge about whether patients in the targeted population will be willing to reply and self-disclose sensitive health information about depression and its related conditions through SMS text message assessments.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

DAS: 9-item Dysfunctional Attitudes Scale
DCAT: Diabetes-Depression Care-management Adoption Trial
DSS: Depression Stigma Scale
GAD-2: 2-item Generalized Anxiety Disorder scale
ICC: intraclass correlation coefficient
INTW: interviewer
PHQ: Patient Health Questionnaire
PHQ-2: 2-item Patient Health Questionnaire
PHQ-8: 8-item Patient Health Questionnaire
SDS: 3-item Sheehan Disability Scale
SMS: short message service
TC: technology-facilitated care
TIPI: Ten Item Personality Measure

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Protocol

The Effects of Positive Affect and Episodic Future Thinking on Temporal Discounting and Healthy Food Demand and Choice Among Overweight and Obese Individuals: Protocol for a Pilot 2×2 Factorial Randomized Controlled Study

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Abstract

Background: Unhealthy behaviors (eg, poor food choices) contribute to obesity and numerous negative health outcomes, including multiple types of cancer and cardiovascular and metabolic diseases. To promote healthy food choice, diet interventions should build on the dual-system model to target the regulation and reward mechanisms that guide eating behavior. Episodic future thinking (EFT) has been shown to strengthen regulation mechanisms by reducing unhealthy food choice and temporal discounting (TD), a process of placing greater value on smaller immediate rewards over larger future rewards. However, these interventions do not target the reward mechanisms that could support healthy eating and strengthen the impact of EFT-anchored programs. Increasing positive affect (PosA) related to healthy food choices may target reward mechanisms by enhancing the rewarding effects of healthy eating. An intervention that increases self-regulation regarding unhealthy foods and the reward value of healthy foods will likely have a greater impact on eating behavior compared with interventions focused on either process alone.

Objective: This study aimed to introduce a protocol that tests the independent and interactive effects of EFT and PosA on TD, food choice, and food demand in overweight and obese adults.

Methods: This protocol describes a factorial, randomized, controlled pilot study that employs a 2 (affective imagery: positive, neutral) by 2 (EFT: yes, no) design in which participants are randomized to 1 of 4 guided imagery intervention arms. In total, 156 eligible participants will complete 2 lab visits separated by 5 days. At visit 1, participants complete surveys; listen to the audio guided imagery intervention; and complete TD, food demand, and food choice tasks. At visit 2, participants complete TD, food demand, and food choice tasks and surveys. Participants complete a daily food frequency questionnaire between visits 1 and 2. Analyses will compare primary outcome measures at baseline, postintervention, and at follow-up across treatment arms.

Results: Funding notification was received on April 27, 2017, and the protocol was approved by the institutional review board on October 6, 2017. Feasibility testing of the protocol was conducted from February 21, 2018, to April 18, 2018, among the first 32 participants. As no major protocol changes were required at the end of the feasibility phase, these 32 participants were included

in the target sample of 156 participants. Recruitment, therefore, continued immediately after the feasibility phase. When this manuscript was submitted, 84 participants had completed the protocol.

Conclusions: Our research goal is to develop novel, theory-based interventions to promote and improve healthy decision-making and behaviors. The findings will advance decision-making research and have the potential to generate new neuroscience and psychological research to further understand these mechanisms and their interactions.

Trial Registration: ISRCTN Registry ISRCTN11704675; http://www.isrctn.com/ISRCTN11704675 (Archived by WebCite at http://www.webcitation.org/760ouOoKG)

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KEYWORDS

obesity; cancer; temporal discounting; food choice; eating behavior; episodic future thinking; positive affect; guided imagery; randomized controlled trial

Introduction

Background and Rationale

Unhealthy behaviors, such as poor food choices and physical inactivity, are associated with numerous negative health outcomes, including, but not limited to, multiple types of cancer and cardiovascular and metabolic diseases [1]. Notably, these behaviors can contribute to weight gain and obesity, which remains one of the top preventable causes of morbidity and mortality worldwide [2,3]. Only 9-13% of US adults met fruit and vegetable intake recommendations (ie, 1.5 to 2 cups of fruits a day, 2 to 3 cups of vegetables a day) in 2013 [4]. Similarly, in England, only 26% of adults consumed 5 or more portions of fruits and vegetables a day in 2016 [5]. Interventions targeting diet may help individuals lose weight in the short term, but often have minimal impact on weight loss maintenance, potentially because they do not target the underlying cognitive and affective mechanisms of eating behavior [6].

Eating behavior is a complex process regulated by homeostatic, physiologic-driven mechanisms that drive eating in response to hunger [7] and nonhomeostatic, reward-driven mechanisms that drive eating in response to highly palatable external cues (eg, foods high in fat and sugar) [8]. The rewarding nature of highly palatable foods can lead to eating in the absence of hunger, and in turn, overeating can result in increased reward responsivity to certain foods and subsequent weight gain [9]. Dual-system neural models of eating behavior theorize that the increased neural reward responsivity can be mitigated by activating areas of the brain associated with regulation to dampen hyperactive reward responses and manage unhealthy eating behaviors [10]. The regulation network, referred to as the *executive* [11], *deliberative* [12], or *reflective* system [13], includes brain regions associated with cognitive control, emotion regulation, and goal-directed behavior. In contrast, the reward network, referred to as the *impulsive* [11,13] or *automatic* [12] system, includes brain regions associated with evaluating, anticipating, and processing rewards. When there is an imbalance between these networks, the reward network can override the regulation network, whereby overeating leads to weight gain and eventually obesity [14]. Thus, among obese individuals, the regulation network is often considered underactive and the reward network is considered overactive [14].

To promote the healthy diet of fruits, vegetables, legumes, nuts and whole grains, and minimal sugars and fats recommended by the World Health Organization [15], healthy eating interventions should build on the dual-system model described above to target both the regulation and reward mechanisms that guide eating behavior. One regulation mechanism relevant to food choice is delayed gratification—the ability to resist the temptation of an immediate reward (eg, highly palatable food) in preference of a later reward (eg, long-term health) [10]. Prior research suggests that individuals who are obese show poor delayed gratification and demonstrate greater temporal discounting (TD), meaning they place greater value on smaller immediate rewards over larger or delayed rewards in the future [16-18]. For example, an individual with a low delay of gratification may value the satisfying taste of savory or sweet food that is available now, over the health benefits of future weight loss. Prior work indicates increased brain activation in regulation regions when participants make decisions involving delayed rewards and increased activation in reward regions when participants make decisions involving immediately available rewards [19]. Decreasing TD may, therefore, make it easier to favor the long-term reward of making a healthy food choice over the immediately available taste reward that may be associated with unhealthy food choice.

Multiple studies have demonstrated that the cognitive process of episodic future thinking (EFT; ie, the ability to imagine or simulate personal experiences that might occur in one's future) reduces TD, especially in overweight and obese individuals [20]. Research delving into the mechanisms of EFT suggests that EFT is derived from episodic memory, which supports future simulation by allowing people to flexibly retrieve and recombine elements of past experiences into novel representations of events that might occur in the future [21]. Evidence from thought sampling procedures indicates that episodic future thoughts occur frequently in everyday life and serve a range of functions, including decision making, emotion regulation, intention formation, and planning [21]. Furthermore, training in EFT (vs episodic recent thinking [ERT]) has been shown to reduce discounting rates and food reinforcement [22] as well as behavioral outcomes such as calorie consumption

[23,24]. These lab studies and pilot interventions suggest that EFT has the capacity to reduce TD and calorie consumption; yet, these interventions do not target the reward mechanisms that impact eating decisions. In addition, targeting the reward mechanisms involved in food choice could strengthen the impact of an EFT-anchored intervention.

One way to target the reward mechanisms involved in obesity is by enhancing the rewarding effects of healthy eating and creating positive associations with healthy food. Descriptive and observational research has shown that positive affect (PosA) is associated with healthier food [25,26], but this association may be bidirectional, with some studies showing fruit and vegetable consumption predicting PosA [27,28]. Affect is the representation of the body's core evaluation, at any level and in any modality (including physiological reactions, emotions, thoughts, and expressions), that an object, event, or person encountered in the world is good for it, bad for it, approachable, or avoidable [29]. Accordingly, PosA is the physiological and emotional experience that an object is beneficial and confers positive value to the body and self. Importantly, a study experimentally manipulating PosA showed that creating positive associations with fruit (as opposed to neutral or negative associations) significantly increased the likelihood of choosing fruit in a behavioral choice task [30]. Consistent with the dual-system model, eating behavior interventions may need to take advantage of the overactive reward system that has been associated with overeating and obesity by enhancing the rewarding associations with healthy eating and its effects.

PosA has also been shown to increase TD [31], indicating that EFT exercises and feelings of PosA may have an interactive or additive effect on discounting rates. Both mechanisms have different underlying neurological pathways, and their interactive effect has not been tested to date. Although programs and interventions to increase healthy food choices exist, new interventions firmly grounded in behavioral, cognitive, affective, and neuroscientific theory may have a stronger impact on increasing healthy food choices than existing interventions. An intervention focused on enhancing both reward for healthy foods and regulation for unhealthy foods is likely to have a greater impact on dietary choices compared with interventions focused on either process alone.

This Study

This protocol aims to test whether an intervention focused on enhancing both the reward value of healthy foods and regulation surrounding unhealthy foods is likely to have a stronger effect on eating behavior compared with interventions focused on either process alone. To achieve this, we will conduct a 2×2 factorial, randomized, controlled lab-based intervention study of brief guided imagery exercises that target regulation (EFT: yes, no) and reward (PosA imagery: positive, neutral) mechanisms of eating behavior.

To assess the individual and combined effects of EFT and PosA on eating behavior, we will examine the effect of PosA, EFT, and their interaction on (1) TD, (2) the reward value of healthy and unhealthy foods (ie, food demand indexed by intensity or the number of items consumed when freely available), and (3) food choice. Our predictions are 3-fold. First, we predict that participants in the EFT condition will demonstrate lower TD, lower demand for unhealthy foods, higher demand for healthy foods, more healthy food choices, and less unhealthy food choices compared with the ERT condition. Second, we predict that participants in the PosA condition will demonstrate no differences in TD, yet exhibit lower demand for unhealthy foods, higher demand for healthy foods, more healthy food choices, and less unhealthy food choices compared with the neutral affect conditions. Third, we predict that participants in the EFT and PosA conditions will demonstrate the lowest TD, the lowest demand for unhealthy foods, the highest demand for healthy foods, the healthiest food choices, and the least unhealthy food choices compared with participants in all other conditions.

Methods

Study Design

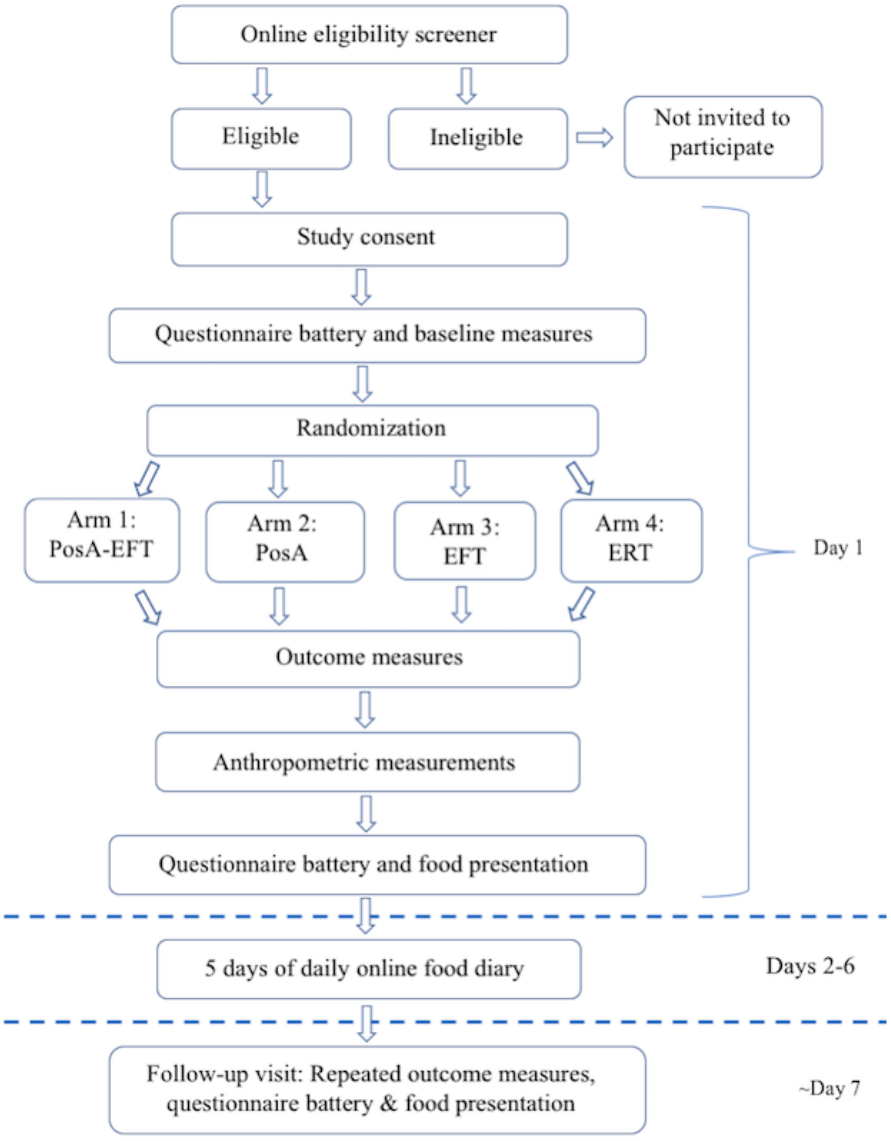
This study is a factorial, randomized, controlled pilot study that employs a 2 (PosA imagery: positive, neutral) by 2 (EFT: yes, no) design in which participants are randomized to 1 of the 4 arms. Figure 1 shows the flow diagram depicting the experimental design. The 4 intervention arms are listed below:

1. Arm 1: PosA-EFT
2. Arm 2: PosA and *no* EFT
3. Arm 3: neutral affect and EFT
4. Arm 4: neutral affect and *no* EFT (ERT control condition)

Sample Size

The target sample size of 156 participants (39 participants per group) is based on 2 prior studies testing EFT interventions. Sze et al [22] found that Web-based training in EFT (vs ERT) reduced TD with an effect size of η^2=0.18. O'Neill et al [23] found that smartphone-delivered training in future (vs recent) episodic thinking impacted food choice by reducing total calorie consumption (η^2=0.28) and percent calories consumed from fat (η^2=0.28). We plan to use a mixed-design analysis of variance (ANOVA) with treatment arm (4 arms) as the between-subject variable and measurement period (baseline, after allocation, and closeout) as the within-subjects variable. As the EFT cue utilized by O'Neill et al was personalized to each participant and was delivered repeatedly via smartphone, and this protocol includes none of those design features (the intervention content is standardized and delivered once), we predict a smaller effect size. To be conservative, we predict the interaction between time and intervention arm variables will yield a standardized effect size of 0.17. Attrition rates commonly observed in brief guided imagery intervention studies are approximately 20% [32,33]. Therefore, we aim to recruit 156 total participants (39 participants per group) to allow for an analytic total sample of 124 participants with 31 participants in each group. This would provide 95% power to detect a statistically significant interaction between intervention arm and measurement period at the .05 level while adjusting for attrition.

Figure 1. Flow diagram of study procedures. PosA: positive affect; EFT: episodic future thinking; ERT: episodic recent thinking.



Participants and Setting

Participants will be recruited from the Charlotte, North Carolina, area community and asked to attend 2 in-person lab sessions separated by 5 days of daily diet tracking. The study will take place in a research lab in the Department of Psychology at the University of North Carolina at Charlotte, with a target recruitment of approximately 50% female. The United States Census Bureau provides estimates about the population characteristics in each state. Our race and ethnicity recruitment targets are derived from the Charlotte, NC 2017 Census [34]. To represent the Charlotte, NC population, we aim to recruit approximately 43% non-Hispanic white, 35% African American, 13% Hispanic or Latino of any race, 6% Asian American, and 3% other race (eg, Native Hawaiian or other Pacific Islander) or 2 or more races.

Study Procedures

Identification

Potential participants will be recruited through postings in classified advertisement websites and on Facebook forums, through flyers posted at community buildings such as libraries and grocery stores, and through recruitment advertisements sent through university listservs reaching students, faculty, and staff. All individuals receiving this recruitment information will be considered potential participants.

Eligibility Assessment

Eligibility will be determined before coming to the lab by a Web-based screening questionnaire delivered via the Qualtrics survey platform. This survey will include basic demographic questions as well as self-reported height and weight (to calculate inclusion body mass index [BMI]) and questions assessing exclusionary medical conditions that could confound dietary choices (see below).

Participants are eligible if they:

1. Are aged between 18 and 63 years. We set the upper age limit at 63 years to limit the potential confounding effect of older age. Older adults may show a greater preference for immediate over delayed rewards [35], and this preference may be stronger among older adults with mild

cognitive impairment [36-38] and Alzheimer disease [37,38]. On the other hand, other studies indicate that older adults may show a greater preference for delayed rewards compared with middle-aged adults [36]. In sum, TD may shift in older individuals as there is potentially less time in the future. Hence, our upper age limit is set at 63 years to minimize this age-related shift.

2. Have a BMI indicative of overweight or obese status (BMI≥25 kg/m^2), measured first through self-report and then verified at the baseline visit with anthropometric measurements.

Participants are ineligible if they:

1. Report any conditions that could affect their food choices (ie, special dietary conditions, including diagnoses of celiac disease or type 1 diabetes; are currently being treated for an eating disorder; have ever had gastric bypass surgery; are allergic to nuts or peanuts; or practice a vegan diet) or responses during the lab tasks.
2. Have any devices (eg, pacemaker) in their body that could be disrupted by the bioimpedance scale measuring body fat percentage.
3. Are currently pregnant.

Consent Procedure

Informed consent for the study will be obtained upon arrival at the study lab in a face-to-face interaction with trained research staff. The research staff will review study information with the participant to ensure good comprehension and understanding and to answer any questions for clarification. A waiver to allow withholding information about several portions of the study procedure during consent was obtained from the ethics board. First, we will not inform the participants that we will be recording their selection of unhealthy and healthy snacks. Disclosure of this portion of the study may bias participants to not select food naturally. Second, we will not be disclosing the BMI inclusion and exclusion criteria, as disclosure could significantly increase the prospective participants' emotional distress as they could learn that they meet criteria for obese or overweight status. Third, we will not disclose inclusion and exclusion dietary health conditions that could impact food choice (eg, gluten intolerance, celiac disease, or type 1 diabetes). Finally, to ensure that participants are blind to intervention condition assignment, the consent form will not disclose the overall factorial design of the study, the number of intervention arms, or the intervention content.

Ethics and Confidentiality

The study has been granted ethical approval by the Health Sciences Research Governance Committee, University of York (December 4, 2017), and the University of North Carolina at Charlotte Institutional Review Board (17-0388; October 6, 2017). A signed copy of the informed consent will be kept by the research staff, and a copy is available to the participants for their records.

Randomization Process and Blinding

All questionnaires and intervention content will be delivered via the Qualtrics Web-based survey platform. After the consent is obtained, randomization will be achieved via the Qualtrics software randomizer function. Upon starting the experimental session on the computer, the Qualtrics survey will randomly deliver 1 of the intervention arms to each participant without any input needed from the researcher, resulting in double blinding. The consent information will only state that the participants will listen to a short recording instructing them to think about physical sensations or future events. There is no information provided in the consent form on the study design, and there is no mention of PosA, EFT, or the number of intervention arms. Therefore, both the researcher and the participant will be unaware of the intervention arm to which the participant is assigned. The Qualtrics randomization procedure will evenly present the 4 intervention arms or guided mental imagery schemes across participants.

Intervention Content

Initial scripts for the interventions were developed and then presented to an advisory panel of professionals who are experts in guided mental imagery stimuli, affect manipulation, future episodic thinking, and eating from the United Kingdom and United States. Guided imagery scripts were also presented to 2 face-to-face community advisory panels, one in the United States and the other in the United Kingdom. The intervention development process is described in detail elsewhere [39].

During the guided imagery including PosA (arm 1 [PosA-EFT intervention] and arm 2 [PosA intervention]), participants will be invited to think of positive feelings and associations surrounding healthy fruits and vegetables. They will be asked to imagine themselves appreciating the healthy food and to bring awareness to the positive aspects of the food, such as its color, feel, smell, taste, and health benefits. Additionally, participants in the PosA-EFT intervention (arm 1) will then be invited to think in detail of a future where they have made healthy food choices. The EFT intervention (arm 3) focuses on future-oriented thinking as described above, but includes no positive emotions surrounding healthy food. Finally, the ERT intervention control (arm 4) asks participants to think about a recent event and aims to rule out potential effects of guided imagery alone on food decision-making and TD and to control for the effort involved in imagining an event at a different time than the present. The interventions will be delivered during the first experimental session (see the Experimental Sessions section below) using Qualtrics survey software to play the audio recording of the guided imagery for each of the 4 intervention arms.

Quality Assurance of Treatment Delivery

The interventions are audio recordings that the participants will listen to during the first experimental session. Thus, they are standardized across all participants to ensure the consistent delivery of each intervention condition. After the intervention is delivered, 3 questions will be asked that function as intervention manipulation checks. Immediately after the intervention, participants will be asked to describe some of the thoughts that came to their minds while listening to the guided imagery recording. Next, participants will be asked to rate how positive and negative they felt *during the guided imagery* on a scale from 1 ("not at all") to 10 ("extremely"). Participants'

written text responses, describing their thoughts during the intervention, will be blindly coded for the occurrence of PosA, EFT, and recent past episodic thinking.

Training

A large team of approximately 6 research assistants, led by 1 or 2 trained lead research assistants, will implement the experimental procedures. A protocol manual will describe the entire experimental session and include information on how to guide the participant through the questionnaires and body measurements. Each research assistant will be trained multiple times in implementing the protocol. In addition, each assistant's first scheduled participant session, for each time point, will be observed by 1 of the lead research assistants. Finally, follow-up drop-in observations will be scheduled periodically to maintain consistently accurate data collection.

Experimental Sessions

The study protocol includes 2 in-lab experimental sessions separated by approximately 5 days of at-home daily food diary entries (see Table 1). All questionnaires, intervention content, and baseline and outcome measures are delivered via the Qualtrics Web-based survey platform. Participants will be asked to fast for 2 hours before each experimental session, and all sessions will be scheduled after 10:00 am.

During the first experimental session, the participants will complete a battery of questionnaires, a baseline TD task, and a baseline food demand task (see the Primary Outcome Measures section below). Then, they will be randomly assigned to receive 1 of the 4 guided imagery intervention arms followed by manipulation check questions. Next, they will complete the TD and food demand tasks again, after which they will be offered a variety of snack foods to assess food choice. Food items will be placed next to the participants while a research assistant reads a standardized food choice script. At the end of the session, the participants' anthropometric measurements will be taken, they will be scheduled for the second experimental session, and they will be instructed on when and how to complete the daily food diaries. The duration of the first session will be approximately 90 min, and each daily food diary entry will take approximately 5 min to complete. During the second experimental session, participants will complete the TD and food demand tasks again. They will be asked to complete another battery of questionnaires while they are again presented with a variety of snacks to eat, to assess their food choices a second time. The duration of the second session will be approximately 40 min. The schedule of enrollment, interventions, and assessments for the study is shown in Table 1.

Reimbursements

Participants will receive US $10 for completing the first experimental session, US $5 for completing at least 3 of the 5 food diaries, and another US $10 for completing the second experimental session, to compensate for potential participation-related expenses. Participants who do not complete all parts of the study (eg, they do not return for the second session) will only be reimbursed for the parts of the study they completed. Participants who complete all parts of the study will also be entered in a random drawing for a chance to win 1 of the 2 Target gift cards worth US $100.

Table 1. SPIRIT Figure**:** Schedule of enrollment, intervention, and assessments.

Time point	Study period							
	Recruitment	Enrollment and allocation	Postallocation daily food surveys					Close out
	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6
Enrollment								
Eligibility screen	X	—[a]	—	—	—	—	—	—
Informed consent	—	X	—	—	—	—	—	—
Allocation	—	X	—	—	—	—	—	—
Interventions								
Positive affect and episodic future thinking	—	X	—	—	—	—	—	X
Positive affect	—	X	—	—	—	—	—	X
Episodic future thinking	—	X	—	—	—	—	—	X
Neutral affect and episodic recent thinking	—	X	—	—	—	—	—	X
Assessments								
Baseline: TD[b]	—	X	—	—	—	—	—	—
Baseline: Food demand	—	X	—	—	—	—	—	—
Outcome: TD	—	X	—	—	—	—	—	X
Outcome: Food demand	—	X	—	—	—	—	—	X
Outcome: Food choice	—	X	—	—	—	—	—	X
Outcome: Daily food surveys	—		X	X	X	X	X	—
Assessments before allocation[c]	—	X	—	—	—	—	—	—
Assessments after allocation[d]	—	X	—	—	—	—	—	—
Assessments at close out[e]	—		—	—	—	—	—	X
Repeated assessments (before allocation and at close out)[f]	—	X	—	—	—	—	—	X

[a]—: not applicable.

[b]TD: temporal discounting.

[c]Assessments before allocation: food frequency, reward-based eating, health-specific self-efficacy, weight related eating, health locus of control, perceived stress reactivity.

[d]Assessments after allocation: emotion regulation, trait mindfulness, behavioral motivations, impulsiveness, mental health history, physical health history, demographics.

[e]Assessments at closeout: global self-reported health, self-reported weight status, social desirability, coping responses, tobacco and alcohol use, sleep quality, loneliness, psychological flexibility.

[f]Repeated assessments (before allocation and at closeout): stages of change in weight management; *Covariate measures included in analyses*: perceived stress, positive and negative affect, and depressive symptoms."

Primary Outcome Measures

Temporal Discounting

The minute monetary TD task will be given at baseline, after allocation, and at closeout to assess TD. During the minute monetary TD task, participants answer 5 questions about their preference to receive specific monetary rewards over time (now vs later). Across consecutive trials, participants are presented with a fixed set of choices between smaller, immediate rewards and larger, delayed rewards (US $1000 in 3 weeks or US $500 now) with the temporal distance being adjusted at each trial (now, 4 days, 1 week, 3 months, and 2 years). The 5 questions are taken from a list of 64-item pairs with differential money and time options. The questions adjust based on the participants' prior response to identify their delay discounting rate. For example, the participants select which option they would rather have "US $500 now" or "US $1000 in 3 weeks." If the "US $1000 in 3 weeks" is selected, the next question will feature the same monetary reward at a more distant time (ie, "US $1000 in 1 year"). However, if the "US $500 now" option is selected, the next question will feature the US $1000 reward at a more proximal time (ie, "US $500 now" or "US $1000 in 1 day"). In

this way, the reward amount or time will be titrated to identify the rate (ie, k-value) at which the participant discounts monetary rewards over time. The TD rate will be calculated for each participant and then compared across treatment group as a between-subjects variable and as a within-subjects repeated measure variable, comparing the effect of the treatment (baseline compared with after allocation and at closeout).

Food Demand

The food demand task will be given at baseline, after allocation, and at closeout. It is based on a food purchasing task [37] that assesses the amount participants are willing to pay (ie, reward value) for different quantities of snack foods. Participants will first view photos of different healthy (eg, apple, yogurt, and popcorn) and unhealthy (eg, potato chips, chocolate chip cookies, and candy bar) snack foods that correspond with the real food items they are presented with in the food choice task (see the Food Choice section below). Participants select their most preferred healthy food and their most preferred unhealthy food from the list and answer the questionnaire for each of the 2 food items. These preferred food photos are displayed on the computer during the task so that participants can refer to them when completing the task. The instructions, modified from the study by Epstein et al [40], are available in Multimedia Appendix 1.

Food demand task responses will be used to generate a food demand curve, reflecting the quantitative relationship between demand for food and escalating price. We will calculate the food demand curve for each of the preferred healthy and unhealthy options. Calculating the food demand curve generates 5 indices: (1) food demand breakpoint (ie, the first price at which consumption was 0), (2) intensity of food demand (ie, consumption at the lowest price), (3) elasticity of food demand (ie, sensitivity of snack food consumption to increases in cost), (4) Omax (ie, maximum expenditure for snack food), and (5) Pmax (ie, price at which expenditure was maximized). Calculating the food demand curve for each of the preferred or chosen healthy and unhealthy options will give rise to 10 values (5 indices for each healthy and unhealthy food categories). The primary index of demand will be intensity of food demand, which will be compared across treatment group as a between-subject variable and as a within-subject repeated measure variable, comparing the effect of the treatment (baseline compared with after allocation and at closeout). However, all indices will be calculated to fully describe the demand curve.

Food Choice

Food choice will be assessed by presenting participants with an array of healthy and unhealthy snack options after allocation and at closeout. Participants will be presented with the snack options on a tray, and all items will be presented as pairs (ie, 2 apples, 2 bags of chips, or 2 candy bars) to encourage selection. Participants will be presented with a total of 9 healthy and 9 unhealthy snack options (excluding drink options). Importantly, 2 of each snack option will be presented, so participants will see a total of 18 healthy and 18 unhealthy snack items (36 total snack items). Healthy snack food items have a total calorie count that ranges from 35 to 180 calories per portion. Unhealthy snack food items have a total calorie count that ranges from 230 to 330 calories per portion. An attempt was also made to match items categorically, for example, an unhealthy option such as potato chips will be provided along with a healthy option such as low-calorie popcorn and rice puffs. The snack items will be arranged neatly on the tray and will resemble the snack tray that is sometimes presented to guests in a hotel room. Alongside the tray, participants will be presented with accompanying unhealthy (soda) or healthy (water) drink choices. As with the snack, 2 of each drink option will be available.

Research assistants will describe the availability of the snack options in the context of the requirement that participants fast before the study appointment. This approach is expected to reduce potential participant bias that could occur if participants are aware their food choices will be recorded. The following is a section of the script that research assistants will deliver at this time:

> *In our lab, we always ask participants not to eat or drink anything before coming into the lab to make sure that differences in how hungry you are or the time since your last meal doesn't affect your choices on the tasks or your preferences. We know it can be hard to fast and since we ask participants to not eat for two hours before coming in, we like to give people a range of snacks to eat.*

Participants will then be encouraged to select any snack option to eat during the session (while completing the final batch of questionnaires) or take the food(s) with them to eat later at their leisure. The research assistant will then leave the participant alone with the snack options while they complete the remaining questionnaire items. All food choices will be recorded by the research assistant after the participant departs. The recorded number of healthy and unhealthy snacks will be summed, respectively, to create *healthy food choice* and *unhealthy food choice* variables for each participant. These variables will be compared across treatment group as a between-subject variable and as a within-subject repeated measure variable, comparing the effect of the treatment (baseline compared with after allocation and at closeout).

Daily Food Diaries

To assess food choice during the 5 days between allocation and closeout, participants will be sent, by email, a link to complete a daily Web-based food diary. This questionnaire is based on the Paffenbarger Physical Activity Questionnaire Dietary Habits subscale [41] and other food frequency questionnaires. Participants will be asked to complete the survey at the end of the day when they do not plan on eating anything afterward. The survey will first ask the participants to briefly describe and/or list the food items or meals they ate that day. Then, participants will be asked to report the number of servings they ate that day for different food categories. The food categories will include fruits; vegetables; grains; eggs; milk and cream; dairy (not including milk); poultry; fish and seafood; beef, pork, lamb, and other red meat; nuts, seeds, and legumes; fats and oils; sweets and desserts (not including candy); candy; salty snacks; drinks; and other foods. For each food category, several examples will be provided to describe what equates to 1 serving of that category. The reported number of daily servings for each

of the food categories will be averaged to create a measure of outside-the-lab food intake. For analysis, outside-the-lab food intake will be compared across treatment groups to assess the impact of the intervention arm on outside-the-lab food choices.

Demographic and Anthropometric Measures

Demographic Information

Participants will self-report their age and biological sex (0=male, 1=female). They will also report their relationship status, education, and income group that best represents themselves from preselected options. Finally, they will be asked to report their racial and ethnic identity by indicating if they identify as Hispanic or Latino and select the racial group that best represents themselves from preselected options.

Anthropometric Measurements

During the first experimental session, height will be measured with a stadiometer and weight will be assessed with an electronic weight scale. Recorded height and weight will be used to confirm the participant's self-reported height and weight on the screening questionnaire. Waist circumference will be measured with a tape measure. Body fat percentage will be assessed with an Omron bioimpedance scale. Blood pressure will be measured with an aneroid sphygmomanometer, Omron blood pressure monitor. Three successive arterial blood pressure readings will be taken on the participant's left arm, with a 2-min interval between each reading.

Covariates

Covariates thought to impact eating behavior will be assessed before allocation and 1 week later at closeout. Covariate measures are indicated in Table 1 in footnote f.

Perceived Stress

To control for the impact of stress on eating behaviors, we will measure self-reported perceived stress using the 14-item Perceived Stress Scale (PSS) [42]. The PSS assesses the extent to which situations in one's life are appraised as stressful during the past month on a 5-point Likert scale (0=never, 4=very often).

Positive and Negative Affect

We will use the 10-item Positive and Negative Affect Scale (PANAS) [43] to control for the impact of dispositional affect on eating behaviors. The PANAS assesses the extent to which the individual felt positive or negative emotions in the past month. Participants rate their affect using a 5-point Likert scale ranging from very slightly or none at all to extremely. During the second experimental lab session, this questionnaire will be administered again, but instead ask about affect in the past week.

Depressive Symptoms

We will control for the impact of depression symptomatology on eating behavior by measuring depressive symptoms with the 10-item Center for Epidemiology Studies of Depression scale (CESD-10) [44]. The CESD-10 assesses mood symptoms during the past 7 days using a 4-point Likert scale.

Exploratory Measures

Several exploratory measures will be included in the study to determine if group assignment or our primary outcome measures are associated with psychological, behavioral, and emotional health constructs. Participants will complete a distinct set of exploratory assessments before allocation, after allocation, and at closeout (Table 1). Trait exploratory measures that are less likely to be impacted by the intervention content will be distributed after allocation and at closeout to also serve the practical design purpose of providing a consistent setting during which the participant is presented with the array of snacks that comprise the food choice measure. The description of each exploratory measure is provided in Multimedia Appendix 1.

Analysis

Primary Statistical Analysis

Our primary statistical analyses will comprise a mixed design (between-subjects and repeated measure) that compares TD, food demand, and food choice measures at baseline, after allocation, and at closeout across treatment arms. Our analyses will control for standard demographic variables such as age, biological sex, race, and income. A series of repeated measure ANOVAs with treatment arm as a between-subject variable and measurement period as the repeated measure will be conducted on TD rates and healthy and unhealthy food demand indices, respectively.

In addition, to examine the effect of the intervention arms on food choices inside and outside the lab, a series of ANOVAs will be conducted on healthy and unhealthy snack food choices and average daily serving intake values for each of the food categories. To probe the effect of the intervention on in-lab food choices, we will conduct a repeated measure ANOVA with measurement period repeated across treatment group on health and unhealthy snack food choices. Next, to probe the effect of the intervention on food choices outside the lab, we will conduct a 1-way ANOVA with treatment arm entered as the between-subject variable on average daily serving intake values for the primary food categories (ie, fruit and vegetable intake).

Secondary Statistical Analyses

In exploratory analyses, we will examine correlations between summary scores on the exploratory questionnaire measures and outcome measures of TD, food demand, and food choice, to explore potential relationships between self-report and primary outcomes. For example, we plan to examine whether there is an association between change in primary outcome measures (from baseline to post allocation), physical activity, smoking, and alcohol use, to examine how these health behaviors influence the efficacy of the intervention. We also anticipate examining the association between trait mindfulness and changes in outcome measures, to determine if trait mindfulness influences intervention efficacy. In another potential exploratory analysis, we will test the association between trait impulsivity and changes in TD over the course of the study, to determine if high trait impulsivity is associated with greater stability in TD over time. These, and other analyses, will be used to explore the extension of the intervention to other health behaviors and

for the development of future research questions and interventions.

Results

Recruitment started on February 19, 2018, to begin feasibility testing of the protocol. Feasibility testing started on February 21, 2018, and continued through April 18, 2018, during which 20.5% (32/156) of the final sample was run through the protocol. As there were no major protocol changes required at the end of the feasibility phase, these 32 participants were included in the target sample of 156 participants. Recruitment, therefore, continued immediately after the feasibility phase. At the time this manuscript was submitted, participants are actively being recruited into this study, and 84 participants have completed the protocol. Recruitment is estimated to last approximately 10 months.

Discussion

Findings and Implications

The overall goal of this research is to develop novel, theory-based interventions to promote and improve healthy decision-making and behaviors. In this study, we focus on eating behaviors and test the overarching hypothesis that guided imagery interventions targeting PosA will increase the rewarding value of healthy foods, indexed by food choice and food demand, and guided imagery targeting EFT will increase regulation, indexed by TD. We predict a novel, synergistic effect between PosA associations toward healthy foods and positive EFT. Both mechanisms have different underlying neurological pathways, and their interactive effect has not been tested to date. Furthermore, we will test these interventions among individuals who are overweight or obese and may show the most benefit from the intervention because of a hypothesized overactive neural system of reward and underactive neural system of regulation. Thus, the findings will advance health behavior decision-making research. Moreover, given that the synthesis of affective and cognitive pathways is novel, the expected findings have the potential to generate new neuroscience and psychological research to further understand these mechanisms and their interactions.

Although the findings from this project will address basic mechanisms in the context of eating behavior, the effect of affective associations and future thinking likely translates across different health behaviors (eg, physical activity, substance use, and sun protection). Thus, developing brief manipulations of these 2 mechanisms (ie, PosA and positive EFT) holds great potential for future translation across multiple health behaviors. Moreover, given that the affective imagery and EFT manipulations are relatively brief and could be easily adapted to Web-based or smartphone app–based interventions, such interventions would be potentially scalable and wide-reaching. In fact, we expect that the findings from this project will directly inform future research targeting the 2 mechanisms (affective associations and future thinking). Moreover, these findings could inform research on existing eating behavior interventions, interventions for other behavioral domains, and interventions that could be Web-based or delivered through mobile phone apps.

Strengths and Limitations

Despite the strengths of this study, some important limitations must be noted. As a pilot study, the sample will be small and will not have the power to examine individual differences in intervention effectiveness. It is also possible that some participants will have difficulty forming PosA associations with healthy food or that the formed positive associations will also extend to nonhealthy foods to increase the overall appeal of food in general. Although we do not expect this to be the case because the PosA-guided imagery stimuli have been designed to focus on the benefits of healthy food, a finding that PosA increases the appeal of food in general would regardless be helpful in designing guided imagery exercises that promote healthful eating. In addition, the guided imagery interventions differ in length—the PosA-EFT intervention arm with both PosA content and EFT content is longer than the other intervention arms as it needs to disseminate more content. It is possible that the difference in length across the intervention arms could affect the outcome measures; however, this confounder was preferable to shortening and potentially decreasing the efficacy of the PosA and future episodic content to match the lengths of the other intervention arms. Future research will be needed to test what guided imagery length is optimal.

With regard to the food choice outcome measure, it is also possible that participants may expect that their food choice is being recorded and they may monitor or alter their food choice to be in line with perceived expectations. Although we have designed our task instructions to mitigate this confounder, it is possible that biases in expectation may still exist as overweight and obese participants may feel that their food choices are being observed in any public setting. If so, the expectation bias may occur regardless of intervention arm; nevertheless, it is important to acknowledge that participants may not be making food choices in the lab as freely as they do in nonpublic settings. In addition, it is possible that our recruitment methods may affect our findings. Although we will recruit through university-based and community-based channels, we will not recruit through any weight loss–associated channels, which could affect our findings. Another limitation of this protocol is that we will not be able to stratify our randomization by biological sex; this will be an important limitation to address in future work.

Conclusions

Despite these limitations, findings from this study have the potential to advance decision making, reward learning, and affective-cognition research as well as form the basis for potentially large-scale brief interventions that have the capacity to impact a range of health behaviors (eg, healthy eating, physical activity, substance use, and sun protection). Accordingly, findings will be disseminated at both basic and applied science conferences. In addition, the affective imagery and EFT manipulations are relatively brief and could be easily adapted to Web-based or mobile phone app–based interventions. If this study supports our hypothesis, then in the future, we will explore the feasibility, effectiveness, cost-effectiveness, and

scalability of developing stand-alone and add-on interventions that manipulate PosA and EFT to promote healthy behavior.

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Authors' Contributions

SML, LEM, EMT, NAC, ASB, APK, and NDM conceptualized the study. SML, LEM, EMT, NAC, ASB, APK, and NDM helped develop the intervention conditions being tested in this protocol. SML, SJS-H, and MP developed the data collection protocol. SML, SJS-H, MP, and LEM wrote the manuscript with critical edits from EMT, NAC, ASB, APK, and NDM.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Food demand instructions given to participants and description of all exploratory measures included in the study.

[PDF File (Adobe PDF File), 24KB - resprot_v8i3e12265_fig1.png]

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Abbreviations

ANOVA: analysis of variance
BMI: body mass index
CESD: Center for Epidemiology Studies of Depression
EFT: episodic future thinking
ERT: episodic recent thinking
PANAS: Positive and Negative Affect Scale
PosA: positive affect
PSS: Perceived Stress Scale
TD: temporal discounting

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Original Paper

A Smartphone App to Promote Healthy Weight Gain, Diet, and Physical Activity During Pregnancy (HealthyMoms): Protocol for a Randomized Controlled Trial

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Abstract

Background: Excessive gestational weight gain is common and associated with adverse outcomes both in the short and long term. Although traditional lifestyle-based interventions have shown to mitigate excess gestational weight gain, little is known about whether mobile Health (mHealth) apps can promote healthy weight gain, diet, and physical activity during pregnancy.

Objective: The primary aim of the HealthyMoms trial is to determine the effectiveness of a smartphone app (HealthyMoms) for mitigating excess gestational weight gain during pregnancy. Secondary aims are to determine the effectiveness of the app on dietary habits, physical activity, body fatness, and glycemia during pregnancy.

Methods: HealthyMoms is a two-arm randomized controlled trial. Women are being recruited at routine visits at the maternity clinics in Linköping, Norrköping and Motala, Sweden. Women are randomized to the control or intervention group (n=150 per group). All women will receive standard care, and women in the intervention group will also receive the HealthyMoms smartphone app.

Results: Recruitment of participants to the trial was initiated in October 2017, and 190 women have so far completed the baseline measurement. The baseline measures are estimated to be finalized in December 2019, and the follow-up measures are estimated to be completed in June 2020.

Conclusions: This project will evaluate a novel smartphone app intervention integrated with existing maternity health care. If successful, it has great potential to be implemented nationally in order to promote healthy weight gain and health behaviors during pregnancy.

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KEYWORDS

telemedicine; pregnancy; gestational weight gain; diet; exercise; smartphone; mobile phone

Introduction

Background

Studies from developed countries including Sweden report that almost half of all pregnant women exceed the Institute of Medicine's recommendations for gestational weight gain [1-3]. This is concerning because excess gestational weight gain is associated with negative outcomes for maternal and child health both in the short term (eg, gestational diabetes, preeclampsia, large for gestational age infants, and cesarean delivery) and long term (postpartum weight retention and obesity in the offspring) [1,2,4-6]. Thus, prevention of excess gestational weight gain is a public health priority. A 2015 Cochrane review concluded that diet, exercise, or both interventions reduced the risk of excess gestational weight gain by 20% [7]. These results are promising and suggest that lifestyle-based interventions can mitigate excess gestational weight gain during pregnancy. Notwithstanding these positive findings, previous studies have used traditional face-to-face education by means of individual or group counselling with heavy reliance on intensive support from clinical providers, which limits the scalability of these programs [7]. Considering the potential public health benefits, it is important to develop interventions that can reach a large proportion of the target group.

In the past 5-10 years, there has been a large increase in research on the use of mobile phones (including smartphones) for delivering behavior change interventions. The benefits of such mobile health (mHealth) programs are that they can be delivered anywhere at any time, they are interactive, and they can be tailored to meet people's needs. Several reviews have concluded that mHealth programs may be effective for achieving changes in behavior and weight loss [8,9]; mHealth interventions may therefore also be effective in promoting a healthy lifestyle and gestational weight gain in pregnant women [10]. Additionally, mHealth offers a potential solution to provide support for pregnant women, in general, since mobile phones are commonly accessible, irrespective of socioeconomic status [10]. However, to date, mHealth interventions to promote healthy gestational weight gain in healthy pregnant women are scarce [11]. Therefore, further studies are warranted to determine the utility of mHealth for mitigating gestational weight gain during pregnancy.

Aim

This paper reports the study design and methods of the HealthyMoms trial (trial registration: ClinicalTrials.gov NCT03298555). The primary aim of the HealthyMoms trial is to determine the effectiveness of a smartphone app (HealthyMoms) for mitigating excess gestational weight gain during pregnancy. Secondary aims are to determine the effectiveness of the app on dietary habits, physical activity, body fatness, and glycemia during pregnancy.

Methods

Study Design

The HealthyMoms trial is a two-arm parallel randomized controlled trial. The intervention group will receive standard care plus the HealthyMoms app (a 6-month program delivered through their smartphones). Participants in the control group will receive standard antenatal care provided by the maternity health care system. The study will be conducted and described according to the Standard Protocol Items: Recommendations for Interventional Trials 2013 statement [12] and the CONSORT-EHEALTH checklist [13]. The outline of the HealthyMoms trial is presented in Figure 1. The baseline measurements and randomization are conducted in gestational week 14, and the intervention will be initiated in gestational week 15. Measurements after the intervention will be conducted in gestational week 37.

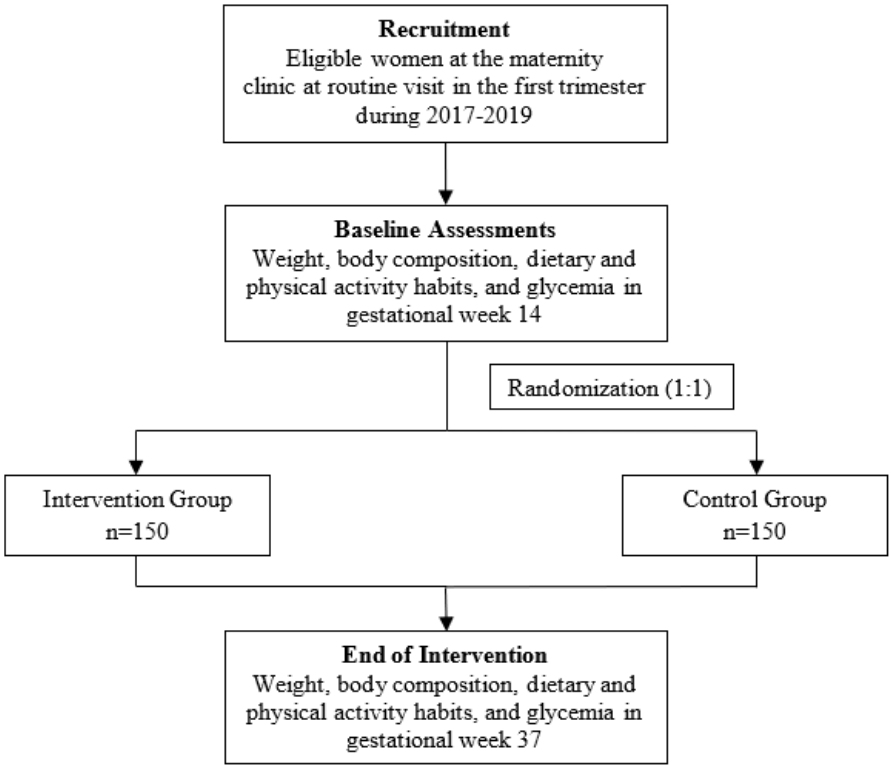
Eligibility and Recruitment

Eligible pregnant women are identified at the routine visits in the first trimester at the maternity clinics in Linköping, Norrköping, and Motala in Sweden. Inclusion criteria are a single pregnancy, age of 18 years or above, and ability to speak and read Swedish sufficiently well in order to understand the content of the HealthyMoms app and provide informed consent. Exclusion criteria are previously diagnosed eating disorder, pre-pregnancy diabetes, other medical conditions, or pharmacological treatments prior to pregnancy that may affect body weight.

Randomization and Blinding

Following baseline measurement, participants will be randomly allocated to either the intervention or control group in a 1:1 ratio using restricted randomization (with a block size of 2) generated using STATA (version 13; StataCorp, College Station, TX) by a statistician. Opaque envelopes will be used for allocating participants to the respective groups, ensuring allocation concealment. Due to the nature of the intervention, participants will not be blinded to their allocation.

Figure 1. Study design of the HealthyMoms trial.



Intervention

Overall

The HealthyMoms app is a comprehensive 6-month program aimed at mitigating excess gestational weight gain by promoting a healthy diet and physical activity. A screenshot of the HealthyMoms app is shown in Figure 2. The app is Android and IOS compatible. Participants who are allocated to the intervention group will receive a text message with a link to a website, which they can access through their phone. Using the website, participants will be instructed to register and download the app from Google Play or App Store.

Development

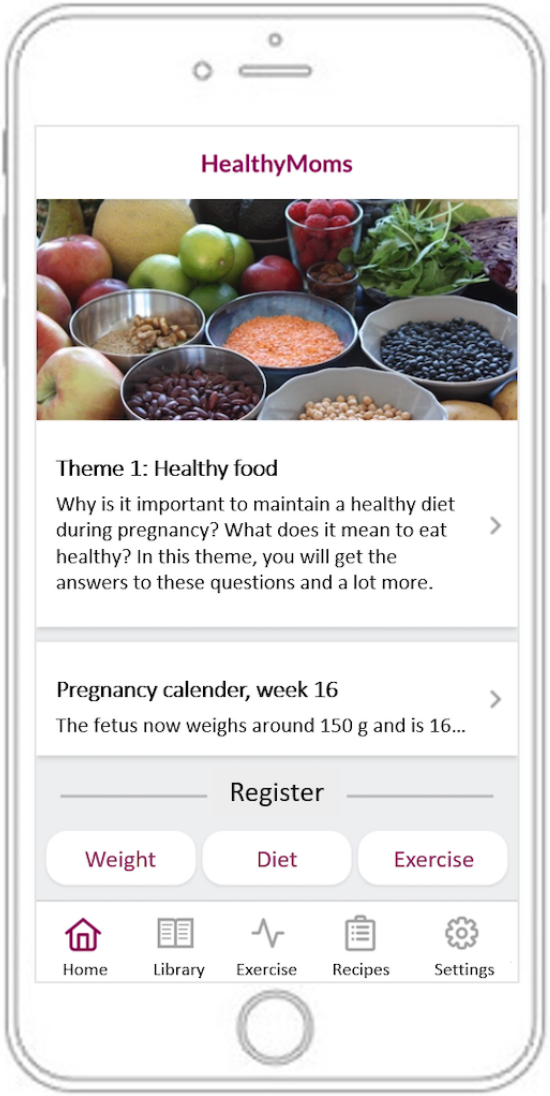
The HealthyMoms app utilizes the same platform (ScientificMed Tech AB) [14] and structure as our previously validated app targeting parents with preschool aged children [15]. The specific content and features for the HealthyMoms app were developed by a multidisciplinary team with expertise in nutrition, behavioral science, obstetrics, psychology, physiotherapy, and physical activity. Intervention development was an iterative process, whereby input from target group members and experts as well as behavior change theory (social cognitive theory [16] and behavior change techniques [17]) were considered. Specifically, input on the content and features were discussed in semistructured interviews with pregnant women and women who had recently given birth (n=10). Further, content regarding maternal and fetal development as well as dietary recommendations were reviewed by midwives and relevant experts at the National Food Agency, Sweden. Theory was used to inform the development of the intervention. For example, key behavior change techniques such as shaping knowledge (eg, general information on healthy diet, physical activity, and gestational weight gain), goals and planning (eg, goal setting and identification of barriers), and feedback and monitoring (eg, self-monitoring of behavior and feedback on behavior).

Content and Use

The HealthyMoms app delivers a comprehensive program of information and push notifications based on evidence-based recommendations for a healthy diet [18], physical activity [19], and weight gain [1] in pregnant women. The app consists of seven features: weekly themes; push notifications; self-monitoring and feedback features of gestational weight gain, diet, and physical activity; recipe feature; exercise feature; pregnancy calendar; and app library (eg, frequently asked questions and practical tips).

The program addresses 12 *themes* that change every other week: healthy foods, healthy weight gain during pregnancy, physical activity and exercise during pregnancy, how to change a habit, cravings, fruits and vegetables, nutrition for the mother and baby, the third trimester, the reasons why we eat, exercise at the end of pregnancy, how to keep a new habit, and the time after the delivery. Participants are alerted when a new theme is initiated via a *push notification* every other week. In total, participants receive eight push notifications for every theme (one message every other day and an additional message). These messages consist of, for example, factual information or behavior change guidance, support and guidance on healthy habits (eg, diet and physical activity), weight gain during pregnancy, strategies for behavior change, encouragement, key messages, and reminders.

Figure 2. Screenshot of the HealthyMoms app.



The app includes a *self-monitoring and feedback feature*, whereby diet, physical activity, and weight gain are reported by the user, which is followed by tailored feedback in the form of graphical illustration and text. Self-monitoring of diet involves answering five questions each week on the intake of fruits, vegetables, sweets, and sugary drinks. Participants receive feedback presented in a graph and in text with a "traffic light" (green: reached the recommendation, yellow: almost reached the recommendation, red: far from reaching the recommendation). Self-monitoring of physical activity entails setting a physical activity goal (in activity minutes) and reporting of weekly activity levels. Individual self-monitoring data are summarized graphically, and participants can see if they are close to or if they have met their own goal as well as the recommendation for physical activity (150 minutes/week) each week [19]. The participants also receive feedback in text format and with the "traffic light," as described above. Self-monitoring of weight consists of reporting current weight. The weight gain is presented graphically; from gestational week 22 until the end of pregnancy, a green field is visible, showing the participant's weight gain in relation to their individual recommended gestational weight gain (in accordance with the Institute of Medicine recommendation and calculated from their pre-pregnancy body mass index).

The app also includes an *exercise feature* and *a recipe feature*. The exercise feature includes information, tips, and exercise programs for the different stages of pregnancy in both text and video format. The recipe feature has a library of healthy recipes and weekly menus. The HealthyMoms app also includes a *pregnancy calendar* that is updated every week. It consists of information on fetal and maternal development during pregnancy as well as texts to the partner (eg practical information, encouraging, and supportive texts). Lastly, the app includes a *library* of practical tips, frequently asked questions, and useful links.

Sample Size and Power Considerations

Power for an independent *t* test was calculated *a priori* using G*Power 3.1 [20]. A total of 226 women (113 in each group) completing the measurements after the intervention provides 80% power (α=.05, two-sided), assuming a common SD in gestational weight gain of 4 kg [21] to detect a difference of 1.5 kg between the groups. Given our previous experiences [22], we anticipate that no more than 25% of the women will drop

out of the study or have a child prematurely. Thus, we will recruit 300 women (150 in each group) to participate in the study.

Primary outcome

Gestational Weight Gain

The primary outcome gestational weight gain is calculated as the measured body weight in gestational week 37 minus the measured body weight in gestational week 14. Body weight is recorded using standardized procedures when the participant is wearing only underwear. We will also analyze gestational weight gain as within or above the Institute of Medicine-recommended levels by using the recommended weekly gains in body weight during the second and third trimester [1].

Secondary Outcomes

Dietary Intake

Dietary intake is measured using Riksmaten FLEX [23], adapted to pregnant women. It combines three 24-hour recalls and a food-frequency questionnaire to measure intakes of foods and drinks. Intakes of energy, macronutrients, and micronutrients are calculated through linkage with the amount of foods assessed through Riksmaten FLEX to the food composition database of the National Food Agency of Sweden [24].

Physical Activity and Sedentary Behavior

Physical activity and sedentary behavior are measured objectively over seven consecutive 24-hour periods with a wrist-worn triaxial accelerometer, Actigraph wGT3x-BT (ActiGraph, Pensacola, FL). Wrist-worn accelerometers including the ActiGraph [25] have been validated previously in adults [25,26] and pregnant women [27]. The recorded movements will be processed as previously described [27,28] and converted to time spent on different activity levels (ie, sedentary behavior as well as light, moderate, and vigorous physical activity) using appropriate cutoffs.

Body Fatness

Body fatness is measured using Bod Pod (COSMED, Rome, Italy), as previously described [29]. This method utilizes air-displacement plethysmography to measure body volume. Body density is then calculated using the measured body volume and body weight. Subsequently, body fatness is calculated using the gestational-age specific densities for fat-free mass published by Van Raij et al [30]. These values from fat-free mass density have previously been shown to be suitable for use throughout pregnancy [31-33].

Glycemia, Gestational Diabetes, and Insulin Resistance

A blood sample is drawn after an overnight fast, and glucose, insulin, and lipid profile (triglycerides and high-density and low-density lipoprotein cholesterol) will be analyzed at the Department of Clinical Chemistry, Linköping University Hospital. Furthermore, systolic and diastolic blood pressure will be assessed in a resting state, following standardized procedures. Gestational diabetes is defined according to the International Association of Diabetes and Pregnancy Study Group's cutoff [34]. Furthermore, insulin resistance, as assessed by the HOMA-IR (homeostasis model assessment - insulin resistance) will be calculated according to the study by Matthews et al [35].

Other Measurements

Demographic Information

The women and their partners complete separate demographic questionnaires, which include information regarding age, country of birth, occupation, educational attainment, previous pregnancies, smoking habits, dietary and physical activity habits, overall health, and use of medications.

Physical Fitness and Subjective Physical Activity

Cardiorespiratory fitness is assessed using the 6-minute walk test, which measures the maximum distance (in meters) the woman can walk in 6 minutes back and forth in a 30-m corridor [36]. Participants are instructed to walk as fast as possible during the test, but they are also informed that they may slow down or rest, if necessary. The 6-minute walk test is only conducted at the baseline measurement, whereas all other measures of physical activity and fitness will be conducted both at the baseline measurement and at gestational week 37. Upper body muscular strength is measured using the handgrip strength test, where the woman is asked to squeeze a dynamometer (TKK 5001; Grip-A, Takei, Tokyo, Japan) as hard as she can with her hand for a few seconds [37]. Physical fitness is also assessed subjectively using an adapted version of the international fitness scale, which includes cardiorespiratory fitness, muscular strength, speed and agility, flexibility, and overall fitness using 5-point Likert-scale questions [38]. As a complement to the objective physical activity data, we also collect data of subjective physical activity using two questionnaires: the short-form International Physical Activity Questionnaire, where participants recall their physical activity over the past 7 days [39], and a 7-day modified version of a questionnaire used by Bexelius et al [40].

Maternal and Infant Body Fatness Postpartum

At 1-2 weeks postpartum, maternal body fatness is measured using air-displacement plethysmography (as described above) utilizing suitable postpartum fat-free mass density values [32]. At the same time, infant body composition is measured using air-displacement plethysmography (Pea Pod, COSMED), as described in detail previously [22]. Briefly, body weight and body volume are measured by the Pea Pod. Body fatness is then calculated using the measured body density and appropriate fat-free mass hydration factors [41].

App Usability and Process Evaluation

Participants in the intervention group will complete a questionnaire including questions on their use and perception of the app with regard to usability, design, features, and overall satisfaction. Furthermore, semistructured interviews (audio) will be conducted within a subsample (n=10-20) of women in the intervention group to gain additional insight about their perceptions of the HealthyMoms app. The interviews will be transcribed and analyzed using thematic analysis, as described elsewhere [42].

Statistical Analyses

Imputed data will be continuously checked against source data, and range checks will be implemented. The primary outcome will be gestational weight gain (kilogram). Analyses will be conducted according to the principles of intention-to-treat and per-protocol procedures using independent *t* tests to test whether gestational weight gain is statistically different between the groups. In the intention-to-treat analysis, missing data will be imputed using multiple imputations with chained equations [43]. In the per protocol, patients will be defined as completers if they have gestational weight gain data (body weight measured at baseline and gestational week 37) and if they have downloaded and used the HealthyMoms app at least once. Furthermore, linear regression will be considered to adjust estimates for the pre-pregnancy body mass index group (ie, underweight and normal weight vs overweight and obese), socioeconomic status (university degree vs no university degree), and parity (0 vs ≥1). In this analysis, treatment will be used as a categorical variable, with the control group as the reference. This model will also be extended to include interactions (one at a time) of the treatment with the pre-pregnancy body mass index, socioeconomic status, and parity, since we want to investigate whether the effect of the intervention differs depending on these factors. In a sensitivity analysis, we will also exclude women diagnosed with gestational diabetes and pre-eclampsia before the follow-up measurement, since these women may have received intensive diet/physical activity support or medication or may have edema, all of which may influence the outcome variables (eg, body weight, diet, physical activity, and glycemia).

Ethical Approval

The HealthyMoms trial was approved by the Regional Ethical Review Board in Linköping, Sweden on April 24, 2017 (DNR: 2017/112-31), with an amendment on May 4, 2018 (DNR: 2018/262-32). All women will provide written informed consent before entering the study. The mother and father/partner will provide informed written consent before any measurements of their infant are performed.

Results

The HealthyMoms app was finalized in September 2017. Recruitment of participants to the trial was initiated in October 2017, and 190 women have so far completed the baseline measurement. The baseline measurements are estimated to be finalized in December 2019, whereas the follow-up of the mothers and infants is estimated to be completed in June 2020.

Discussion

The HealthyMoms trial will examine whether a novel mHealth app can mitigate excess gestational weight gain and promote healthy dietary habits, physical activity, healthy levels of body fatness, and normal glycemia. The trial has several strengths including the objective and accurate methodology to measure physical activity and body composition, close collaboration with existing maternity health care services, and a large sample size. The latter represents a distinct strength, considering that previous studies that have investigated the effect of a mHealth app on gestational weight gain have been relatively small pilot studies, although some have shown promising results. For instance, in a study of 100 overweight and obese Australian women, Wilcox et al [44] found that women in the intervention group had significantly lower gestational weight gain than women in the control group. Similarly, in a trial of 54 overweight/obese American women, Redman et al [45] found lower gestational weight gain in those receiving an intensive intervention delivered in-person or via smartphone as compared to those receiving usual care [45]. However, Chao et al [46] did not find any effect of a telemedicine intervention on gestational weight gain in 41 American women with overweight or obesity. Hence, the HealthyMoms trial will make an important contribution to the existing literature, considering the study size and that normal weight women are included in the study. This is important because excessive gestational weight gain is common among women having normal weight before pregnancy [1,3]. Finally, the intervention content is grounded in the social cognitive theory [16] and uses well-recognized behavior change techniques [17].

The HealthyMoms trial also has several limitations. First, although all eligible women are approached to enter the study, it is possible that an overrepresentation of highly educated, health conscious, and normal-weight women enter the trial. However, we will also examine whether there are any differences in the effect of the intervention in terms of maternal pre-pregnancy body mass index, educational attainment, and parity. Second, due to the time and budget constraints, we did not individually tailor push notifications; however, women have an individually tailored weight gain chart depending on their pre-pregnancy body mass index. Third, due to the thorough baseline measurement and to ensure that most women would be able to participate in the trial, women will receive the HealthyMoms app in gestational week 15. However, if the app is proven effective, an earlier introduction in pregnancy should be considered when fully implementing the app as a supportive tool in maternity health care. Finally, women need to be able to speak and read Swedish sufficiently well to understand the content of the HealthyMoms app in order to be eligible for participation. Hence, we aim to translate and modify the HealthyMoms app in order to make it widely accessible.

Excessive gestational weight gain is a major public health issue globally [1,2] and in Sweden [3], and it is associated with adverse outcomes both during pregnancy as well as later in life [1,2,4-6]. If effective, the HealthyMoms app has potential to be implemented in maternity clinics nationally and offer an evidence-based intervention program to women at relatively low costs. This is of particular importance, given the ubiquity of mobile phone ownership, irrespective of socioeconomic status [10].

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Authors' Contributions

ML, RM, PH, MB, and YTL have contributed to the study design. ML is the principal investigator and responsible for the study. JS is responsible for data collection under the supervision of PH and ML. MB, CA, KS, HH, MHL, JS, PH, and ML developed the app content. JHM is responsible for the accelerometer protocol and data processing. LW contributed to the study size dimension and randomization and is responsible for statistical analyses. KT contributed with her expertise in behavior change techniques. PH, JS, and ML drafted the manuscript, which was critically reviewed by all authors. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report 1.

[PDF File (Adobe PDF File), 82KB - resprot_v8i3e13011_app1.pdf]

Multimedia Appendix 2

Peer-reviewer report 2.

[PDF File (Adobe PDF File), 104KB - resprot_v8i3e13011_app2.pdf]

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Abbreviations

HOMA-IR: homeostasis model assessment - insulin resistance
mHealth: mobile health

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Protocol

Healthy Eating and Active Living for Diabetes-Glycemic Index (HEALD-GI): Protocol for a Pragmatic Randomized Controlled Trial

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Abstract

Background: Rigorous evidence is needed regarding the best approach for increasing the uptake of Diabetes Canada's evidence-based recommendations to include low-glycemic index (GI) foods in daily meal planning as an effective dietary self-care strategy for glycemic control among people with type 2 diabetes (T2D).

Objective: This study aims to present the study design and baseline data from the Healthy Eating and Active Living for Diabetes-Glycemic Index (HEALD-GI) trial, which was designed to evaluate the effectiveness of an enhanced GI-targeted nutrition education on GI-related knowledge and mean daily GI among adults with T2D in Edmonton, Alberta.

Methods: We used a pragmatic randomized controlled trial design and allocated 67 adults (aged ≥18 years) with T2D living in Edmonton, Alberta, Canada, to a control group that received standard printed copies of Canada's Food Guide and Diabetes Canada's GI resources or to an intervention group that received the same materials, plus a customized Web-based platform with 6 self-directed learning modules and print material. Each module included videos, links to reliable websites, chat rooms, and quizzes. Evidence-based GI concept information included GI values of foods and low-GI shopping, recipes, and cooking tips by a registered dietitian. In addition, support through email, text messaging (short message service), phone calls, or postal mail was provided to reinforce participants' learning. The primary outcome, average dietary GI, was assessed using 3-day food records. Additional measures including GI knowledge and self-efficacy, glycated hemoglobin (HbA_{1c}), lipids, systolic blood pressure, body mass index (BMI; weight, height), waist circumference, and computer proficiency were assessed at baseline and at 3-month postintervention.

Results: Between November 2017 and February 2018, we contacted adults (aged ≥18 years) with T2D living in Edmonton, Alberta, screened and recruited eligible participants into the study. All data collection ended in June 2018. Overall, 64% (43/67) participants were males; mean age was 69.5 (SD 9.3) years, with a mean diabetes duration of 19.0 (SD 13.7) years. Mean BMI was 30.1 (SD 5.7) kg/m^2, and mean HbA_{1c} value was 7.1% (SD 1.2%). Data analysis was completed in December 2018.

Conclusions: The GI concept is often difficult to teach. The HEALD-GI study aims to provide evidence in support of an alternative approach to translating the GI concept to adults with T2D. Findings from this study may help registered dietitians to better disseminate low-GI dietary recommendations using efficient and cost-effective, patient-centered approaches. Furthermore, evidence generated will contribute to addressing some of the controversies regarding the clinical usefulness of the GI concept.

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KEYWORDS

glycemic index; randomized controlled trial; type 2 diabetes mellitus

Introduction

Increasing prevalence of type 2 diabetes (T2D) remains a major public health challenge with adverse effects for individuals and health care systems globally. Currently, diabetes affects approximately 7.3% of Canadians, and the prevalence has been projected to rise to about 10% by 2020 [1]. Health outcomes for individuals with diabetes, however, largely depend on their ability to self-manage the disease. Lifestyle interventions including healthy eating, physical activity, and smoking cessation, which enhance the acquisition of knowledge, skills, resources, and support to boost self-efficacy for day-to-day living, are, therefore, important for T2D management and prevention of long-term complications [2,3].

Healthy eating remains a key strategy for diabetes self-management, and dietary carbohydrates constitute one aspect of the diet with significant influence on blood glucose control. Different types and quantities of carbohydrates have been shown to impact blood glucose concentration differently [4,5]. This property of foods, referred to as glycemic index (GI), is used to rank how quickly a given dietary carbohydrate raises blood glucose concentration immediately following a meal [4]. Using GI and the portion size of a given food, glycemic load (GL), a composite measure of carbohydrate quality and quantity, can be calculated to predict blood glucose response to a specific type and amount of a dietary carbohydrate [6]. Consuming low-GI foods is beneficial for metabolic control in diabetes management [7]. Adopting a low-GI dietary pattern as part of a healthy eating lifestyle has been shown to markedly reduce cardiovascular risk factors (eg, total cholesterol, high-density lipoprotein); improve glycemic control, postprandial glycemia, and beta cell function; and decrease the need for antihyperglycemic agents among patients with diabetes [8-18]. Outlining effective approaches to promoting the concept of low-GI intake among individuals with T2D has been problematic. Hence, examining effective modes of delivery is necessary to support one aspect of T2D.

Effective and widespread use of information technologies (ITs), including the internet and mobile-based tools, is revolutionizing the traditional approaches for engaging, educating, and empowering individuals with chronic diseases such as diabetes [19,20]. Increasing use of IT by diverse audiences, occasioned by low-cost Web- and mobile-based tools may, therefore, offer viable prospects for promoting swift and cost-effective GI concept education and support among people with T2D. Features of modern IT tools such as websites, chat rooms, social networking sites (eg, Facebook), and short message service (SMS) text messaging apps allow creation and exchange of health-promoting information and enable individuals to interact with other users who share connections with them [21,22]. Properly designed and managed websites can serve as credible sources of evidence-based GI-targeted messages. Websites enable integration and presentation of text, graphics, or audiovisuals on one platform, while chat rooms and emails facilitate engagement between users and health professionals in addressing pertinent issues [23]. Furthermore, chat rooms provide Web-based social forums for peer group discussions, exchange of ideas, encouragement, and support [24,25].

Knowledge gaps exist between GI concept clinical guidelines and their translation to adults with T2D in Canada due to debates over clinical utility of GI, inconsistencies in teaching the GI concept by registered dietitians [26,27], and limited patient-dietitian interactions [28]; these limit patients' knowledge and skills for uptake of GI dietary behavior. Patients lose out on the additional benefits of improving carbohydrate quality by consuming healthy, low-GI foods as part of healthy eating strategy for diabetes self-management. Hence, this study aims to examine the effectiveness of Web-based, GI-targeted nutrition education on dietary behavior and intakes among adults with T2D. We hypothesize that after 3 months, adults with T2D who were randomized to receive Web-based, GI-targeted nutrition education will consume a lower-GI diet and show improved glycemic control compared with a control group. Findings from this study will help determine whether, and how, current approaches to disseminating dietary recommendations pertaining to GI concept could be improved for better uptake using alternative, efficient, and cost-effective patient-centered approaches to nutrition self-care. Furthermore, the outcomes of this study will add to the body of evidence regarding the GI concept.

Methods

Study Design: Setting, Recruitment, Ethical Considerations, and Intervention

Setting and Population

Adults (aged ≥18 years) living in Edmonton, Alberta, Canada, with T2D and currently enrolled in the Alberta's Caring for Diabetes (ABCD) cohort study [29] constituted the target population for this study. The ABCD cohort study [29] was designed to explore different aspects of diabetes care and the development of complications among individuals with T2D in Alberta. The ABCD cohort enrolled 2040 participants between 2012 and 2013 from all over the province of Alberta at inception and provided a suitable eligible population from which to draw participants for this intervention. The characteristics of the ABCD cohort have been reported elsewhere [29].

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: individuals aged ≥18 years identified as having T2D and currently enrolled in the ABCD cohort study; able to read, understand, and converse in English; and willing to provide informed consent. For practical considerations, we prescreened all cohort participants living in Edmonton for enrollment in the intervention. Based on postal codes, 745 cohort participants who participated in the year 1 ABCD survey lived in Edmonton. However, due to relocation and mortality-related attrition, we invited only 485 ABCD cohort participants living in Edmonton between July 2017 and October 2017 to participate. Those who responded were screened for

eligibility and subsequent recruitment into the study between November 2017 and February 2018. Those taking exogenous insulin and having physiological or medical conditions that interfere with usual digestive functions were excluded.

Participants Screening Procedures

We sent letters explaining details of the study to all eligible participants, asking them to contact the study staff if they were interested in participating in this study. We performed detailed prescreening over the phone to determine full eligibility once we received responses from those invited to participate. A maximum of 2 telephone contacts were made to remind eligible individuals who did not contact the research staff after 2 weeks of expressing their interest in participating in the study. We invited eligible participants to complete baseline anthropometry, biochemical, clinical, and dietary data collection at the Human Nutrition Research Unit located within the Alberta Diabetes Institute at the University of Alberta. A trained dietitian and registered nurse with data collection experience collected anthropometric data and relevant clinical measures using point-of-care instruments (DCA Vantage, Cholestech LDX, and BPTru).

Ethical Considerations

The University of Alberta and Athabasca University Health Research Ethics Boards reviewed and approved the study protocol. In line with research ethics requirements, all participants received adequate information about the study and had the opportunity to ask questions. We obtained written informed consent from participants prior to obtaining any study measurements after providing them an explanation of (1) the purpose of the study; (2) the allocation process; (3) the use of data and the means of assuring confidentiality; (4) voluntary participation and the participants' right to withdraw from the study at any time; and (5) any potential harm that could occur as a result of the intervention.

Randomization and Treatment Allocation

Using a pragmatic randomized trial design, we randomly allocated 67 eligible participants drawn from the ABCD cohort [29] who provided informed consent and completed baseline anthropometry, clinical, and dietary measurements to either the usual care or to intervention in a 1:1 ratio using a computer-generated allocation sequence (Stata SE 12.1; StataCorp) [30]. Allocation sequence and group assignments were generated centrally and enclosed in sequentially numbered and sealed envelopes. A statistician not involved with other aspects of the trial performed all randomization-related procedures.

Usual Care

Study participants allocated to the usual care (control arm) received standard printed copies of Canada's Food Guide and Diabetes Canada (formerly Canadian Diabetes Association) GI resources in line with current Diabetes Canada Clinical Practice Guidelines [31,32]. The control group did not receive extra support aimed at increasing knowledge or skills for daily consumption of low-GI foods.

Enhanced Glycemic Index-Targeted Nutrition Education

Participants (n=33) allocated to the enhanced low-GI education intervention group received the same information as the control group in addition to vetted, evidence-based, learner-centered, low-cost, and actionable low-GI messages delivered through a Web-based platform with chat rooms, customized videos featuring a registered dietitian, and print material. Based on individual preference and needs, we provided additional support through email, SMS text messages, phone calls, or mail to reinforce participants' learning. The GI concept and content of this intervention were in line with current Diabetes Canada Clinical Practice Guidelines as well as T2D patients' suggested content and preferred modes of learning GI information [16,25]. The intervention website was managed by a trained research assistant who also moderated chat room discussions under the supervision of coinvestigators: KS, a registered dietitian and researcher, and STJ and JAJ, who also possess extensive research experience.

Participants received brief tutorials on website log-in, navigation, and usage during baseline data collection, which was reinforced at first log-in with a short video introduction to the program. The video emphasized the importance of low-GI eating and summarized the various aspects of the intervention. Those allocated to the intervention group covered a total of 6 modules over 12 weeks. These modules were aimed at enhancing knowledge and skills for improved GI dietary behavior change. Each module included customized videos featuring a registered dietitian, links to reliable websites, chat rooms for social support, and quizzes. Evidence-based GI content included GI values of foods; low-GI shopping, recipes, and cooking tips; and advice for eating out. Participants received a new module every 2 weeks. Specific topics covered in these modules included (1) general healthy eating for diabetes patients; (2) summary of the GI concept; (3) identifying, choosing, and shopping low-GI foods; (4) low-GI recipes, menus, and meal planning; (5) guidelines for eating out and snacking; and (6) GI concept and general diabetes self-management and healthy lifestyles. Participants were encouraged to outline and track personal, easily achievable goals that could enhance their GI knowledge and skills under each module. For example, in module 3, a participant could set a simple goal to learn how to identify low-GI versions of foods that he or she usually consumed. We delivered each module through the intervention website using user-friendly text, graphical displays, and module summary videos. All videos were developed in line with Canada's Food Guide and Diabetes Canada Nutrition Therapy Clinical Practice Guidelines-based GI recommendations [31,32] to teach participants "hands-on" application of GI to daily meal planning.

To sustain enthusiasm, participants were granted access to subsequent modules at the end of the preceding module on the first day of each 2-week cycle; this was accompanied with electronic reminders delivered through email or SMS text message based on participants' choosing. Participants responded to short quizzes meant to bolster key GI principles and lessons learned. Chat rooms were activated for each module to enable participants to share experiences in the form of success stories, challenges, and tips that enhance a sense of community for

social support among participants. The chat room forum was monitored, and timely responses were provided to questions and concerns of participants. In addition, we provided weblinks to the international tables of GI and GL values of foods [33] and additional evidence-based information on GI concept as well as general diabetes self-management and healthy lifestyles. A review of similar Web-based studies has shown that interventions that provide interactive elements such as the following have been effective at generating and sustaining participants' interest and exposure to Web-based interventions: (1) quizzes, searchable database, audio or video; (2) counselor support through counselor-led chat sessions, email, or phone contacts; (3) peer support through Web-based discussion forums or chats; and (4) regular updates of information on intervention websites [34].

Participants in the enhanced GI education arm also received copies of "The Shopper's Guide to GI Values: the Authoritative Source of Glycemic Index Values for More Than 1,200 Foods" [35] in line with T2D patients' preference for print-based material as a source GI information [25]. Briefly, the Shopper's Guide, which was recommended to participants seeking to know more about GI in a previous study [36], is a lightweight, handy book coauthored by expert GI research scientists. It contains GI values of over 1200 foods arranged by categories to help identify healthier low-GI carbohydrate alternatives using handy household measures. The Shopper's Guide is updated regularly and has comprehensive data on carbohydrates per serving and GL, a shopping list of low-GI essentials, ideas for gluten-free meals, facts about sugar and sweeteners, and tips for everyday meals and dining out. Furthermore, the Shopper's Guide provides links to supplementary resources with reliable, evidence-based GI information [35].

In addition to the website and the Shoppers Guide [35], participants in the intervention arm were offered periodic emails, SMS text messages or telephone calls, or postal mail prompts to visit the website and/or use the print materials to acquire more GI knowledge as per individual preference. Participants were encouraged to use these mediums to seek assistance regarding specific personal dietary issues, which they may not want to post in the chat room discussion section of the website.

Assessment of Study Outcomes

Primary Outcome

Our primary outcome measure was GI-related dietary behavior change and intake, measured using a 3-day food record.

Dietary Assessment, Glycemic Index, and Glycemic Load Estimation

Daily dietary intake was assessed for all participants at baseline and at 3 months using a 3-day food record. The 3-day food records are valid and reliable for capturing dietary behavior change by asking participants to record their food consumption as they eat [37]. All participants were asked to record, in as much detail as possible, descriptions of foods and beverages consumed over a 3-day period (ie, 2 weekdays and 1 weekend day). Participants were given further instructions on how to fill out the 3-day food record. Color photographs were provided to assist participants with estimating and recording appropriate portion sizes of foods and beverages they consumed in the 3-day food record logbooks. Pictures showing sample portions sizes of foods measured against items including a finger, palm of a hand, and a hockey puck were included and participants were encouraged to choose photographs that best represented their portion sizes or specify whether they consumed more or less. Mean daily food consumption and nutrient intake were estimated using the Food Processor Diet Analysis and Fitness Software (ESHA Research) at baseline and 3 months using the Canadian nutrient file.

All carbohydrate-containing foods identified from the 3-day food records were assigned GI values corresponding to the best geographic and botanical matches in the published International Table of Glycemic Index and Glycemic Load Values [33,38] or the updated University of Sydney Web-based database [39,40]. GI values were averaged for foods having more than one GI value from very similar matches. As the International Table and the University of Sydney Web-based databases do not provide an exhaustive entry of glycemic data for every food, the instances where foods could not be matched directly to those in the International Tables or Web-based database, GI values were calculated from the estimated GL [39] or matched to listed foods with similar characteristics (ingredients, composition, and physical properties) based on all information available to HMA, a trained dietitian, and from his subjective experience and knowledge of foods [41-43]. As recommended [41,43,44], daily average GI and GL was calculated for all carbohydrate-containing foods identified from the 3-day food records using published international GI tables [33,38] (Figure 1).

Figure 1. Mean daily glycemic index (GI) and glycemic load (GL) calculation.

$$\text{Total Dietary GL} = \left(\sum_{X=1}^{n} GI_x * CHO_x\right)/100$$

$$\text{Total Dietary GI} = \left(\sum_{x=1}^{n} GI_x * CHO_x\right)/\sum_{x=1}^{n} CHO_x$$

where for *n* foods in the diet, GI*x* is the GI of food *x*, CHO*x* is the gram weight of available carbohydrate (total CHO−dietary fiber) consumed from food *x*, and ΣCHO*x* is the total amount of available carbohydrate eaten over the 3 days [44].

Secondary Outcomes

Secondary outcome measures, including GI knowledge and skills, self-efficacy, body mass index (BMI; weight and height), waist circumference, clinical measures (glycated hemoglobin [HbA_{1c}], systolic blood pressure, total cholesterol, and high-density lipoprotein), and computer proficiency were assessed at the baseline and at 3 months after completing the intervention. In addition, demographic data were collected.

Glycemic Index Knowledge and Self-Efficacy Assessment

Pre- and postintervention GI concept knowledge and self-efficacy were assessed and quantified using the Glycemic Index Foods Quiz from a previous study [45]. Dietary data from a previous intervention within the same population showed that, out of 196 participants, 16% were not familiar with low-GI eating and 28% did not include low-GI foods in their diets [46]. About 35% (70/199) indicated that they did not know about GI, and of those who claimed the knowledge of GI, only 34% reported choosing low-GI foods for >6 months in another study [47]. These corroborate previous findings in which only 38% of people with diabetes received nutrition therapy across Canada [28] with <40% of dietitians including the GI concept in T2D dietary self-care counseling [26,27]. Overall dietary self-care behavior was assessed using dietary items in the validated and widely used Summary of Diabetes Self-care Activities measure [48]. The Glycemic Index Foods Quiz, therefore, enabled assessment of the net change in GI knowledge and self-efficacy due to the intervention.

Clinical and Anthropometric Measures

Clinical outcome measures included HbA_{1c}, systolic blood pressure, and lipid profile. Capillary blood samples (35 µL) were collected from participants to assess HbA_{1c} value using previously validated point-of-care testing device for HbA_{1c} (DCA Vantage) [49] and lipid profile (Cholestech LDX). Systolic blood pressure was measured according to the standard protocols using (BPTru) [50].

In addition, weight, height, and waist circumference were assessed according to the Canadian Physical Activity, Fitness and Lifestyle Appraisal procedures [51]. Body weight in kilograms (kg) and height in meters (m) were measured for each subject in light clothing and with no shoes on. Body weight was measured to the nearest 0.1 kg with a portable digital scale (Tanita BWB-800S, Arlington Heights, IL, USA), and height was measured using a portable stadiometer (Tanita HR-100). Waist circumference was measured to 1 mm at the top of the iliac crest using a spring-loaded Gulick anthropometric tape (FitSystems Inc, Calgary, AB, Canada). Regular, monthly quality assurance checks were conducted on the point-of-care devices and scale.

Physical Activity

Self-reported physical activity was assessed using the Godin Leisure Time Exercise Questionnaire [52]; the validity of this questionnaire is well established [53], and data suggest that self-reported physical activity estimates function as a suitable predictor of future behavior [54]. Participants were asked to report the frequency and duration of light-, moderate-, and vigorous-intensity leisure-time physical activity that lasted at least 10 minutes over a typical week during the past month. The number of weekly minutes for each intensity level was calculated by multiplying the frequency of activity by the duration in minutes. The sum of weekly minutes of moderate-to-vigorous physical activity (MVPA) gave the total MVPA minutes per week.

Computer Proficiency

Participants' computer proficiency was measured using the Computer Proficiency Questionnaire (CPQ) at baseline and 3-month postintervention. The CPQ was developed for evaluating the competencies of seniors with regards to use of computers and associated applications such as the internet [55]. The CPQ assesses competence across 6 different subscales: computer basics, printing, communication, internet, scheduling software (calendar), and multimedia use (entertainment) for

gauging an individual's specific and overall computer proficiency.

Sociodemographic Covariates

Demographic information including age, sex, marital status, education, employment status, income, and personal history of cardiovascular disease risk factors (eg, smoking) and time since T2D diagnosis were collected at baseline using a questionnaire.

Intervention Preference and Website Usage Data

Preference and usefulness of the Web-based, print [35], email, SMS text messages or telephone call, and postal mail were assessed by asking participants how many times they visited the webpage, read and made references to Shopper's Guide [35], and how much time they spent on the website or reading the book. In addition, participants were asked which medium they found most helpful and whether the information about the GI concept was informative and helped increase their knowledge and self-efficacy for consuming low-GI foods. Website data measurement programs were built into the website design to compile data points as connections occur with the target audience [56]. Regularly collecting, tracking, and using measurement data makes it possible to understand participants' characteristics and helps keep the intervention appealing and relevant for achieving the greatest effect [56].

Statistical Analysis, Power, and Sample Size Rationale

Statistical Analysis

Change in the mean daily GI of dietary carbohydrates from baseline to 3 months will be used as our primary effectiveness measure for improved low-GI knowledge and application. Descriptive statistics will be computed for all variables to determine the nature of the data and to test for normality assumptions. Changes in outcomes will be assessed using repeated-measures 2-way analysis of covariance. Potential sociodemographic and clinical factors associated with enhanced GI learning will be evaluated using generalized linear mixed-model analysis. Treatment condition, baseline scores, participant characteristics (eg, sex, education, and income), and computer proficiency that may be significantly related to outcomes will be controlled for. All data will be analyzed using Stata SE 12.1 (StataCorp).

Power and Sample Size Rationale

Based on previous studies regarding the efficacy of GI-based nutritional education and glycemic control [14,45] and meta-analysis of studies on low-GI diets and diabetes management [8], an estimated effect size of d=1 was set for this intervention. Previous data [46] suggest an SD of GI intake of 4-5 units; thus, an effect size d=1 could be achieved with an absolute mean difference of 5 units of GI intake. Given the estimated effect size, 42 participants (21 per arm) would be sufficient for detecting an absolute mean difference of 5 units on the GI intake scale between means with an error of alpha=.05 (2-sided) and beta=.1 (power 1−β=.90; Multimedia Appendix 1); this difference is considered to have significant health benefits from a previous study in which a change of 15 GI units yielded a corresponding HbA_{1c} change of −1.5% [45] and another study in which a change of 4.6 GI units yielded an HbA_{1c} change of −0.25 (95% CI −0.50 to −0.004) [14]. With an estimated attrition rate of 30% (based on the ABCD cohort year 2 participation rate), eligible participants were oversampled (N=67) during recruitment to account for possible loss to follow-up during randomization and intervention periods. This sample size was feasible in view of the dietary assessment (3-day food record) method used to assess food intakes and change in dietary GI, the cost of biochemical and clinical measurements, and the duration of the study.

Results

Summary of Progress to Date

Intervention milestones including ethics application, hiring and training of research assistants, and development and pilot-testing of intervention materials ran from July 2016 to October 2017. Data Analysis was completed December 2018.

Recruitment or Enrollment Status and Timelines

Recruitment and enrollment in the Healthy Eating and Active Living for Diabetes-Glycemic Index (HEALD-GI) trial ran from November 2017 to February 2018. Figure 2 shows the flow diagram detailing the recruitment, screening, random allocation, and baseline and follow-up data collection. Baseline and 3-month follow-up data collection were completed in June 2018. Currently, the study database is being compiled in preparation for performing appropriate analyses and dissemination of findings.

Participant Characteristics

Overall, 64% (43/67) participants were males; mean age was 69.5 (SD 9.3) years, with a mean diabetes duration of 19.0 (SD 13.7) years, BMI of 30.1 (SD 5.7) kg/m^2, and HbA_{1c} value of 7.1% (SD 1.2%) (Table 1).

Figure 2. Flow diagram showing participant recruitment and treatment allocation in the Healthy Eating and Active Living for Diabetes-Glycemic Index (HEALD-GI) study.

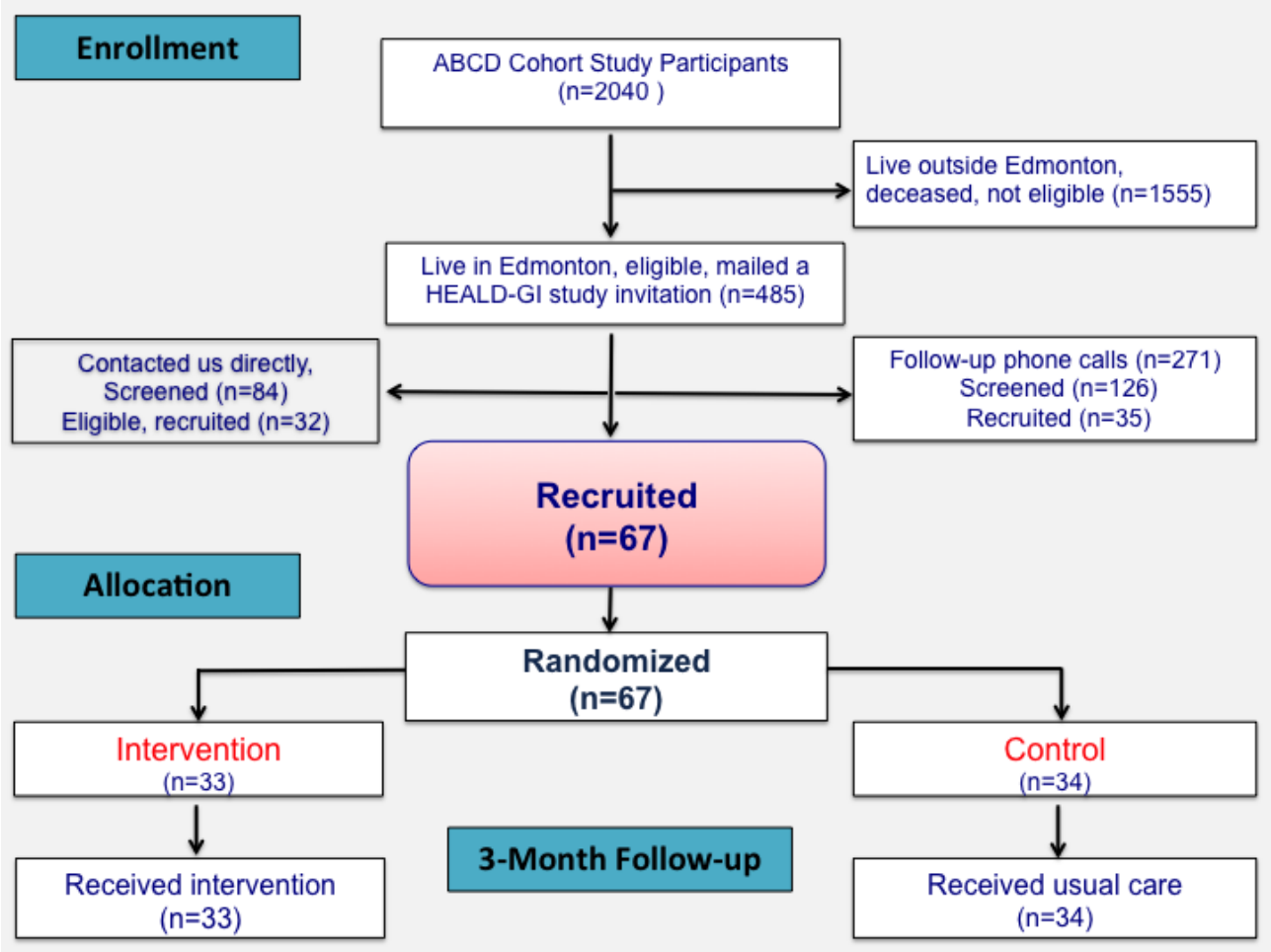

Table 1. Participant characteristics.

Characteristics	All (n=67)	Intervention (n=33)	Control (n=34)
Males, n (%)	43 (64)	20 (61)	23 (68)
Age (years), mean (SD)	69.5 (9.3)	70.7 (9.0)	68.4 (9.6)
Marital status, n (%)			
Married or common law	47 (70)	20 (61)	27 (79)
Not married (never married, widowed, divorced, or refused to answer)	20 (30)	13 (39)	7 (21)
Ethnicity, n (%)			
Caucasian	62 (93)	30 (91)	32 (94)
Non-Caucasian	5 (7)	3 (9)	2 (6)
Education, n (%)			
High school and less	21 (31)	12 (9)	12 (35)
College and higher	46 (69)	24 (73)	22 (65)
Employment, n (%)			
Employed	10 (15)	2 (6)	8 (23)
Unemployed	5 (7)	1 (3)	4 (12)
Retired	52 (78)	30 (91)	22 (65)
Annual household income (Can $), n (%)			
<40,000	8 (12)	3 (9)	5 (15)
40,000-79,999	30 (45)	16 (49)	14 (41)
≥80,000	20 (30)	7 (21)	13 (38)
Do not know or refused to answer	9 (13)	7 (21)	2 (6)
Diabetes duration (years), mean (SD)	19.0 (13.7)	20.0 (11.7)	18.0 (15.5)
Glycated hemoglobin value (%), mean (SD)	7.1 (1.2)	7.0 (1.4)	7.1 (0.9)
Lipid profile, mean (SD)			
Total cholesterol (TC; mmol/L)	4.4 (1.0)	4.3 (1.0)	4.5 (0.9)
HDL (High-density lipoprotein; mmol/L)	1.3 (0.4)	1.4 (0.4)	1.3 (0.4)
TC/HDL ratio	3.6 (1.5)	3.3 (0.9)	3.9 (1.9)
Blood pressure (BP; mm Hg), mean (SD)			
Systolic BP	127.9 (12.4)	127.7 (9.9)	128.2 (14.6)
Diastolic BP	70.1 (10.6)	69.8 (8.1)	70.5 (12.8)
Resting heart rate (bpm), mean (SD)	77.8 (14.5)	78.8 (15.3)	76.8 (13.9)
Body mass index (kg/m^2), mean (SD)	30.1 (5.7)	28.0 (5.1)	32.0 (5.6)
Waist circumference (cm), mean (SD)	107.4 (16.1)	102.5 (15.5)	112.2 (15.4)

Discussion

Principal Findings

This protocol outlines the study rationale, design, and evaluation of the HEALD-GI pragmatic randomized controlled trial and reports the baseline characteristics of 67 individuals living with T2D in Edmonton, Alberta, Canada. The HEALD-GI trial was designed to evaluate the effectiveness of Web-based, GI-targeted nutrition education on GI-related knowledge and intakes among adults with T2D.

Major strengths of this trial include the evidence-informed components of the Web-based enhanced, GI-targeted nutrition education including internet chat rooms for peer support and use of email, SMS text messages, and telephone support, which have been shown to enhance the intervention uptake and effectiveness [34,57]. Emails, SMS text messages, and telephone support enable educational content-related exchanges, while chat room platforms in Web-based learning environments enhance social support through creation of relationships that support collaborative learning and sharing of relevant experiences [58-60]. In addition, the involvement of a health

professional as a moderator of the Web environment has been shown to enhance Web-based intervention outcomes [57,61]. The provision of "The Shopper's Guide to GI Values: the Authoritative Source of Glycemic Index Values for More Than 1,200 Foods" [35] also supports preferences for print-based material as a source GI information [25]. This may enhance participant knowledge and self-efficacy for low-GI concept uptake. Use of a 3-day food record method for dietary intake data will help curb recall bias, which is often associated with memory-dependent dietary assessment methods such as 24-hour recall [37].

Conclusion

The GI concept is often difficult to teach. The HEALD-GI study aims to provide evidence in support of an alternative approach to translating the GI concept to adults with T2D. Findings from this study may help registered dietitians to better disseminate low-GI dietary recommendations using the efficient and cost-effective patient-centered approaches. Furthermore, evidence generated will contribute to addressing some of the controversies regarding debates surrounding the clinical usefulness of the GI concept.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Sample size and power calculations.

[PDF File (Adobe PDF File), 40KB - resprot_v8i3e11707_app1.pdf]

Multimedia Appendix 2

CFDR peer-review feedback.

[PDF File (Adobe PDF File), 37KB - resprot_v8i3e11707_app2.pdf]

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Abbreviations

ABCD: Alberta's Caring for Diabetes Cohort Study
BMI: body mass index
CPQ: Computer Proficiency Questionnaire
GI: glycemic index
GL: glycemic load
HEALD-GI: Healthy Eating and Active Living for Diabetes-Glycemic Index
IT: information technology
MVPA: Moderate-To-Vigorous Physical Activity
SMS: short message service
T2D: type 2 diabetes

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Protocol

An Evidence-Based Health Care Knowledge Integration System: Assessment Protocol

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Abstract

Background: The rapid advancements in health care can make it difficult for general physicians and specialists alike to keep their knowledge up to date. In medicine today, there are deficiencies in the application of knowledge translation (KT) in clinical practice. Some medical procedures are not required, and therefore, no value is added to the patient's care. These unnecessary procedures increase pressures on the health care system's resources, reduce the quality of care, and expose the patients to stress and to other potential risks. KT tools and better access to medical recommendations can lead to improvements in physicians' decision-making processes depending on the patient's specific clinical situation. These tools can provide the physicians with the available options and promote an efficient professional practice. Software for the Evolution of Knowledge in MEDicine (SEKMED) is a technological solution providing access to high-quality evidence, based on just-in-time principles, in the application of medical recommendations for clinical decision-making processes recognized by community members, accreditation bodies, the recommendations from medical specialty societies made available through campaigns such as Choosing Wisely, and different standards or accreditive bodies.

Objective: The main objective of this protocol is to assess the usefulness of the SEKMED platform used within a real working clinical practice, specifically the Centre intégré de santé et des services sociaux de l'Outaouais in Quebec, Canada. To achieve our main objective, 20 emergency physicians from the Hull and Gatineau Hospitals participate in the project as well as 20 patient care unit physicians from the Hull Hospital. In addition, 10 external students or residents studying family medicine from McGill University will also participate in our study.

Methods: The project is divided into 4 phases: (1) orientation; (2) data synthesis; (3) develop and validate the recommendations; and (4) implement, monitor, and update the recommendations. These phases will enable us to meet our 6 specific research objectives that aim to measure the integration of recommendations in clinical practices, the before and after improvements in practices, the value attributed by physicians to recommendations, the user's platform experience, the educational benefits according to medical students, and the organizational benefits according to stakeholders. The knowledge gained during each phase will be applied on an iterative and continuous basis to all other phases over a period of 2 years.

Results: This project was funded in April 2018 by the Fonds de soutien à l'innovation en santé et en services sociaux for 24 months. Ethics approval has been attained, the study began in June 2018, the data collection will be complete at the end of December 2019, and the data analysis will start in winter 2020. Both major city hospitals in the Outaouais region, Quebec, Canada, have agreed to participate in the project.

Conclusions: If results show preliminary efficacy and usability of the system, a large-scale implementation will be conducted.

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KEYWORDS

knowledge translation; practice guideline; community medicine; group practice; evidence-based medicine; clinical decision making; educational technology; decision support systems, clinical

Introduction

Background

The rapid advancements in health care can make it difficult for general physicians and specialists alike to keep their knowledge up to date. In medicine today, there are deficiencies in the application of knowledge translation (KT) in clinical practice. The Canadian Institutes of Health Research (CIHR) defines knowledge translation as "a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically sound application of knowledge to improve the health of Canadians, provide more effective health services and products, and strengthen the health care system" [1].

KT is of critical importance, considering the numerous gaps between what we know and the actual care delivered. The CIHR has come to the conclusion that "it has become clear that the creation of new knowledge often does not, on its own, lead to widespread implementation or impacts on health," [2].

In fact, the best evidence and best practices promoted by scholarly institutions and organizations are not always implemented, and some patients do not receive the most appropriate treatment. According to the Choosing Wisely campaign, it is estimated that up to 30% of examinations, treatments, and interventions performed in Canada are potentially useless or harmful [3-5]. Some studies demonstrated that 30% of patients in Ontario underwent unnecessary cardiac testing and blood analysis before a low-risk noncardiac surgical intervention [4,6]. Still, other studies have shown that up to 50% of trauma patients passing through the emergency do not receive all the prescribed treatments because of a lack of KT [7]. In other instances, from the expectations in regard, a prescribed test or a specific treatment is not aligned with evidence [8].

Adoption of Clinical Recommendations and Guidelines Into Practice

Throughout the world, including Canada, it is increasingly recognized that some medical procedures are unnecessary and provide no added value to the treatment [3]. These unnecessary medical procedures, which may not even address patient need, then increases pressures on the health care system's resources, reduces the quality of care, adds to patient stress, and exposes them to other potential risks [9,10]. The context described leads to the delivery of less efficient care for the patients exposing them to potential risks and stress [11]. Knowledge creation (ie, primary research), knowledge distillation (ie, the creation of systematic reviews and guidelines), and knowledge dissemination (ie, appearances in journals and presentations) are not enough on their own to ensure the use of knowledge in decision making [12]. It might be possible to guide the clinicians with a platform that proposes better KT and knowledge-to-action tools and really permits adoption in the clinical setting of recognized and approved clinical recommendations and guidelines. This has the potential to improve not only patient care but also the doctor-patient relationship which is based on communication, trust, and information exchange.

Selection and Adaptation of Recommendations

The Choosing Wisely campaign aims to help clinical practitioners and patients engage in dialogue about unnecessary examinations, treatments, and interventions and to make stronger and more efficient choices regarding quality care. This initiative is now implemented in 18 countries across the world, including Canada, where several recommendations have been issued pertaining to a wide range of clinical specialties, which enable an improved information exchange on best practices [13-15]. Several studies have demonstrated the relevance of their implementation in various clinical practices [16-17]. Like the Choosing Wisely campaign, the Institut national d'excellence en santé et en services sociaux (INESSS) mission is to promote clinical excellence and the efficient use of resources in the health and social services sector [18]. KT is also an integral part of their mission in "fostering the implementation of the recommendations and practice guides, using various information, knowledge transfer and awareness tools, p. 3" [19]. The INESSS also develops clinical recommendations and clinical practical guidelines intended for various communities of practice (CoP), supported by evidence, experiential, and contextual data provided by medical professionals [20].

Problem

The challenge for the health care system is to help physicians adequately implement exemplary practices. For professional guidelines to be implemented and to improve the quality of care, it is essential that doctors become aware of the existence of these practices through appropriate methods of dissemination and implementation in day-to-day practice.

Furthermore, the transfer of theoretical knowledge and practical experience from one context to another is a focus in medical education [21-23]. This is a major concern in professional sectors and is central to the debate surrounding reforms. According to Kontoghiorghes [24], only 10% to 15% of learning translates from training to clinical practice. It is, therefore, essential to focus on the capacity to mobilize and combine knowledge to efficiently address new situations [25]. The mobilization resulting from the creation of a community of practice could promote learning and promote working with other health care professionals to solve concrete clinical problems [25]. Collaborative learning reinforces learned knowledge and encourages practical changes. For this reason, knowledge and expertise sharing between professionals and between clinical CoP is a recognized strategy to bring change to clinical practice [26,27].

Some models proposed in recent years promote the development of CoP and the continuity of patient-centered care [28-33]. These models aim at creating proactive, interdisciplinary professional teams and CoP who interact at various levels of the health care

system. Studies have demonstrated the added value through the quality of interventions [34-36] of this organizational system. Integrated CoP would support clinical practitioners across various clinical settings in carrying out their daily activities and developing better patient-centric practices.

A CoP is defined as a group of individuals who are interacting to share information, experiences, models, views, advices, and best practices, as well as to solve problems and extend their knowledge in an area of practice in which they share a common interest [37]. Each member of a CoP is supported by a peer group belonging to an area of expertise or a professional practice where he can ask questions, share, and create new knowledge. Relationships with other CoP can also be established. In that respect, the creation of integrated CoP would enable the support of clinical practitioners in their daily activities as well as the growth and development of best practices. However, to make that a reality, an integrative model favoring the implementation of a knowledge-sharing structure between members of a CoP must be used to promote the emergence of collective intelligence.

Information technology (IT)–enabled CoP can support the knowledge learning and sharing activities within interdisciplinary health care teams. A study based on the Hoyman model demonstrated how computer applications can ensure the continuity and flow of the care [38].

KT tools and access to the guidelines can guide and improve physician decision-making processes depending on specific clinical situations of the patient. These tools can provide them with the available options for care, ultimately helping them promote a more efficient professional practice [26,27,39-41]. Scientific studies are published; best practices are documented; and, however, they are slow to be implemented. We are trying to evaluate if an innovative solution would allow for the application and integration of this knowledge into clinical practice. Interventions supported by IT can promote the creation, access, and application of clinical recommendations, care protocols, and regulations, as well as best practices, bringing KT to practice.

IT–enabled CoP can support learning and knowledge sharing within health care teams as well as promote best practices in a variety of clinical areas [26,27,40-42]. Wikis are being used to encourage and make it easier for clinical practitioners to share their knowledge and expertise [43-45]. Wikis can also help users adapt their knowledge for local contexts, making it more relevant and user-friendly [46,47] and to encourage collaboration between patients and clinical practitioners when developing support tools for patients [48,49]. As such, several authors suggested exploring collaborative Web-based platforms to share, create, and update content of clinical decision-assistance systems [46,50-53].

Systematic reviews have demonstrated the value of support tools for integrated clinical approaches [54]. Studies have also shown that the mere availability of Web-based resources is not sufficient. Even if clinical practitioners could reliably find the answers to their questions in about 50% of cases, for some reason, they do not follow through on the inquiry. Researchers suggest that technological solutions should provide access to high-quality evidence, as per the just-in-time principles, in the clinical decision-making process [55].

Technological Solution: Software for the Evolution of Knowledge in MEDicine

An innovative platform was created in the Outaouais Region in Quebec, Canada, in 2014. Initially used in the emergency area, this platform is now being assessed at the institutional level and is an integral part of the Centre intégré de santé et des services sociaux de l'Outaouais and Relations and Educational Research Department (RERD) approach. Software for the Evolution of Knowledge in MEDicine (SEKMED) is an interactive and dynamic working Web platform employing a multidimensional approach to knowledge, which considers the various dimensions linked to clinical practice such as scientific, organizational, professional, and experiential. The solution also allows collaboration and interactions through an iterative and continuous process of knowledge generation supported by the involvement of CoP.

The platform aims to facilitate the coordination of efforts deployed by members of a CoP, the accreditation and standards bodies, within an advanced Wiki-type tool dedicated to the creation, aggregation, and updating of interactive resources supporting the patient's clinical history intake, physical examination, differential diagnosis consideration, take over, and therapeutic or orientation processes by the clinical practitioners. Moreover, these resources are, then, made available, as per the just-in-time principles, directly in the clinical practitioners' processes using an ontological recognition engine which recognizes the terms associated with resources.

SEKMED assists clinical practitioners in their efforts to stay up-to-date and enables the integration of best practices as well as a better use of diagnostic and therapeutic resources. This project is destined to clinical practitioners but it can be interfaced with other health professions. There is an introductory video about the SEKMED platform [56].

Figure 1 illustrates the dashboard of SEKMED. The platform is designed in 9 sections.

Note that every section of the menu could be accessed by clicking in the SEKMED logo so that we can choose the appropriate section.

SEKMED aims at giving the clinician a representation of all the different elements that constitute its practice and facilitate the exchange with the community they are a part of. Those elements are represented in the different sections of the platform and are represented in the dashboard that we see in Figure 1. We will give a brief description for those sections, but the main focus of SEKMED is to facilitate the creation of interactive resources that support the different clinical processes, the discussion of those resources to improve them and validate them at a higher level, and to give just-in-time access to high-quality evidence in the context of patient care decision making.

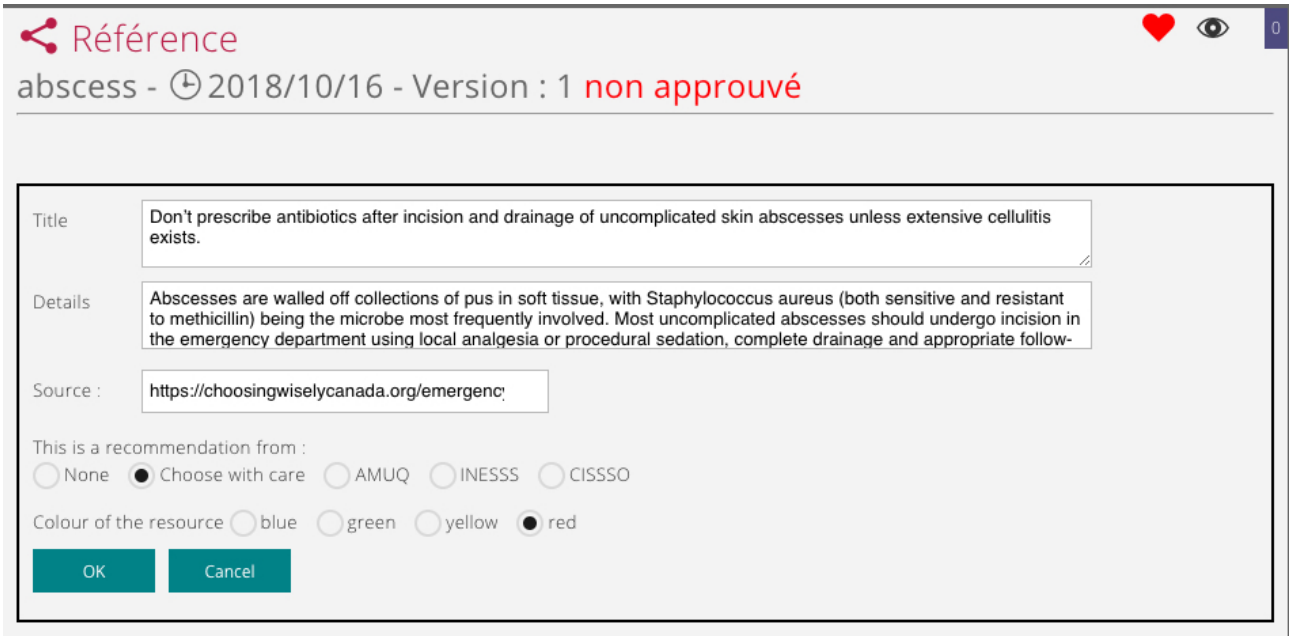
Figure 1. View of the platform dashboard.

The following is a brief description of every section:

1. Resources: Here we can search for specific resources in one community or in other communities. Resources are built by the community with tools that are provided. They are formatted in a way to be immediately clinically useful. A resource could be an interactive template for history taking, physical examination, investigation, treatment, and recommendation to patients. It can also be references or educational videos that are provided in the clinical process, following the just-in-time principle. Filters could be applied during that search (type of resource, owner of the resource, and community). This process is completely distinct from the discovery of resources in the clinical setting. It is also where one can decide to add a resource. It is where the process of creation happens.
2. Communities: A list of all communities, my own communities, and pending request to adhere to one. The concept of community is important when we understand that the content that will be made available to the clinician is dependent on the fact that he or she is a member of one of them specifically.
3. SEKMED Café: A section where you can interact with your community. (Chat, message from the community, from the center where the clinician is working, a forum for longer discussion around subjects proposed by the members, a humor section, a list of the members, and a means of communication between members).
4. PDF: A section facilitating storage of PDF. From there, they can be made available to the communities. Note that most resources are not PDF, but it is often the start of the evolution from a more static to fully interactive template.
5. Patients: Index of existing patients.
6. Episodes: When a patient is selected, an episode is created for every specific encounter. Here, we can find a list of the still opened episodes, or search for one based on different criteria.
7. Latest Tasks: A list of the resources a community would like to see implemented. Each task links to a real document. This document only has a title and, in some cases, instructions for specific objectives associated. This document, in task, is then attributed or available to the members of the community of practice as a specific project.
8. New resources: A list of the most recent resources created.
9. Tweets: The Twitter feed of the community.

The SEKMED platform allows the creation of different kinds of resources, permitting the integration recommendations from normative or accrediting bodies. As shown in Figure 2, we see the implementation of a compass kind of resources. This type of resources informs the clinician about one specific recommendation of the campaign, Choosing Wisely.

Figure 2. Integration of clinical recommendation.



As shown in Figure 2, the title is the specific recommendation made by the normative body, the details represent the justification for the recommendation, there is and shall always be a link to the source of the information, a specific element of the resources permit the insertion of that link, there is a list of the normative or accrediting bodies from which to choose, this selection will also insert the logo of the later in the resource itself. There is a choice of color providing a visual clue as to the fact that something should not be done (red), should be done (green), or one should be careful about something (yellow), and there is also neutral powder blue for more information. That kind of resource is inserted into a template for a specific condition (Figure 3). When the template is used, the information reaches the clinician in its process. Figure 3 is a template for abscess with the usual questions, the technique for drainage, and the specific recommendation for not prescribing antibiotics in uncomplicated cases.

Figure 3. Template for abscess.

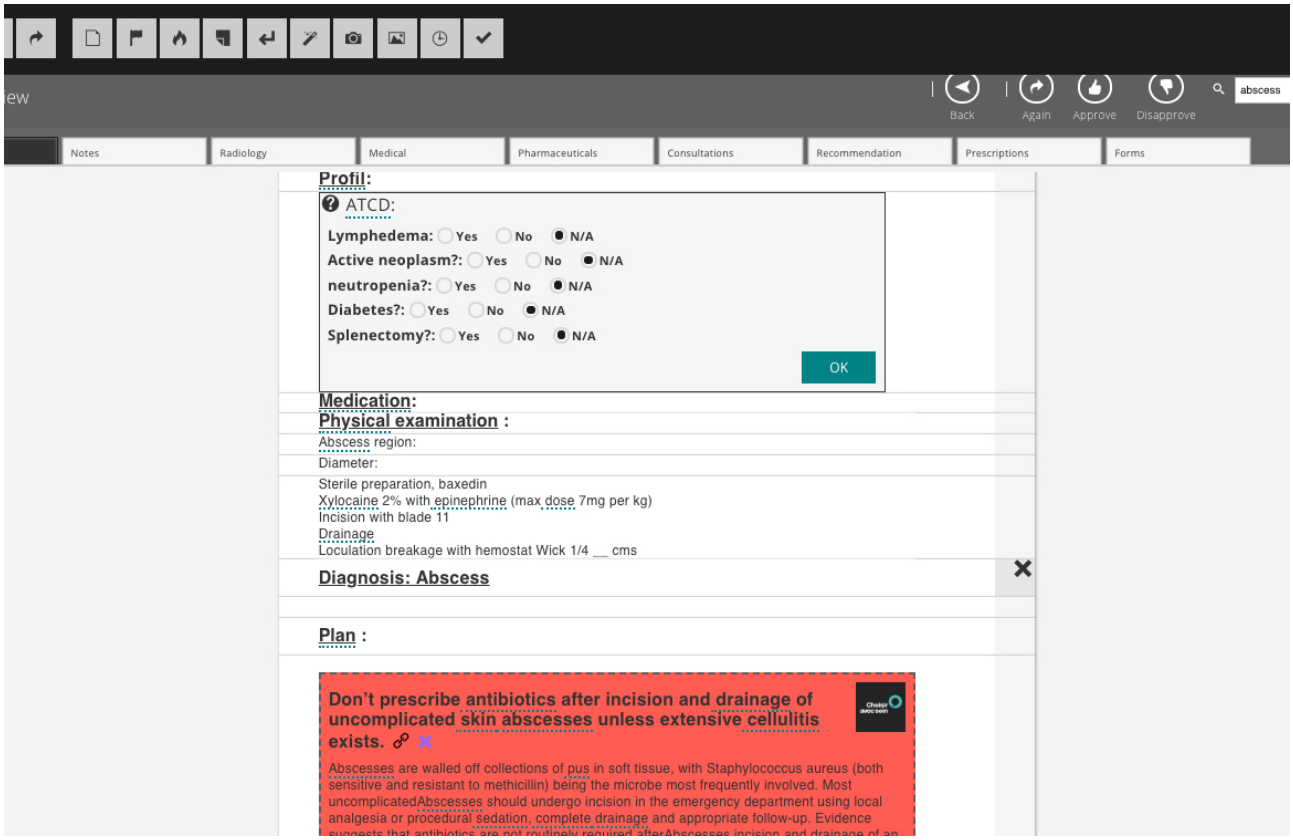
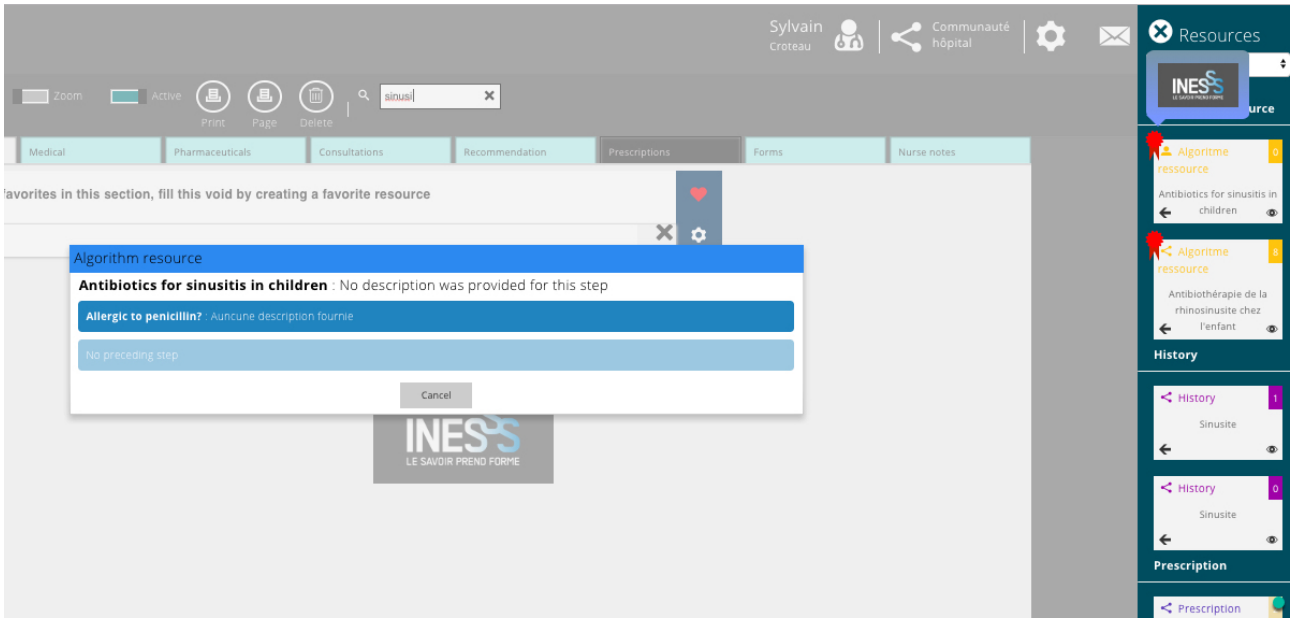


Figure 4. Recommendation from Institut national d'excellence en santé et en services sociaux (INESSS) for antibiotic treatment of sinusitis in children.



In certain cases, a full template or an algorithm could represent the recommendation of a normative body or an organization (Figure 4). It is then possible to identify resources that would have been validated at a high level by the application of a certificate. Here, a recommendation from the INESSS for the antibiotic treatment of sinusitis in children is presented as an algorithm. The certificate identifies those resources that come from normative of accrediting bodies in comparisons with the one that is created by the individuals in the community and have not gone through a process of intensive review and accreditation.

The certification needs to go to a review committee. The editing process is then blocked for the CoP. The certificate is set in advance, and the process for adding it is fairly simple.

Objective

The main objective of the pilot project is to assess the usefulness of the SEKMED platform in the implementation of medical recommendations recognized by the members of CoP, accreditation bodies (Association des médecins d'urgence du Québec or AMUQ), a campaign such as Choosing Wisely and standards bodies (INESSS) in clinical practice in real health care settings within the province of Quebec, Canada.

As part of the project, SEKMED will be assessed with 3 CoP: (1) emergency physicians, (2) general medicine patient care unit physicians, as well as (3) external students and residents studying family medicine. Group 1 will be composed of 20 emergency physicians from the Hull Hospital and the Gatineau Hospital. Group 2 will have 20 patient care unit physicians from the Hull Hospital, and the third group will consist of approximately 10 external students and residents in family medicine from McGill University.

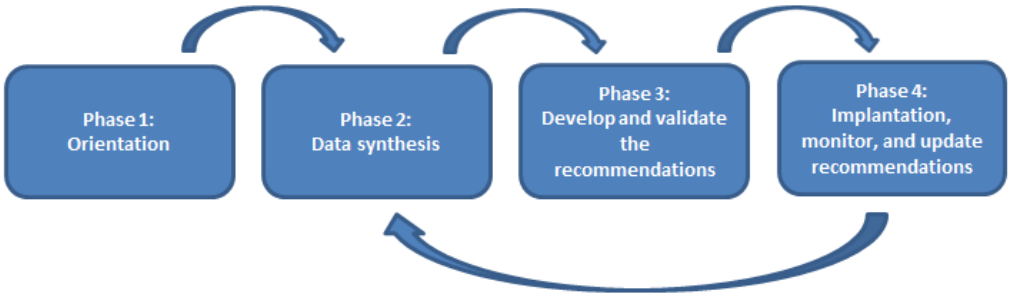
Methods

Validation and Evaluation Methodology in a Real Caregiving Situation

The project will focus strictly on (1) the research over a 24-month period, (2) the ethical and scientific endorsement of the project; (3) the employment of students; (4) the recruitment and training of participants; (5) the initial implementation of the 6 specific objectives through the analysis and interpretation of quantitative and qualitative data generated during the study; (6) continuous improvement; and (7) the dissemination of results within health care work environments as well as stakeholders and academic audiences.

The project will be completed in 4 phases (Figure 5). The knowledge gained during each phase will be applied on an iterative and continuous basis to all other phases over a 2-year period.

Figure 5. Research program.



Phase 1: Orientation

This will consist in the consultation and mobilization of participants in the 3 CoP to better understand the culture, practical settings, values, and preferences, as well as to identify their local decision-making needs at the clinical and practical level. Three work teams will then be created to represent each CoP: (1) emergency physicians; (2) patient care unit physicians; as well as (3) external students and residents in family medicine. Each community will be represented by a voluntary champion. All participants will complete training during this phase to familiarize themselves and master the SEKMED platform's functions. Each will receive a user guide with up-to-date content presenting among other things, video clips and screenshots to ensure a better understanding of the platform.

Phase 2: Data Synthesis

This will aim to rigorously collect, integrate, and synthesize the recommendations provided by the members of each community of practice, accreditation bodies (AMUQ), and standards bodies (INESSS and Choosing Wisely). Recommendations are based on 3 types of data: scientific, contextual, and experiential. An initial information search will be conducted with each team to identify the educational and informational content, templates, forms, follow-up sheet, decision-making algorithms, and other relevant resources used by the CoP. A second information search will be undertaken with accreditation and standards bodies only with the vision to compile a comprehensive list of recommendations for each specialty.

Phase 3: Develop and Validate the Recommendations

This will consist in mobilizing work teams to (1) collect and integrate scientific information, within the implementation context (contextual data) and practical experience context (experiential data), and better understand the values and preferences of each community of practice; (2) verify if the recommendations are available or not. If they are available via the accreditation and/or standards bodies, they can be considered as they stand or be adapted for local usage; (3) propose recommendations in a concise manner that are lacking and have not been listed by members of each CoP, by accreditation bodies, or by standards bodies but are deemed useful, relevant, acceptable, and applicable in the field by teams; (4) select recommendations from a list provided by accreditation and standards bodies that meet the CoP's clinical and practical needs; and (5) review and validate all recommendations that are considered essential to the practice and relevant to be applied and monitored on the SEKMED platform (Phase 4).

Phase 4: Implantation, Monitor, and Update Recommendations

In the final phase of the project, recommendations will be implemented, monitored, and updated. The implementation step aims to integrate, disseminate, and transfer recommendations across the SEKMED platform so that users may use them in their own CoP. Implementation support strategies will be available at this stage to promote ownership and facilitate the dissemination of the recommendations. The monitoring step will measure the degree of implementation of recommendations and their impact on clinical practices, care, and services management as well as the health and well-being of populations. Finally, the last step consists in making regular updates with working teams, ensuring continuous access and use of the best evidence and the recommendations provided by accreditation and standards bodies in clinical practice by sharing and making them available. Following phase 4, there will be an iterative and continuous process, starting at phase 2, throughout the project.

Data Collection Methods

The 4 phases described above will enable us to meet our 6 specific research objectives. The recommended data collection methodology aims to achieve deliverables based on qualitative and quantitative methods. This triangulation of methods is vital for an understanding of complex phenomena, and it allows data enhancements, questioning, monitoring, and verification [57]. Some authors suggest that the triangulation of data sources, which compares data produced by 2 or several different and independent methods, increases the interpretive power [58]. This method, whether parallel or sequential, seeks using different measures and observations, to reduce bias in each method. The goal is to exploit the complementary nature of methodological processes to get the very best out of them.

Specific Objective 1

This objective was to measure the integration of recommendations in clinical practices. This objective will demonstrate through SEKMED the uptake of medical recommendations in clinical practices. This will enable us to determine if users really take ownership and integrate the recommendations into their daily work. To do so, we will export the SEKMED data in a Microsoft Excel file to produce descriptive statistics. The information provided by the data will allow us to measure the monthly progress of the following indicators:

1. The number of recommendations used by each physician in clinical practice.
2. Percentage of specific recommendations used at specific clinical situations,
3. Percentage of physicians who are still using recommendations in clinical practice.

Specific Objective 2

This objective was to measure the before and after improvements in practices. The objective aims to compare improvements in practices, before and after the intervention, by using medical recommendations. We will be using the same approach as Specific Objective 1 for the data extraction, analysis, and processing.

The following indicators will be measured:

1. The number of new recommendations integrated into the platform that is used by physicians;
2. Average and median time required for the integration of recommendations in a work environment.

Specific Objective 3

This objective was to measure the value attributed by physicians to recommendations. This objective will appraise the overall

value (experience and satisfaction) attributed by physicians to recommendations provided by members of the community of practice, as well as accreditation and standards bodies in their field of practice. A total of 4 focus groups will be held during the project. The data collected with the first 2 specific objectives will be discussed at each focus group. This approach aims to foster reflective practices in providing an opportunity to step back and collectively review the experiences and the participants' point of view on this practice and how it facilitates the KT process.

Our approach must be flexible to produce the desired change and to adapt to the situation while allowing knowledge development, experience sharing, and ideas exchange to ultimately find solutions to common health care problems [59-61]. The assessment of this intervention will be completed using a mixed approach, which combines a qualitative approach with a quasi-experimental–type quantitative approach focused on the measured experience and satisfaction levels. Using this approach, we will be able to determine the extent to which reflective learning can facilitate the transfer and use of recommendations made by the CoP.

Specific Objective 4

This objective was to measure the user's platform experience. This objective will measure the user's experience with the platform. The user experience is defined as an individual's perception and response resulting from his or her use or the anticipated use of a system [62]. This understanding of the user experience is also essential in nature for these organizations who wish to offer interfaces that meet the various users' evolving needs in an efficient manner [63]. As part of our project, we are developing a conceptual model of the user experience based on the rich conceptual framework of IT usage prepared by Barki, Titah, and Boffo [62], which takes simultaneously into account the characteristics of the technology (eg, usability), the user (eg, expertise), and the task to achieve (eg, complexity) to better understand the concept of utilization. We will also integrate technology acceptance and utilization models based on behavioral intents which are influenced by IT usage perceptions and its usability [63-66].

The research team will administer a questionnaire after each experimental period with the tool. We have chosen to analyze the data using the partial least squares structural equation modeling (PLS-SEM) to verify and refine the proposed theoretical models. PLS-SEM is a second generation multivariate statistical analysis method. Although first generation techniques usually rely on traditional research statistical methods such as regression and analysis of the variance, second generation techniques compensate the first generation techniques' shortcomings by notably taking the errors in measurement into account. PLS is relevant for our project because it is used for exploratory assessment purposes such as the analysis of trends and the identification of relationships.

Specific Objective 5

This objective was to measure the educational benefits according to medical and external students. This objective consists of assessing the attitude and intent of external students and residents in family medicine toward the educational benefits of SEKMED. We will administer the same questionnaire used for Specific Objective 4. We will also organize focus groups to learn about the user's experience in the adaptation and learning process. A total of 4 focus groups will be held during the project.

Several studies have shown that IT promotes the adoption of a pedagogical approach which places the student or the learner at the center of the learning process. IT indeed provides the innovative means, not only for the dissemination of knowledge, but also for the exploration of learning strategies promoting competency development—access to information, real-time communication, and exchange with CoP. Many papers focus on experimentation with a Wiki, but fewer studies explain the rationale and the pedagogical foundations [67,68]. Several authors think it is possible to improve the teaching system on clinical reasoning by using techniques that are more efficient than conventional teaching [69]. We wish to demonstrate that SEKMED enables learning, including accompanying and complementary skills evaluation support by governing the problem-solving process and by assessing the students' and residents' ability to process the information. In that respect, SEKMED could be used as a diagnostic assessment in providing a more personalized support program to learning.

Specific Objective 6

This objective was to measure the organizational benefits according to stakeholders. This objective will assess the attitude and intent of the RERD and the stakeholders toward the changes resulting from the use of the platform and the achievement of their specific objectives. In view of the specificity of this objective and the target audience, an interview guide will be developed and validated before its use. The interview guide will measure the attitude and intent of the RERD and the stakeholders toward the changes resulting from the use of SEKMED and the achievement of their specific organizational objectives.

RERD will benefit from a tool facilitating the transfer, mobilization, and validation of knowledge gained within the organization while driving innovation. In support of all management bodies governing the clinical practice, they will be able to monitor medical and social interventions more rigorously in real time. Statistical functions and the ability to extract granular data actually make it possible to assess all medical acts, track changes, and implement best practices while also validating the application and the relevancy of the recommendations issued by the organization or the accreditation and standards bodies. In other words, all actions performed by caregivers become traceable and measurable.

Stakeholders supporting the clinical practices are the Directorate of Professional Services, Directorate of Multidisciplinary Services, and the Nursing Directorate. As mentioned above, SEKMED has the ability to extract data at the granular level, which reduces the amount of time they require to complete specific tasks. As an example, the review of medical records, also known as audits, will be improved owing to the ability to track all actions performed by a health care professional. SEKMED also promotes the dissemination, among clinical practitioners, of clinical tools and best practices, thus simplifying

their implementation and training needs. To conclude, these data allow the development of follow-up and performance indicators that will facilitate the monitoring activities performed by management bodies supporting the clinical practice.

Results

This project was funded in April 2018 by the Fonds de soutien à l'innovation en santé et en services sociaux for 24 months. Ethics approval has been attained, the study began in June 2018, the data collection will be complete at the end of December 2019, and the data analysis will start in winter 2020. Both major city hospitals in the Outaouais region, Quebec, Canada, have agreed to participate in the project.

Discussion

If results show preliminary efficacy and usability of the system, a large-scale implementation will be conducted.

The expected benefits generated by this protocol on the improvement of care and service delivery are as follows:

1. The use of better evidence and recommendations issued by the accreditation and standards bodies in clinical practice, by continuously sharing and making them available within the context of their implementation.
2. To gain efficiencies in the dissemination, usage, and update of institutional protocols.
3. Gaining efficiencies for clinical practitioners.
4. The rationalization of the resource and budget use.
5. The efficient harmonization of practices.
6. The improvement of the teaching quality.
7. The use of granular data to assess the quality of the act as well as administrative and research purposes.

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Authors' Contributions

VN and SC were the lead in designing and writing the protocol for obtaining the funding. VN was responsible for revising the manuscript multiple times for methodological, conceptual, and intellectual content. The final version of the manuscript was approved by all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report from the granting agency.

[PDF File (Adobe PDF File), 156KB - resprot_v8i3e11754_app1.pdf]

Multimedia Appendix 2

Scientific validation from the Scientific Committee of the Centre intégré de santé et des services sociaux de l'Outaouais in support of the peer-review report from the granting agency.

[PDF File (Adobe PDF File), 582KB - resprot_v8i3e11754_app2.pdf]

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Abbreviations

AMUQ: Association des médecins d'urgence du Québec
CIHR: Canadian Institutes of Health Research
CoP: Communities of practice
INESSS: Institut national d'excellence en santé et en services sociaux
IT: information technology
KT: knowledge translation
PLS-SEM: partial least squares structural equation modeling
RERD: Relations and Educational Research Department
SEKMED: Software for the Evolution of Knowledge in MEDicine

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Protocol

Using Targeted mHealth Messages to Address Hypertension and Diabetes Self-Management in Cambodia: Protocol for a Clustered Randomized Controlled Trial

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Abstract

Background: Hypertension and diabetes represent the first and third highest contributors to global disability. While mobile health (mHealth) messaging programs have rapidly increased in low- and middle-income countries (LMIC), adaptations for specific patient health needs is a new approach to manage chronic conditions.

Objective: The primary aim of this study is to develop and test an mHealth communication intervention using electronic data capture (by tablet) and voice messaging to improve hypertension and diabetes self-management in Cambodia. The secondary aim is to share results with the Cambodian Ministry of Health and development partners to inform health policy and develop strategies for hypertension and diabetes control.

Methods: The study design is a cluster randomized controlled clinical trial randomizing each of 75 Community peer educators (PEs), trained and coordinated by MoPoTsyo Patient Information Center in Phnom Penh, into one of 3 groups of 25 (approximately 60 patients each) to receive either tablet+messages, tablet only, or no intervention (control). The total sample within each group includes 25 clusters and approximately 1500 patients located in 7 Operational Districts in rural regions or urban slums in Cambodia. The interventions (groups 1 and 2) were compared with usual PE monitoring without the tablet or mHealth messaging interventions. Focus groups and informant interviews were conducted to develop messages according to specific themes—medications adherence, laboratory testing, physician visits, obesity, smoking, and general lifestyle issues. Using the data received at monthly PE monitoring meetings, patients will receive specific messages based on their individual health challenges. Following the intervention completion, clinical and process outcomes will be compared with baseline metrics between groups.

Results: PEs were randomized in July 2017, and the intervention was implemented in September 2017 through June 2018. Analyses are underway.

Conclusions: This project is unique in its combination of electronic data transfer, which can be accessed immediately, with voice messages most relevant to individual patients' needs. Positive results will indicate the value of using targeted messaging in patient-specific, self-management issues to improve hypertension and diabetes control.

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KEYWORDS

Cambodia; diabetes; hypertension; mHealth; mobile phone

Introduction

The incidence and prevalence of cardiovascular disease and its risk factors, including hypertension and diabetes mellitus, is increasing rapidly in low- and middle-income countries (LMIC) [1-3]. After the turn of the century, epidemiological trends emerged that were characterized by a major shift in the size and relative magnitude of many risk factors for mortality and disability. High systolic blood pressure and high fasting plasma glucose increased steadily in impact on the global burden of disease [4]. Between 1990 and 2015, systolic blood pressure increased across the globe with associated increases in both mortality and disability [5]. In 2015, the top 3 greatest contributors to global disability-adjusted life-years among level 3 risks were high systolic blood pressure, smoking, and high fasting plasma glucose [6]; these increases are noteworthy as their sequelae, heart disease and stroke, are now the leading cause of death in these nations [7]. In Cambodia, it has been estimated that more than half (52.0%) of the total diabetic population is untreated, and despite treatment, only 24% of all diabetes is adequately controlled [8]. Poverty, inequality, lack of education, along with the nature of the nutritional transition, are root causes of the problem while limited resources mean that noncommunicable diseases (NCDs) must compete for political attention and financial investment. The global trend of increasing risk factors for cardiovascular diseases will continue unless effective methods are implemented to not only identify high-risk individuals but also implement effective and sustainable lifestyle and pharmacological interventions [9]. Tools and interventions to improve the self-management of cardiovascular disease risk factors, such as hypertension and diabetes, are greatly needed in community settings where health care resources may be limited.

Mobile health (mHealth) messaging programs have rapidly increased in LMIC and provide a means to support self-management programs especially needed for NCDs. A number of studies have focused on short message service (SMS) text messaging to improve outcomes for hypertension [10,11] and diabetes [11,12-14]. While these studies have generally shown messaging to be an acceptable format to participants, results have been mixed, with several showing small changes in some disease outcomes [10,12-14] or behavioral change [11,15]. However, no consistent patterns between intervention and control groups have been found. While mHealth messaging systems in the literature have varied in terms of features provided, the evaluation of targeting patients with voice messages to address individualized problems has been limited.

This study aims to leverage the activities of a Cambodian nongovernmental organization, MoPoTsyo Patient Information Center, to test if improvement of data transfer using electronic data capture combined with sending targeted voice messages to patients, would improve outcomes for hypertension and diabetes. As peer educators (PEs) were already established in the MoPoTsyo system to monitor hypertension and diabetes across the country, it provided us with the opportunity to both increase the time from patient measurement to data utilization (through e-tablets) and to use these data to individualize messages targeting specific issues revealed from the data (voice messages).

The primary aim of this study is to develop and test an mHealth communication intervention using electronic data capture and voice messaging to improve hypertension and diabetes self-management in Cambodia by implementing a combined electronic health (eHealth) and mHealth intervention. The secondary aim is to share results with the Cambodian Ministry of Health and development partners to inform health policy and develop strategies for hypertension and diabetes control.

Methods

Human Subjects Approval

This is a randomized controlled clinical trial to test an intervention comprising faster data capture plus targeted voice messages compared with PE monthly monitoring in a community-based sample in Cambodia for improvement of hypertension and diabetes outcomes. This study received Institutional Review Board approval from the University of Washington Division of Human Subjects and the National Ethics Committee for Health Research in Cambodia. All PEs, regardless of study allocation, and participants assigned to the telephone message intervention provided written informed consent. Informed consent from community participants who did not receive mHealth messages were waived by the Institutional Review Boards as routine monitoring provided study outcome data for these groups. This study was determined to not qualify as an “Applicable Clinical Trial” according to the National Institutes of Health definition [16] at the time it was initiated and, thus, was not registered in clinicaltrials.gov. As the risk of harm is minimal in this study, no criteria for discontinuation were developed. An Advisory Committee comprising Cambodian Ministry of Health officials, health care providers, and technology experts was convened to provide oversight and guidance to the study.

Study Setting

In Cambodia, where greater life expectancy is causing rapid increases in NCDs [17], nongovernmental organizations have stepped in when government programs have not been able to address disease locally. MoPoTsyo Patient Information Center is a Cambodian nongovernmental organization for people with chronic disease in Cambodia [18]. It was established in 2004 to provide an institutional and practical response to the information and care needed by patients with hypertension and diabetes. Their model recruits and involves patients as volunteers and trains them to provide counseling on NCDs and monitor key health indicators over time. PEs see patients on a monthly basis to reinforce training and monitor key metrics, including

blood pressure, glucose, weight, and adherence to medications. Patients keep paper logs of their health information that are updated at each PE visit. Currently, logs summaries are transferred to the MoPoTsyo Patient Information Center for manual entry and to update patient histories. Since 2005, MoPoTsyo has trained >200 PEs who have registered >31,000 patients in 7 rural provinces and poor urban slum areas of Phnom Penh. Patient and pharmacy records have been used to document the success of the program showing dramatic improvement in chronic disease management [19].

Seven Operational Districts (ODs) representing rural geographic regions or urban slums were selected for inclusion in the project; these included 4 ODs in Kampong Speu province, 2 ODs in Kampong Thom province, 1 OD in Kampong Cham province, and the municipality of Phnom Penh. This area includes 87 PEs who were included for simple randomization (by computer-generated random numbers) into the 3 arms of the study. All patients registered into the MoPoTsyo Patient Information Center system at the time of PE randomization were included as the community sample to receive mHealth messages with no exclusion criteria. Owing to the nature of this intervention, it was not possible to blind participants to study allocation. However, as patients of PEs were clustered geographically, there was a minimum chance of patients interacting across clusters to discuss the study.

Approach

In this study, we are collaborating with MoPoTsyo Patient Information Center to enhance their Peer Educator Network model through the application of mHealth-tailored phone messaging and improved eHealth communication throughout the system. A focus on hypertension, justified by the extremely low medication adherence of hypertensive patients compared with diabetic patients, shifts the intervention to an area of great need. Two interventions will be tested, one at the PE level and one at the patient level. The first includes providing electronic tablets to PEs for data collection and transfer to the MoPoTsyo database in Phnom Penh. The tablets are intended to speed up data collection and entry, reduce paper, increase accuracy, and eliminate lengthy distances that must be traveled to bring paperwork to MoPoTsyo. In addition, the tablets will allow PEs to scan a patient's record "handbook" (log kept with the patient) to be verified by MoPoTsyo quality control staff should data appear suspicious. At the patient level, voice messages developed to address specific patient problems (eg, uncontrolled blood pressure or glucose, medications not picked up at the pharmacy, weight gain, etc) will be sent to patients based on the data received from the monthly visits to the PE. This study has randomly selected 75 PEs for assignment to 1 of 3 intervention groups—tablet+messaging, tablet only, or control (no tablet or voice messages). Figure 1 shows the study design. As we estimate that each of the 25 PEs in each group monitors about 60 patients, each arm of the study will include about 1500 participants for a total community sample of about 4500.

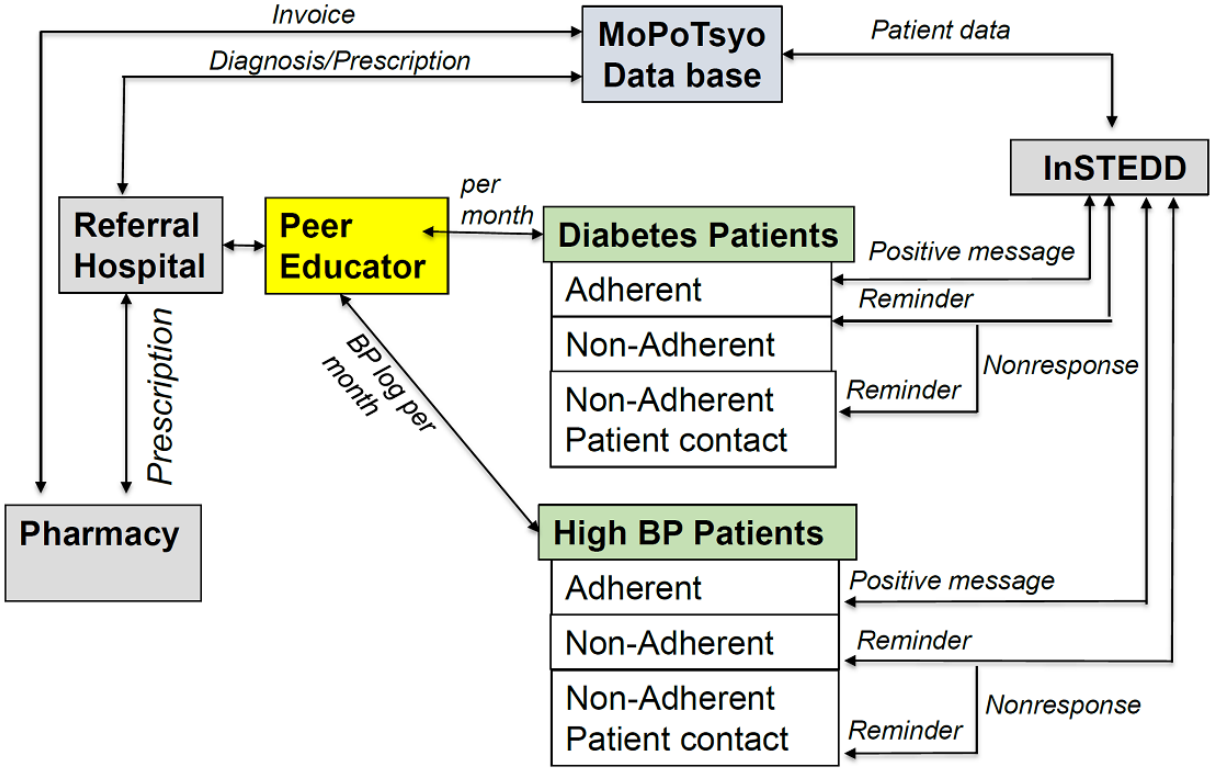
Electronic Data Capture

Fifty PEs (25 in the tablet+messaging group and 25 in the tablet only group) received a 12-inch Chuwi Hi12 Tablet with touchscreen compatible for Windows 10-Android 5.1 to record patient information each month. Data are entered online or offline during the patient visit with backup recorded in the patient handbook (log). Data are transferred to the MoPoTsyo database stored on a Dell PowerEdge T630 Server, RAM 32GB (Gigabytes), HDD 4TB, (hard disk 4 Terabytes), speed 2.4 GHz, Cache 20MB. The operating system is Windows Server 2012R2 with database application Microsoft SQL server 2014. Initial training has been provided by MoPoTsyo staff to assure PEs are comfortable with using the tablets for their monthly monitoring visits. It has become clear, perhaps because of their older age and lack of experience, that many of the PEs are challenged by the technical aspects of this new tool. We have begun weekly Web-conferences (broadcast on the tablets) to help address problems and increase PE skills in tablet use. In addition, pharmacies have received tablets to input prescriptions and provide information to MoPoTsyo regarding invoices when medications are purchased. We do not anticipate significant dropout of PEs based on historical experience. PEs seldom leave MoPoTsyo unless illness or death intervenes. Retention efforts for community participants include the free health monitoring provided by PEs and the social interactions that result in this popular program. PEs in all groups are coached to be vigilant in responding to patient questions and needs as well as to contact the MoPoTsyo Center with any issues that arise.

Voice Message Development

We used an exploratory qualitative study design to hear patient and PE perspectives on NCD management and mHealth. We used the 32-item checklist Consolidated Criteria for Reporting Qualitative Research [20] to guide our study design, data collection, analysis, and reporting of our research study. The Information-Motivation-Behavior theoretical framework was used to guide mHealth message development [21] based on providing accurate information, personal motivation, and social motivation to impact behavioral change in chronic disease self-management. We conducted focus groups (N=59) in Khmer with MoPoTsyo patients at 6 ODs within the study territory (Kampong Speu, Chamkar Leu, Baray-Santuk, Stoong, Kong Pisey, and Phnom Penh) to better understand the content of messages that would be most effective and provide guidance on logistics for sending them. Focus groups were held at community Health Centers and lasted for approximately 1.5 hours each. Focus group discussions were audiorecorded with participant permission. For the message content, the focus groups discussed current activities for managing NCDs (eg, medication use, doctor's visits, lab tests and monitoring, PE groups, and lifestyle changes in diet, physical activity, smoking, and alcohol use), as well as facilitators and barriers to these activities. For the message format, questions included the frequency and duration of messages, preference for text or voicemail format, access to cell phones, the best time of day to send, and ability to respond to a text. At each district, 2 PEs (convenience sample) were also interviewed to evaluate features of the tablet for tracking their patients, to provide outreach and assure usability.

Figure 1. Study design of the project. BP: blood pressure; InSTEDD: Innovative Support to Emergencies, Diseases and Disasters.



The taxonomy of behavioral change communication deemed most appropriate for our intervention can be best described by the Behaviour Change Wheel [22] using the following: sources of behavior of psychological capability, reflective motivation, and automatic motivation; intervention functions of education, persuasion, incentivization, and enablement; and policies driven by communication, marketing, and service provision.

Voice Message Implementation

We are contracting with experts at Innovative Support to Emergencies, Diseases and Disasters (InSTEDD) Southeast Asia to develop and implement the mHealth app for sending targeted phone messages to MoPoTsyo patients. The app "Verboice" is being used to access the information available in the MoPoTsyo database to tailor messages according to the specific characteristics of patients' disease. Verboice is a free and open-source tool developed by InSTEDD that runs apps through voice, allowing users to listen and record messages in their own language. At the time of informed consent, patients provided 2 current cell phone numbers, their own plus a backup belonging to a family member. Following the development of specific content for message themes identified in the focus groups, electronic capture of data provided by the PEs will allow us to match the specific issues and needs related to hypertension and diabetes management and send relevant messages to individual patients.

Outcomes

Process outcomes will follow guidelines of the RE-AIM Model [23] to include Reach (how representative is the sample to the targeted population?), Effectiveness (clinical and intermediate outcomes), Adoption (uptake, utilization, and initial implementation), Implementation (fidelity including adherence and delivery), Maintenance (sustainability), as well as acceptability (satisfaction with the intervention). Key clinical outcomes will include control of blood pressure and glucose, medication adherence, use of medical services (laboratory and physician office visits), and improvement in lifestyle factors such as smoking, body mass index, diet, and exercise. Comparisons will be made by the study intervention group at the end of the trial and by changes in clinical outcomes pre- and postintervention period. Furthermore, comparisons will be made for message effectiveness to determine whether certain message topics led to better clinical outcomes.

Data Management

Data collected by PEs during the pilot study will be entered into the tablet at their homes and will be transferred electronically to the newly enhanced Patient Information System database at MoPoTsyo headquarters. The collected data will be stored on a relational database management system and will be securely backed up to an offsite data center affiliated with MoPoTsyo. All data, however, will become a part of the patients' medical record for longitudinal tracking and access to clinical staff. These data will be available for inclusion in individual, as well as combined, data reports that are a part of the proposed information system.

All data will be monitored by a trained information techinology staff funded under the program dedicated to overseeing data. He will check for missingness and consistency using preprogrammed algorithms to identify problems. After cleaning, data to be analyzed for outcomes will be deidentified and formatted into analytic files for use by coinvestigators and analysts for evaluation.

Data Analysis

Qualitative Analysis

Audiorecordings from the focus group discussions will be transcribed and translated into English. A subset of transcripts will be back-translated to assure accuracy. The transcripts will be analyzed thematically according to the grounded theory approach. Analysis and interviewing will proceed concurrently so that participant responses and emerging themes can shape future focus group discussions and interviews. A coding scheme will be developed on the basis of the topic guide and emerging themes from the transcripts. Two researchers will independently code all transcripts and compare results. Any discrepancies in coding will be discussed and resolved by the research team. Results will be used to inform researchers of the content of messages within the mHealth app and improve the protocol for the introduction of eHealth communications within this project.

Statistical Analyses

Statistical analysis will be performed collaboratively between Cambodian collaborators and the University of Washington to provide experience to them in this activity. All outcomes, both process and clinical, will be described as N (%) or mean (SD) for categorical and continuous data, respectively. Changes in primary study outcomes, including blood pressure, fasting glucose, and medication adherence, will be calculated as the difference from the baseline to 12-month follow-up. We will evaluate study results 3 ways—first as an intention-to-treat comparison of study outcomes associated with patients in the intervention group versus the control group compared by a change in PE overall clinical outcomes for their patients (mean blood pressure, fasting glucose, and medication adherence). In addition, we will conduct an efficiency analysis using linear regression for the study outcomes evaluating group assignment, as well as other variables, calculated at the PE level (ie, % women, mean education, etc). Finally, we will analyze data at the patient level using Generalize Estimating Equations for each outcome evaluating group assignment and clustering data on PE. Primary dependent variables will include changes in the 3 pre and post continuous clinical outcomes—systolic and diastolic blood pressure, fasting blood glucose, and medication adherence as an intermediate outcome. Covariates will include demographics, baseline clinical values, and urban or rural residency of patients. In these analyses, we will use complier-average causal effects (CACE) to look at the efficacy and effectiveness of the mHealth intervention, which takes the clustering effect of PEs, as well as response of patients into consideration. In these patient-level models, we will conduct an intention-to-treat analysis to evaluate the total causal effect of assigning a PE to the mHealth intervention, regardless of compliance. CACE will also allow us to estimate the mHealth intervention's effectiveness on patient compliers, considering phone messages received and listened to. In CACE, actual treatment received (compliance to the mHealth treatment) becomes a postrandomized variable and effectiveness based on process outcomes (reach and compliance) are addressed. Analyses will be performed using STATA (StataCorp College Station). No interim analyses are planned.

Power

We will conduct the primary analysis evaluating mean differences of change in study outcomes by PE group assignment. With a sample of 50 (PE pairwise comparisons between the 2 intervention groups and controls) assuming an alpha of.05 and improvements of controls at a rate similar to 12-month change previously seen, we have 94% power to assess a 50% greater improvement in systolic blood pressure in the intervention group, and 79% power to assess a 40% greater improvement. We will have >99% power to detect differences in efficacy analyses. We believe that these are realistic goals based on results of other rigorous mHealth studies in LMIC [24]. Power calculations were completed using STATA (StataCorp College Station).

Results

Results of the qualitative research were used to develop the telephone messages according to 6 themes—medications adherence, laboratory testing, physician visits (either annual or for alert determined at PE visit), obesity and weight gain, smoking, and general lifestyle issues (diet, exercise, salt intake, etc). Based on the identified facilitators and barriers, the messages are designed to provide education, motivation, and reminders to help support self-management and address obstacles. Specific scripts were tested with patients and recorded in Khmer by a professional recording studio (Women's Media Center of Cambodia) using music and voice intonations suggested by advisors.

An algorithm was developed to identify patients needing specific content messages based on the most recent data that were sent electronically to the MoPoTsyo database by the PEs. The delivery of messages was decided according to focus group suggestions, including the use of voicemails rather than text, sending messages at dinnertime or shortly afterward so that a person is at home and can share with family members, limiting frequency to 2-3 messages per week, and eliminating interactive requirements owing to limited access to smartphones and lower cell phone literacy in many rural communities. Results of Verboice tracking allows us to determine which messages successfully reached patients (for later efficacy analyses) and allows the system to send messages additional times when not initially completed.

The focus groups and informant interviews used to develop the mHealth messages were completed during the Spring of 2017. Results of this qualitative work were used to develop the mHealth messages, which were then tested over the summer. Following several revisions of content wording, music, and messenger voice, messages were finalized in July 2017 after which InSTEDD provided channels for delivery of specific themes of message to patients identified by PE data. While the implementation was originally scheduled for 6 months from September 2017 to March 2018, the period was extended 4 additional months because of budgetary efficiencies. Data are currently being cleaned and analyzed. We project that we will have results by Spring 2019.

We plan to disseminate results of this study through workshops and presentations to our Advisory Committee, the Cambodian Ministry of Health (Department of Preventive Medicine), and other health partners (eg, National Institute of Public Health in Phnom Penh) and technology experts (private and public). Furthermore, results will be available in report and presentation format on the website of MoPoTsyo Patient Information Center and the University of Washington Department of Family Medicine. We will use the results of the study to provide evidence-based recommendations to the Ministry of Health as they prepare pilot and other programs and policy for addressing NCDs across Cambodia.

Discussion

This protocol provides information on a new intervention to develop and test mHealth and eHealth interventions to utilize an existing peer support network for improving hypertension and diabetes management in Cambodia. Our formative work, to develop and pilot-test the messages and distribute the tablets, suggests that his approach may be feasible in other LMIC.

The value of peer support in chronic disease management has been well documented and is a viable alternative when health care infrastructure is inadequate to meet needs [25]. While mHealth messaging programs have rapidly increased in LMIC, evaluations of these programs remain limited and provide inconsistent results [26]. The variety of different features and measured outcomes included in such studies also makes comparisons difficult. While the majority of studies in the literature utilize SMS text messaging, we chose voice messages in our intervention owing to the low literacy rate of our target population. In addition, other mHealth studies in low-resource settings have documented a preference for voice messages by targeted populations. For example, 99% of mothers participating in the Mobile Midwife program in Ghana preferred voice messages over text [27]. Similarly, a study of 488 mobile phone users in India found that 89% preferred to receive medication reminders by voice calls over SMS text messages [28]. Several other studies selecting a voice approach have reported positive results [29-31].

Interactive systems, allowing the recipient to respond to a message on their phone pad, have suggested benefits, although we chose to exclude such a feature as our focus groups informed us that this was confusing to patients. In terms of outcomes, many studies have reported benefits in proxy measures, such as medication adherence, clinic attendance, or behavioral change [30,32-36]. Although improvements in clinical outcomes may be of greatest value in disease control, studies reporting these outcomes are unfortunately less common [13,29,37,38]. Finally, while it is established that mHealth messaging systems involving personalized content are generally more successful [39], personalized interventions are also less common in LMIC, and accessing patient data that are both appropriate and timely may not be possible in many of these settings. As mHealth solutions for electronic health recording and data capture increase, tools for monitoring and accessing timely patient data can provide community health workers, PEs, and providers the information they need to offer relevant and personalized care to patients. Such an approach may be especially useful for managing patients with chronic conditions. This protocol was designed to address these barriers.

While this protocol has many strengths, including the stable infrastructure and PE training already in place by MoPoTsyo, there are a number of limitations, which primarily involve the ability of the targeted messages to reach participants. Problems may involve cell phone network coverage and reliability, cell phone number changes, use of phones across family members, and lack of interest in listening to the messages. Other problems may include the reluctance of PEs to use the tablets in a timely manner, loss of tablets, and factors outside of our control (ie, lack of money to cover medications, etc). While strategies have been developed to minimize these issues, they may still impact the effect of the intervention.

The protocol described here represents an effort to integrate improved data technology for collecting data (eHealth) with individualized voice messaging (mHealth) to encourage self-management of hypertension and diabetes in a low-resource setting. We hypothesize that targeting specific health issues of relevance to patients will be more effective in encouraging good behavior than generic messaging often used in mHealth studies. We hope to show that the promotion of greater communication across providers and patients is feasible in LMIC and will result in better clinical outcomes for their patients.

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Authors' Contributions

The overall study direction and monitoring was provided by ALF and MvP; study design by ALF, JPL, MvP, and CC; operational activities, including data collection, by HH and LS; data management by HH; data analysis by ALF, LS, and HH; study monitoring and advisement by JPL and CC; and writing by ALF, LS, and NI.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report from the National Institutes of Health.

[PDF File (Adobe PDF File), 151KB - resprot_v8i3e11614_app1.pdf]

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Abbreviations

CACE: complier-average causal effects
eHealth: electronic health
InSTEDD: Innovative Support to Emergencies, Diseases and Disasters
LMIC: low- and middle-income countries
mHealth: mobile health
NCD: noncommunicable disease
OD: Operational District
PE: peer educator
SMS: short message service

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Protocol

Using Values Affirmation to Reduce the Effects of Stereotype Threat on Hypertension Disparities: Protocol for the Multicenter Randomized Hypertension and Values (HYVALUE) Trial

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Abstract

Background: Medication nonadherence is a significant, modifiable contributor to uncontrolled hypertension. Stereotype threat may contribute to racial disparities in adherence by hindering a patient's ability to actively engage during a clinical encounter, resulting in reduced activation to adhere to prescribed therapies.

Objective: The Hypertension and Values (HYVALUE) trial aims to examine whether a values-affirmation intervention improves medication adherence (primary outcome) by targeting racial stereotype threat.

Methods: The HYVALUE trial is a patient-level, blinded randomized controlled trial comparing a brief values-affirmation writing exercise with a control writing exercise among black and white patients with uncontrolled hypertension. We are recruiting patients from 3 large health systems in the United States. The primary outcome is patients' adherence to antihypertensive medications, with secondary outcomes of systolic and diastolic blood pressure over time, time for which blood pressure is under control, and treatment intensification. We are comparing the effects of the intervention among blacks and whites, exploring possible moderators (ie, patients' prior experiences of discrimination and clinician racial bias) and mediators (ie, patient activation) of intervention effects on outcomes.

Results: This study was funded by the National Heart, Lung, and Blood Institute. Enrollment and follow-up are ongoing and data analysis is expected to begin in late 2020. Planned enrollment is 1130 patients. On the basis of evidence supporting the effectiveness of values affirmation in educational settings and our pilot work demonstrating improved patient-clinician communication, we hypothesize that values affirmation disrupts the negative effects of stereotype threat on the clinical interaction and can reduce racial disparities in medication adherence and subsequent health outcomes.

Conclusions: The HYVALUE study moves beyond documentation of race-based health disparities toward testing an intervention. We focus on a medical condition—hypertension, which is arguably the greatest contributor to mortality disparities for black patients. If successful, this study will be the first to provide evidence for a low-resource intervention that has the potential to substantially reduce health care disparities across a wide range of health care conditions and populations.

Trial Registration: ClinicalTrials.gov NCT03028597; https://clinicaltrials.gov/ct2/show/NCT03028597 (Archived by WebCite at http://www.webcitation.org/72vcZMzAB).

International Registered Report Identifier (IRRID): DERR1-10.2196/12498

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KEYWORDS

hypertension; social values; African Americans; medication adherence; health care disparities

Introduction

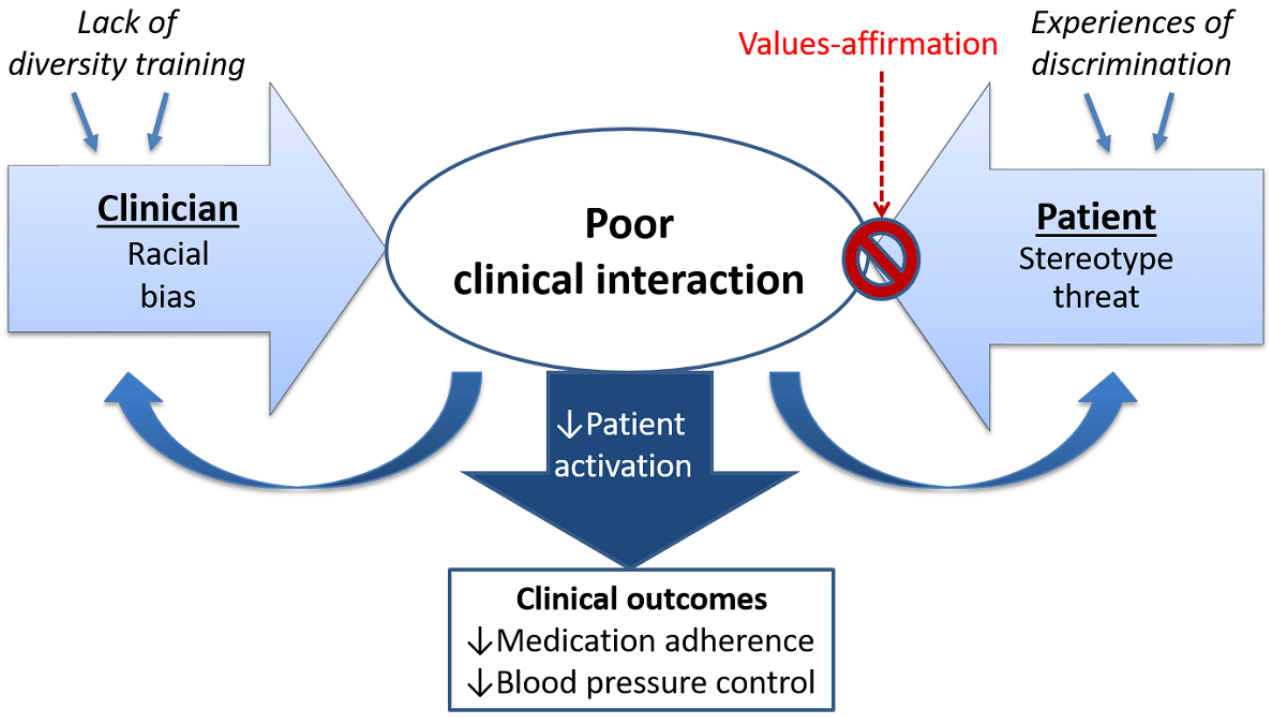
Black Americans have a higher prevalence of uncontrolled hypertension than white Americans, leading to disparities in cardiovascular outcomes [1-4]. Uncontrolled hypertension disproportionately affects black patients than white patients. A 10 mm Hg difference in systolic blood pressure (SBP) is associated with an 8% increase in stroke risk for white patients and a 24% increase in risk for black patients [5]. Targeting uncontrolled hypertension has the potential to improve health outcomes for black patients.

The Institute of Medicine, World Health Organization, and others have identified poor adherence to medications as the most significant, modifiable contributor to uncontrolled hypertension [6-11]. The prevalence of poor adherence to antihypertensive medications ranges from 43% to 78%, with approximately 50% of hypertensive patients discontinuing the use of their medications after 1 year [11,12]. Poor adherence to antihypertensive medications is associated with poor outcomes and improving adherence reduces blood pressure (BP) [9-11,13-16]. Adherence rates are lower in black than white patients, with hypertension, and nonadherence has been shown to contribute to racial differences in hypertension control [7,17-20]. Targeted interventions to improve adherence in black patients have the potential to reduce racial disparities in hypertension outcomes.

Stereotype threat may contribute to the racial disparity in adherence. Stereotype threat occurs when cues in the environment (such as visiting a white doctor's office) trigger the threat of confirming, as self-characteristic, a negative stereotype about one's group [21]. Although any individual may experience stereotype threat, black patients are at a greater risk due to widespread negative stereotypes and past experiences of discrimination [22-37]. In the clinical setting, black patients report stereotype threat related to being viewed as unintelligent, *second class citizens*, and unworthy of good care [21,36,38-40]. Stereotype threat triggers psychological and physiological responses including reduced memory capacity, impaired communication, disengagement, and reduced motivation [41,42]. Stereotype threat may contribute to racial disparities in adherence to treatment by hindering a patient's ability to process information and actively engage in a discussion about their health during a clinical encounter [21,43]. On the basis of this poor clinical interaction, the patient may feel less activated to adhere to treatment recommendations [21,44]. Therefore, interventions targeting stereotype threat have the potential to reduce disparities in adherence and potentially in BP control among populations that experience widespread discrimination (Figure 1).

Interventions based on values affirmation have been shown to reduce stereotype threat and decrease racial disparities in academic outcomes [45]. These interventions typically ask participants to write about their core values, such as family, religion, or art [45]. By focusing on values that are important to them, values affirmation helps people to view themselves as worthy, effective, and able to control important outcomes despite perceived threats to oneself (eg, stereotype threat) [46-48]. Values-affirmation interventions have been associated with reduced stress and improved academic performance among stigmatized group members [49-53]. Cohen et al demonstrated that participation in an affirmation exercise at the beginning of the academic term reduced racial achievement gaps among black children by 40%; these effects were sustained 2 years later [49,50]. Our pilot work among 99 black patients at a single clinic analyzed the audiotaped patient-provider interactions and demonstrated that values affirmation significantly improved patient and clinician communication [54]. However, whether the intervention improves clinical outcomes such as adherence has not been evaluated. Furthermore, as the intervention was only conducted among black patients, our pilot study cannot determine whether values affirmation is targeting stereotype threat related to race or the general threat of illness. On the basis of the evidence supporting the effectiveness of values affirmation in educational settings and our pilot work demonstrating improved patient-clinician communication, we hypothesize that values affirmation disrupts the negative effects of stereotype threat on the clinical interaction and can reduce racial disparities in medication adherence and subsequent health outcomes.

Figure 1. Conceptual model for reducing adherence disparities via targeting stereotype threat.



We are conducting the Hypertension and Values (HYVALUE) study—a randomized controlled trial (RCT) in black and white patients with uncontrolled hypertension—to compare a values-affirmation intervention with a control exercise in 3 health care systems. Our primary objective is to examine whether patients in the intervention condition experience improvements in medication adherence relative to the control condition and compare these effects by race. Our secondary objective is to compare the intervention effects on BP over time, time for which BP is under control, and treatment intensification. Finally, we seek to determine moderators and mediators of intervention effects on patient outcomes over time.

Methods

Study Design and Setting

The HYVALUE study is designed as a patient-level, randomized, controlled, double-blinded, multicenter trial in primary care clinics in the United States. Clinics reside within 3 large health care systems that care for diverse populations: Denver Health Medical Center, Kaiser Permanente Colorado, and Kaiser Permanente Mid-Atlantic States. The study was registered on ClinicalTrials.gov on January 23, 2017 (NCT03028597). Recruitment began in February 2017 and is anticipated to continue through 2020 at medical centers in Colorado and Maryland. Enrollment is currently occurring in 10 clinics and we will add more clinics as needed to meet recruitment targets. As of December 10, 2018, a total of 623 patients are enrolled and a total of 1130 are planned.

Study Population and Recruitment

The HYVALUE study is enrolling self-identified black and white patients who have uncontrolled hypertension, who meet all eligibility criteria, and who consent for the study. Patients with a diagnosis of hypertension with an upcoming clinic visit in a participating primary care clinic are screened on a regular basis for inclusion criteria using the electronic health record (EHR). Diagnosed hypertension is defined as having an outpatient visit in the past 24 months with a primary or secondary ICD-10 (International Classification of Diseases, 10th revision) code diagnosis of hypertension. Uncontrolled BP is defined as having SBP ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg at least once during the preceding 12 months [54]. We have chosen a broad definition of uncontrolled BP as over 25% of patients with previously controlled BP lack BP control over the following year, likely due to nonadherence [55,56].

Additional inclusion criteria are age 21 years or above, self-described race and ethnicity as non-Hispanic black or non-Hispanic white, currently taking antihypertensive medications that are filled within patients' health system's pharmacy, and the ability to read and write English. Patients who are currently pregnant, have pregnancy-related hypertension, or have end-stage renal disease are excluded as not being representative of the broader population of patients with chronic hypertension. Patients are also excluded if they are unable to provide consent.

Patients meeting inclusion criteria are identified by data analysts from each site's EHR and eligible patient lists are provided to the site research assistants on a weekly basis. Research assistants invite eligible patients to participate via telephone. The study team has implemented contingency strategies for meeting our target sample size. Such strategies have included adding recruitment locations in each health system, reallocating site-level resources toward recruitment efforts, and sending

invitation postcards and emails to eligible patients before phone contact to introduce and increase interest in the study. Telephone contact is made before patients' scheduled appointments to describe the study and answer any questions. If patients express interest in the study, eligibility is confirmed and patients are asked to arrive 1 hour before their clinician's appointment to complete the baseline enrollment (index) visit (described below). Patients are asked to bring all BP medication bottles with them to appointments and are compensated for their time with a $20 (US) gift card at each visit.

Study Protocol and Randomization

At the index visit, the on-site research assistant obtains informed consent and measures BP in accordance with policies set at each participating clinic. BP measurements are taken by standard clinic-grade calibrated automatic monitors at each site. To standardize methods across sites, BP is measured using the right arm, while patients are relaxed with both feet on the floor, using a well-fitting and calibrated cuff per guideline-recommended procedures [57]. A second BP measurement is taken at least 30 seconds after the first. Data are entered into the study database in real time and research assistants are prompted to take a third measurement when there is a large discrepancy between the first 2 measurements (at least 20 mm Hg systolic or 10 mm Hg diastolic). As part of the index visit, research assistants count the pills in each patient's BP medication bottles and the patient completes surveys including (1) a demographics questionnaire, (2) a measure of past experiences of discrimination [58-62], and (3) a self-reported adherence measure [63].

After patients complete the previsit surveys, they are given a prerandomized, consecutively numbered packet containing either an intervention or control version of the values-affirmation exercise. Packets are randomized into separate series by race and medical center, using block randomization with random block size to ensure balanced randomization. The randomization was created by the data coordinating center analyst before the initiation of patient recruitment using SAS 9.4 (SAS Institute, Cary NC). The randomization lists for each site are stored in an access-restricted electronic folder and neither the research staff nor clinic staff know the patient's study condition. Study packets are prepared by staff who are not involved in recruitment or enrollment. Each study packet contains a second, unlabeled envelope inside with either the intervention or control writing exercise. On-site research assistants provide general instructions that apply to both the intervention and control exercises. The patients complete the writing exercise on their own and are reminded not to unblind study staff to their condition. After completion of initial study activities, patients then proceed to their scheduled appointment with their clinician (Figure 2).

Following the appointment with their clinician, patients complete postvisit surveys including (1) a measure of patient activation [64]; (2) a measure of attitude, perceived social norms, perceived behavioral control, and emotion toward BP control [65,66]; and (3) a measure of satisfaction with their clinician [67]. Patients are contacted to schedule 3- and 6-month follow-up visits and, where possible, visits are scheduled during preexisting follow-up appointments scheduled with clinicians. Research assistants call patients 1 or 2 days ahead of time to remind them of the upcoming appointments. At 3 months, patients complete a follow-up study visit that includes measures of BP, pill counts, self-reported adherence, patient activation, and attitudes. Patients return at 6 months for a visit identical to the 3-month study visit (Figure 2). When patients choose to discontinue further study visits, are unreachable, fail to attend follow-up visits, or otherwise deviate from the study protocol, we continue to collect adherence and BP data over time via electronic pharmacy fill and the EHR.

Values-Affirmation Intervention

All patients are randomized to either the values-affirmation intervention or control writing exercise. When the research assistants introduce the intervention tasks to the patient, they remain available for questions but otherwise do not participate in the completion of the task and remain blinded to the instructions and content of the exercise. The intervention task asks patients to reflect on a list of 11 personal values or self-defining skills and circle the 2 or 3 that are *most important to them* or that characterize them best (Figure 3). Next, patients are asked to think about the times when the values chosen were important and then write a few sentences to describe why they were important. Finally, the self-affirmation of values is reinforced by asking patients to indicate their level of agreement with 4 statements concerning the selected values: (1) *these values have influenced my life*, (2) *in general, I try to live up to these values*, (3) *these values are an important part of who I am*, and (4) *I care about these values*.

The control writing exercise asks patients to circle the 2 or 3 values that are *least important to them*. Control patients receive the same instructions to write a few sentences about the values chosen but are asked to describe when and why these least important values might be *important tosomeone else*. The final rating task asks patients to indicate their level of agreement with slightly altered statements: (1) *these values have influenced some people*, (2) *some people may try to live up to these values*, (3) *these values may be important to some people*, and (4) *some people care about these values*. After the task, patients place their responses in an envelope, seal them, and return them to the research assistant.

Figure 2. Study protocol flowchart.

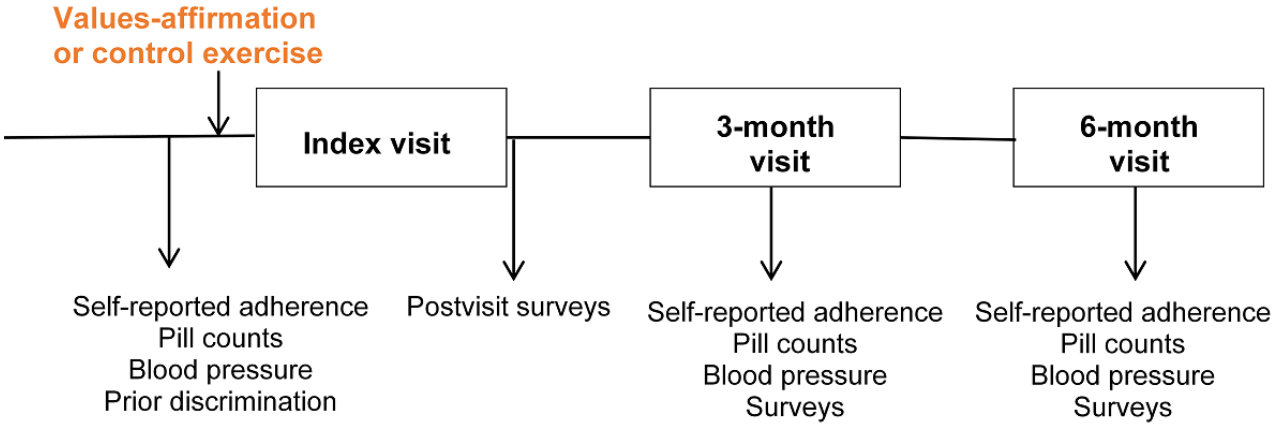
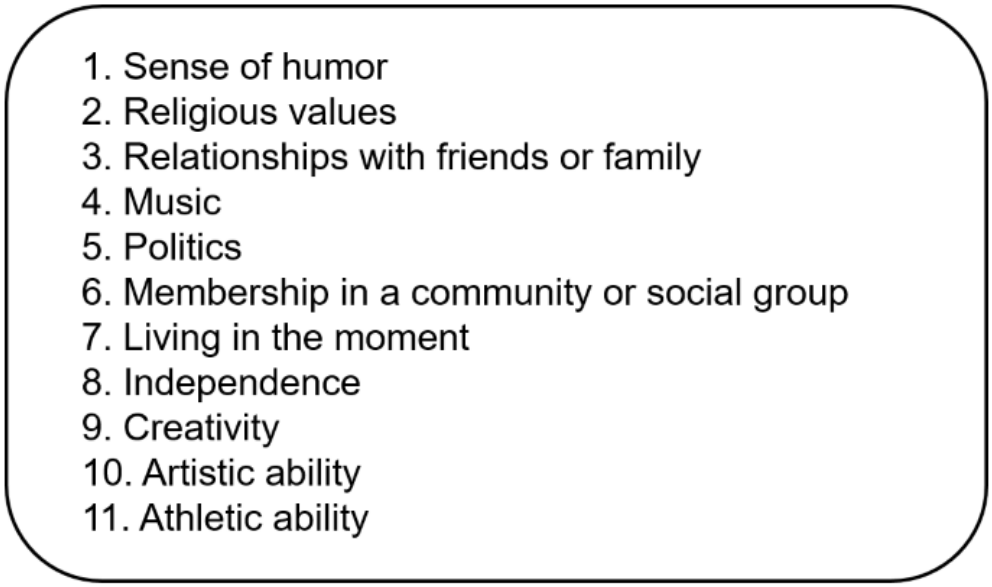


Figure 3. List of values for the intervention and control exercises.



Outcomes

The primary outcome is medication adherence over time. To address limitations inherent to each measure of medication adherence, 3 measures that differ in the behavior measured and time frame of observation are collected. The first measure of adherence reflects the intent to take a medication based on electronic pharmacy fill data. Pharmacy fill–based adherence assesses the proportion of days over the period of observation for which a patient obtains antihypertensive medications [68-73]. Pharmacy fill–based adherence will be calculated for each antihypertensive drug in the regimen and averaged across drugs into a summary measure of adherence for the entire drug regimen using the method developed by Steiner et al [68]. We will calculate pharmacy fill–based adherence for the 12 months before the index visit, 0 to 3 months, and 3 to 6 months after the index visit. The second measure of adherence is based on self-report of pill taking behavior over the previous 7 days [74]. This validated self-report instrument [63,75] is administered at each study visit. The third measure of adherence is based on pill counts that estimate pill taking behavior since the last medication refill. At each study visit, the research assistant enters the antihypertensive medication name, prescription fill date, number of pills prescribed, number of pills the patient should take every day, and recorded number of pills in the bottle into the research database. An embedded algorithm calculates pill count–based adherence for each medication [73]. All measures of adherence will be analyzed separately as primary outcomes. Medication adherence over time will be compared for intervention versus control patients and by race, as described below. Secondary outcome analyses will consider a composite adherence variable that takes missing data into account.

Secondary outcomes include SBP and DBP over time, time for which BP is under control (the proportion of time over follow-up with a BP ≤140/90 mm Hg) [57], and treatment intensification, which will be calculated by subtracting the number of expected intensifications (number of visits after enrollment with a BP ≥140/90 mm Hg) from the number of observed intensifications (either an increase in dose or addition of a new medication class) and then dividing this difference by the number of office visits over the study period [76].

Patient Moderators and Mediators

We will assess patients' prior experiences of discrimination as a potential moderator of the intervention effects [58-62]. We are using a 4-item questionnaire about prior experience of discrimination modified from prior scales measuring lifetime discrimination related to health care [58-62]. Responses are on a 5-point Likert scale ranging from *never* to *all of the time*.

Cognitive factors will be explored as mediators [77] of the intervention effect on adherence, including patient activation [64,78,79], patient impressions of their visits [67], and constructs from a modification for hypertension of the theory of planned behavior (attitude, perceived social norms, perceived behavioral control, and anticipated emotion toward managing their BP) [65,66].

Patient activation is measured by a low-literacy version of the 13-item instrument developed by Hibbard, the Patient Activation Measure (PAM) [64]. Increases in the PAM are associated with increased self-management behavior including adherence [78-80]. Patient activation measured with the PAM is lower for black patients than it is for white patients and is therefore hypothesized to be a contributing factor to racial health disparities [81].

Patients' impressions of their visits are measured using Barr's 4-item clinician-specific modification of the Medical Outcomes Study Visit Satisfaction Questionnaire, which is sensitive to differences in patient satisfaction by race [67].

Patient attitudes regarding their BP are measured by relying on constructs from the Theory of Planned Behavior, which posits behavior intention as the most proximal predictor of behavior and that intention is influenced by an individual's attitude toward the behavior, the perceived social norms surrounding the behavior, and an individual's perceived control over the behavior [82]. Taylor et al modified this theory by adding the concept of desire for the behavior and its consequences, which in turn is influenced by the anticipated positive and negative emotions associated with the behavior [65]. Perugini and Bagozzi tested the theoretical constructs in patients with hypertension [65,66]. We have adopted the questions from this study to assess patient attitudes, norms, perceived control, and emotions around BP management. We have added an additional question to include physicians' opinions in the patients' perception of social norms: *I care what my doctor thinks about my efforts to control my BP*.

Clinician Substudy

As the clinical encounter may also be affected by clinician factors, we are conducting a substudy with clinicians. The primary aim of this substudy is to evaluate clinician factors that may moderate the relationship of the intervention with patient adherence including clinician implicit racial bias, prior cultural awareness training, and self-efficacy regarding caring for black patients. These measures were chosen based on literature suggesting that these factors influence the quality of the patient-clinician interaction and are associated with differences in racial attitudes among health care clinicians [83-85].

Clinician measures include the Black-White Implicit Association Test (IAT), which uses reaction times to assess the strength of automatic associations between race (black and white) and evaluations (eg, positive words and negative words). Results indicate that participants have an implicit preference for white over black individuals if they are faster to categorize words when white faces and positive words share a response key and black faces and negative words share a response key, relative to the inverse. The larger this performance difference, the stronger the implicit bias. The IAT has been widely validated, is reliable over time, and is associated with discriminatory judgments and behaviors [86-93]. The IAT has been used in the health care setting to measure clinician bias [20,94]. We also ask participating clinicians about past exposure to cultural awareness or diversity training and the degree to which they feel (1) *prepared to care for a patient who identifies as African American*, (2) *skilled about overcoming unintended or implicit racial bias related to African American patients*, and (3) *skilled about developing a positive relationship with African American patients* [83].

All clinicians at the participating clinics are invited to complete the clinician surveys; patient participation is independent of whether their clinician participates. Clinician recruitment began in November 2017.

Sample Size Justification

For our primary analysis, we assume a 3-level model, with patients nested within clinicians and clinicians nested within clinics. Assuming comparable variation in adherence and alpha=.05, a sample size of 960 participants and 1:1 enrollment by race (240 in each study condition, for each racial group; approximately 480 black and 480 white patients) will be required to detect a 0.26 effect size difference in adherence between any 2 cells with a power of 80%. A 0.26 effect size is approximately a 4.7% absolute difference in adherence scores (assuming SD=18.1) between black and white patients using the pharmacy fill data. A 2:1 enrollment ratio for black versus white patients (approximately 640 black and 320 white patients) would provide >80% power to detect a 0.28 effect size difference or an absolute difference in adherence scores of 5.1% between black and white patients receiving the intervention. We anticipate enrolling an additional 170 patients to compensate for attrition, for a projected final sample size of 1130. As randomization is at the patient level, the intraclass correlation coefficient for patients nested within clinicians will have a negligible effect on power.

For the secondary outcome measure of BP, this sample size has a power of 80% to detect a 4.7 mm Hg difference in SBP between any 2 cells (based on data from patients meeting criteria for another study). For perspective, in a study of a pharmacist-led multimodal intervention, an increase in adherence from 62% (n=179) to 97% (n=159) at 6 months (a 35% absolute increase) was associated with a decline in SBP from 133.2 mm Hg to 129.9 mm Hg (a 3.3 mm Hg absolute decrease) [16]. Thus, the study is likely underpowered to detect a difference in SBP through adherence change alone. Given the established link between higher adherence rate and improved clinical outcomes, we believe a study powered to detect an adherence difference will be sufficient evidence to move this intervention forward into clinical practice [71,95,96]. Sample

size calculations were generated using SAS 9.4 (SAS Institute, Cary NC).

Statistical Analysis

Data analysis of the trial results will begin when all enrolled patients have completed follow-up. Descriptive statistics (chi-square and *t* tests) will be computed to determine whether there are differences between eligible patients who have enrolled and those who have not enrolled, between patients randomized to different study arms, or between dropouts and nondropouts.

Before beginning analyses of outcomes, we will examine the data to determine whether patterns of missingness are ignorable (Missing Completely at Random or Missing at Random) or nonignorable (Missing Not at Random) [97-99]. We will employ likelihood–based methods that utilize all available data, adjusting for covariates that are associated with missingness. If missingness is nonignorable we will employ pattern mixture models [100]. Sensitivity analyses will be carried out using multiple imputation approaches.

The 3 primary measures of adherence will be evaluated in separate analysis. The pharmacy fill– based adherence measure is continuous; in the event that normality assumptions are not met, we will use transformations to normalize distributions. For the primary comparisons, we will employ intent-to-treat analyses, although we expect few or none of the randomized patients to not complete an exercise. We will create models with adherence over time as the dependent variable and assignment to values affirmation or control exercise as the treatment variable. We will examine the effect of values affirmation on change in overall medication adherence and by racial groups. We will use general linear mixed models with random effects for patient and clinic to determine whether change in adherence differs by study arm and race. Fixed effects will include time (preintervention, 0 to 3 months, and 3 to 6 months), race, study arm, all 2-way interactions, and the 3-way interaction. The 3-way interaction term (time×race×study arm) will test for a differential intervention effect by race. Models will then be assessed after including potential moderator variables (eg, patients' prior experiences of discrimination) and similarly for potential mediator variables (eg, patient activation, attitude, social norms, perceived behavioral control, and anticipated emotion) [101]. Analysis using the pill count measure of adherence will be similar to the methods described for the pharmacy fill measure. For analysis using the self-reported adherence measures, we will dichotomize the groups into nonadherent (score ≥2 on any *extent* item) and adherent. For this analysis we will use a mixed effects logistic regression model (generalized linear mixed model).

For the secondary outcome of BP, we will examine differences in SBP over time by intervention group and race using longitudinal mixed effects models with random intercepts and slopes. Similar to the analysis described above, the 3-way interaction term (time×study arm×race) will test for differential intervention effectiveness (differences in slopes).

Given evidence suggesting bias effects vary by age, the intervention effect will be compared by patient age [84]. Other a priori planned subgroup comparisons for hypothesis generation include patient gender, number or years living in the United States, socioeconomic status, BP control status, clinician race, and number of medications.

In the clinician substudy, among the patients whose clinicians submitted a survey, we will explore whether the collected clinician variables (implicit racial bias, past cultural competency training, and self-efficacy) moderate the relationships. We will also include patient gender and clinician race as possible moderating variables.

All hypothesis tests will be 2-sided with alpha=.05. Statistical analysis will use SAS 9.4 (SAS Institute, Cary NC).

Study Ethics

The principal investigators are ensuring the conduct of and oversight for the study according to National Institutes of Health (NIH) and national policies. The institutional review boards (IRBs) for the University of Colorado School of Medicine and Denver Health (the Colorado Multiple Institutional Review Board), Kaiser Permanente Colorado, and Kaiser Permanente Mid-Atlantic States have reviewed and approved the study. Continuing review of study enrollment and procedure is required annually by each IRB and adverse events are required to be reported on an ongoing basis.

Patient informed consent is obtained in a clinic examination room or other private area to allow the process to be private and confidential. Following elucidation of the nature, risks, and possible benefits of the study, patient participants are asked to sign written informed consent as approved by the IRB for their respective health system. The consent process explicitly states the decision on whether or not to participate will in no way affect current or future care. Furthermore, the consent process is carried out by research staff, not clinic personnel, further decoupling the research and patients' usual care.

For the clinician substudy, clinician informed consent is administered at the survey website. After using their unique study identifier to log on to the study website, clinicians are informed about the goals and procedures of the research including information about both their direct participation (ie, completing the online survey) and the participation of their patients (ie, associating their attitudes data to patients' data). No signature or any other paperwork is collected from the clinician participants, thereby eliminating identification from sources outside of study personnel.

Data Management and Monitoring

The risk of inadvertent or unauthorized release of confidential participant information is prevented in a number of ways. As a general step, all paper documents are stored in a locked file whose sole purpose is storage of clinical research material. Patient survey data are collected and managed using REDCap hosted at the University of Colorado [102]. REDCap is a secure, Web-based application designed to support data capture for research studies. Each health system maintains extensive patient clinical data in a series of standardized virtual data warehouses that are available for research applications; deidentified data from each site will be transferred to the primary analytic site via a secure encrypted website at the time of analysis. Clinician

survey data are collected using a Web server at the University of Colorado, which uses encryption for data transfer between the respondent's computer and the research server. All data will be deleted from the site servers 5 years following completion of analyses.

In addition to multisite IRB oversight, a data safety monitoring board (DSMB) is in place. The board has 3 members with expertise in biostatistics, primary care, and cardiology who are outside of the investigative team. The DSMB reviewed the protocol before the implementation and will continue to meet at least every 12 months throughout the study. The board reviews evidence of any study-related adverse events, data quality and completeness, and adherence to the protocol. DSMB meeting summaries are reported to each site IRB and to the project funder. Interim analyses and protocol revisions are currently not planned but will be conducted upon the request of the board.

Study results will be disseminated to researchers and the public via publication and conference presentations, to participating clinicians via site-level meetings, and to other stakeholders as appropriate.

Results

This RCT was funded by the National Heart, Lung, and Blood Institute, and the results can provide evidence for a low-resource intervention that may reduce health care disparities across health care conditions and populations. Planned enrollment is 1130 patients. Data collection is ongoing and the results are expected in early 2021. On the basis of the evidence supporting the effectiveness of values affirmation in educational settings and our pilot work demonstrating improved patient-clinician communication, we hypothesize that values affirmation disrupts the negative effects of stereotype threat on the clinical interaction and can reduce racial disparities in medication adherence and subsequent health outcomes. If successful, a values affirmation intervention could reduce disparities in hypertension outcomes.

Discussion

The primary objective of the HYVALUE study is to assess the effect of a values-affirmation exercise on medication adherence of black and white patients with hypertension, using a blinded RCT. Widespread exposure to discrimination among minority populations increases stereotype threat, making intervention even more important. Stereotype threat may impair communication between minority patients and their clinicians because of increased stress, resulting in interactions that are less successful at enhancing patient engagement with hypertension treatment, which in turn could result in lower rates of adherence with antihypertensive medication (Figure 1). This notion implicates stereotype threat as a cause of poor health outcomes for minority patients.

We hypothesize that a values-affirmation exercise performed before a patient-clinician visit reduces the impact of stereotype threat, ultimately resulting in better adherence to prescribed antihypertensive medications. The HYVALUE trial includes a sample of patients with uncontrolled hypertension from 3 health care systems, who are randomized to perform a brief values-affirmation writing exercise or a control writing exercise before a scheduled clinic visit. The primary outcome is adherence to antihypertensive medications and the secondary outcomes are BP over time, time for which BP is under control, and treatment intensification. To better understand the effects of the intervention, we are measuring theory-driven potential mediators and moderators. If the intervention improves adherence, this study will be the first to implicate stereotype threat related to race directly in the genesis of health disparities and will provide evidence for a low-resource intervention that could substantially reduce health disparities across a wide range of conditions and populations.

The HYVALUE study is innovative for the following reasons. First, we use a unique intervention that has been widely successful at reducing racial disparities in other domains [48-52]. Values affirmation has been shown to improve communication between black patients and white clinicians; however, no study has examined whether the intervention improves clinical outcomes [103]. Second, the theoretical model (Figure 1) on which this proposal is based is supported by patient engagement theory [104]. The HYVALUE study will be the first study to evaluate whether values affirmation improves patient activation and reduces racial disparities in clinical outcomes. Third, compared with existing interventions to improve adherence, values affirmation is significantly less time and resource intensive, enhancing the potential for the intervention to be embedded in primary care [105]. Finally, stereotype threat is not specific to hypertension outcomes or black patients. Health care disparities have been demonstrated across numerous disease states and minority groups [106]. Therefore, a simple intervention targeting a common mechanism has the potential to significantly reduce a wide range of health disparities.

Conclusions

The HYVALUE study moves beyond documentation of race-based health disparities towards testing an intervention. We focus on a medical condition – hypertension – that is arguably the single greatest contributor to mortality disparities for blacks. Our pilot data suggest a values-affirmation intervention improves patient-clinician communication. The HYVALUE trial is comparing a brief values-affirmation writing exercise with a control writing exercise among black and white patients with uncontrolled hypertension. If successful, this trial will provide evidence for a low-resource intervention that has the potential to substantially reduce health care disparities across a wide range of health care conditions and populations.

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Conflicts of Interest

This study and all authors are supported by R01 HL133343 from the National Heart, Lung, and Blood Institute. SLD, IVB, EPH, and JFS are supported by award 15SFDRN24470027 from the American Heart Association. JFS is supported by research funding from Kaiser Permanente. SV is supported by research funding from Sanofi Inc. The views expressed in this manuscript represent those of the authors and do not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the American Heart Association. All other authors report no additional conflicts in relation to this manuscript.

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Abbreviations

BP: blood pressure
DBP: diastolic blood pressure
DSMB: data safety monitoring board
EHR: electronic health record
HYVALUE: hypertension and values
IAT: implicit association test
IRB: institutional review board
NIH: National Institutes of Health
PAM: patient activation measure
RCT: randomized controlled trial
SBP: systolic blood pressure

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Protocol

Brief Exercise Counseling and High-Intensity Interval Training on Physical Activity Adherence and Cardiometabolic Health in Individuals at Risk of Type 2 Diabetes: Protocol for a Randomized Controlled Trial

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Abstract

Background: Worldwide incidence of type 2 diabetes (T2D) is rapidly increasing. Given the numerous negative health consequences associated with T2D, prevention of this disease has become a priority. Lifestyle changes, including regular exercise, can reduce the onset of T2D in those at elevated risk. However, long-term adherence to exercise is often poor in this population. Existing lifestyle interventions targeting exercise are labor intensive and costly for staff and participants. Evidence-informed counseling delivered in a manner that reduces dependence on staff and facilitates self-regulatory skills could alleviate time and financial barriers while promoting independent exercise.

Objective: This protocol outlines the design, recruitment, and proposed analysis of a brief, 2-week evidence-informed exercise counseling intervention combined with either high-intensity interval training (HIIT) or traditional moderate-intensity continuous training (MICT).

Methods: Small Steps for Big Changes is a 2-arm randomized controlled trial that will examine the effectiveness of combining brief exercise counseling with HIIT or MICT on adherence to moderate and vigorous exercise over 1 year. Cardiorespiratory fitness will be assessed at baseline, post intervention (2 weeks), and at 6- and 12-month follow-up. Physical activity behavior will be examined at baseline, post intervention, and 3-, 6-, 9-, and 12-month follow-up. The impact of the intervention on psychosocial outcomes pertinent to exercise adherence will be examined.

Results: Data collection was complete in March 2017. Data analysis is currently underway, and the first results are expected to be submitted for publication in 2019.

Conclusions: The results of this brief intervention have the potential to inform future public health efforts designed to increase exercise in individuals at risk of T2D.

Trial Registration: ClinicalTrials.gov NCT02164474; https://clinicaltrials.gov/ct2/show/NCT02164474 (Archived by WebCite at http://www.webcitation.org/74Hx1ipj6)

International Registered Report Identifier (IRRID): DERR1-10.2196/11226

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KEYWORDS

exercise; type 2 diabetes; high-intensity interval training; prediabetes

Introduction

Background

Type 2 diabetes (T2D) is one of the fastest growing diseases in Canada, with approximately 60,000 new cases diagnosed each year [1]. Globally, it is estimated that 592 million individuals will be diagnosed with T2D by 2035 [2]. Given the numerous negative health outcomes associated with T2D, including heart disease, retinopathy, cataracts, neuropathies, and kidney failure [3-6], increasing attention has turned to intervening with individuals at increased risk of developing T2D (ie, individuals living with *prediabetes*).

Physical activity has been highlighted as beneficial for preventing the progression of prediabetes to T2D [7,8]. However, individuals at risk for T2D often fail to meet the physical activity guidelines of 150 minutes of moderate-to-vigorous aerobic exercise per week [9,10]. Innovative trials, such as the Diabetes Prevention Program (DPP), have demonstrated that a lifestyle intervention incorporating 150 minutes of moderate-intensity physical activity per week can reduce the progression of prediabetes to T2D by up to 58% compared with a non-exercise control and is almost twice as effective as the leading pharmaceutical intervention [11]. At 7-year follow-up, moderate-to-vigorous physical activity behavior was higher among individuals that completed the Diabetes Prevention Program Outcome Study (DPPOS) compared with an equivalent cohort [12]. The DPP and DPPOS follow-up represented a landmark trial designed to assess the potency of lifestyle modification for the prevention of T2D. The trial involved extensive patient contact and monetary incentives to ensure adherence to the prescribed 150 minutes of exercise per week and dietary and weight loss goals. The cumulative cost of the DPP and DPPOS for the lifestyle intervention group was US $4601 per person [13]. Community sites aspiring to achieve similar rates of adherence to physical activity are likely to be constrained by financial and time burdens associated with implementing (and participating in) the DPP. The intensity and expense associated with the DPP and DPPOS could limit the scalable implementation of such interventions. There is an urgent need for affordable and practical interventions that can be delivered in real-world health care or community settings with similar degrees of effectiveness [14]. *Small Steps for Big Changes* is a brief, evidence-informed lifestyle intervention that seeks to overcome the limitations of feasibility and sustainability in previous interventions with the aim of increasing physical activity adherence in individuals at elevated risk of T2D.

Promoting Physical Activity Adherence

To increase the potential for long-term behavior change, it is important to target theoretically proposed mechanisms of change and incorporate evidence-based behavior change strategies to maximize potential intervention success. Hardeman et al [15] refer to this as a causal modeling approach to intervention development. Interventions that incorporate psychological theory and empirical evidence about how best to support behavior change have been found to be effective [16,17].

Social cognitive theory (SCT) provides a conceptual framework through which to design physical activity interventions. A key construct of SCT is the confidence in one's ability to carry out and self-manage behavior (ie, *self-regulatory efficacy beliefs*). Self-regulatory efficacy is essential in promoting long-term engagement in behaviors such as physical activity [18]. Another form of self-efficacy, concurrent self-regulatory efficacy, reflects an individual's confidence to manage health and life goals simultaneously and has been shown to predict physical activity levels [19]. Self-efficacy has been consistently found to be a significant predictor of the adoption and maintenance of physical activity behavior [20,21] and has been reported as the most influential construct on physical activity behavior change [22]. In relation to T2D, self-efficacy has been shown to increase after free-living exercise interventions [23] and has been found to mediate the relationship between intervention delivery and objectively measured physical activity behavior [24]. In addition, personally held efficacy beliefs influence the outcomes an individual anticipates attaining by engaging in the target behavior [25]. These outcome expectations and the value individuals attach to these outcomes can impact physical activity motivation. Individuals who perceive little value or likelihood of achieving benefits associated with physical activity are less likely to self-manage their behavior [25]. As such, fostering positive beliefs about the outcomes an individual will stand to gain from physical activity, which are of value to the individual, will positively influence motivation.

Given the role of self-efficacy beliefs and outcomes expectations as psychological mechanisms of behavior change, a growing body of research has sought to examine the utility and effects of different behavior change techniques (BCTs) in relation to both social cognitions and thereafter physical activity behavior in individuals at risk of T2D [26-28]. For example, Williams and French [27] reported that action planning, reinforcing effort or progress toward behavior, and providing instruction produced significantly higher self-efficacy and physical activity effect sizes compared with interventions that did not incorporate these techniques. A meta-regression by Michie et al [28] reported that interventions that incorporated self-monitoring and self-regulation techniques were significantly more effective at increasing general physical activity behavior than those that did not include these techniques. In the context of T2D, Cradock et al [29] highlighted 4 BCTs associated with reductions in glycated hemoglobin. These techniques included instruction on how to perform a behavior, behavioral practice rehearsal, demonstration of the behavior, and action planning.

Small Steps for Big Changes was developed to target the underlying theoretical- and evidence-informed mechanisms of behavior change within a brief intervention to promote long-term physical activity behavior in individuals at risk of T2D. Findings from a pilot feasibility study provided preliminary evidence that the *Small Steps for Big Changes* intervention protocol

resulted in significant increases in self-regulatory efficacy and outcome expectations and a significant increase in purposeful moderate-to-vigorous physical activity (MVPA) 1 [30] and 6 months following the program [31].

Moderate-Intensity Continuous Training: A Traditional Approach

In addition to consideration of the psychological constructs to be targeted within a physical activity intervention, it is also important to consider the modality of exercise prescribed. Traditionally, individuals at risk of T2D embarking on a new exercise regime are prescribed moderate-intensity continuous training (MICT; eg, steady-state walking), with limited free-living adherence typically reported [11]. Given the low rates of adherence to this exercise prescription [32], alternative training protocols, such as high-intensity interval training (HIIT), are increasingly being explored.

High-Intensity Interval Training: A New Approach for Individuals With Prediabetes

HIIT has received considerable attention as it elicits positive metabolic and cardiovascular adaptations that are similar, or even superior, to MICT in a variety of populations with lower time commitments [33,34]. Specific to diabetes prevention, a recent meta-analysis demonstrated that HIIT leads to greater improvements in insulin resistance compared with MICT [35]. Given the positive health adaptations, HIIT may represent a promising physical activity strategy for individuals with prediabetes.

HIIT involves brief, repeated bursts of vigorous exercise separated by periods of recovery. In a cross-over study of inactive adults, comparable exercise enjoyment and confidence were found between HIIT and MICT, with a greater proportion of participants reporting a preference to engage in HIIT (62%) over MICT (20%) after a single bout of each exercise modality [36]. Similar results are reported in individuals with overweight and obesity [37-39]. Surprisingly, few studies have examined free-living adherence to HIIT in individuals at risk of T2D, despite the known benefits of HIIT on glucose control in this population [40]. In our previous pilot study of individuals living with prediabetes, participants demonstrated greater free-living adherence to HIIT when compared with MICT 1 month following 10 sessions of supervised training and counseling [30]. In addition, accelerometer analysis of physical activity behavior revealed that participants randomized to the HIIT protocol engaged in significantly more vigorous exercise than those randomized to the MICT protocol. Furthermore, after 6 months of independent exercise, participants in the HIIT condition engaged in significantly more moderate-intensity activity compared with those randomized to MICT [31]. Although these initial findings are promising, further research is needed to confirm these results and determine whether individuals with prediabetes can adhere to HIIT over the *long term* (ie, 12 months). Furthermore, trials with greater power are needed to explore whether psychological responses associated with these modalities of activity impact adherence rates.

Small Steps for Big Changes Objectives

The objectives of this randomized controlled trial are to:

1. Compare differences in cardiorespiratory fitness between HIIT and MICT at 6 and 12 months after the intervention.
2. Examine accelerometry-measured purposeful moderate-to-vigorous physical activity in bouts of ≥10 minutes (MVPA10+) and total accelerometer counts throughout the follow-up year (ie, 3, 6, 9, and 12 months) after the HIIT and MICT intervention. Self-reported adherence to HIIT and MICT exercise prescriptions will be collected at 3-, 6-, 9-, and 12-month follow-up.
3. Examine the following psychological outcomes to explore their potential relationship with free-living adherence: task self-efficacy, self-regulatory efficacy, concurrent self-regulatory efficacy, self-monitoring, outcome expectations, exercise enjoyment, and instrumental and affective attitudes. In addition, differences in acute affect, in-task enjoyment, and perceived exertion between HIIT and MICT will be compared.
4. Examine differences in cardiometabolic health markers. Glucose control and insulin sensitivity will be assessed at baseline, post intervention, and at 6- and 12-month follow-up. Body composition will be assessed at baseline, post intervention, and at 12-month follow-up. Differences in average blood glucose levels between conditions will be examined immediately after the intervention in a subsample of participants.

Methods

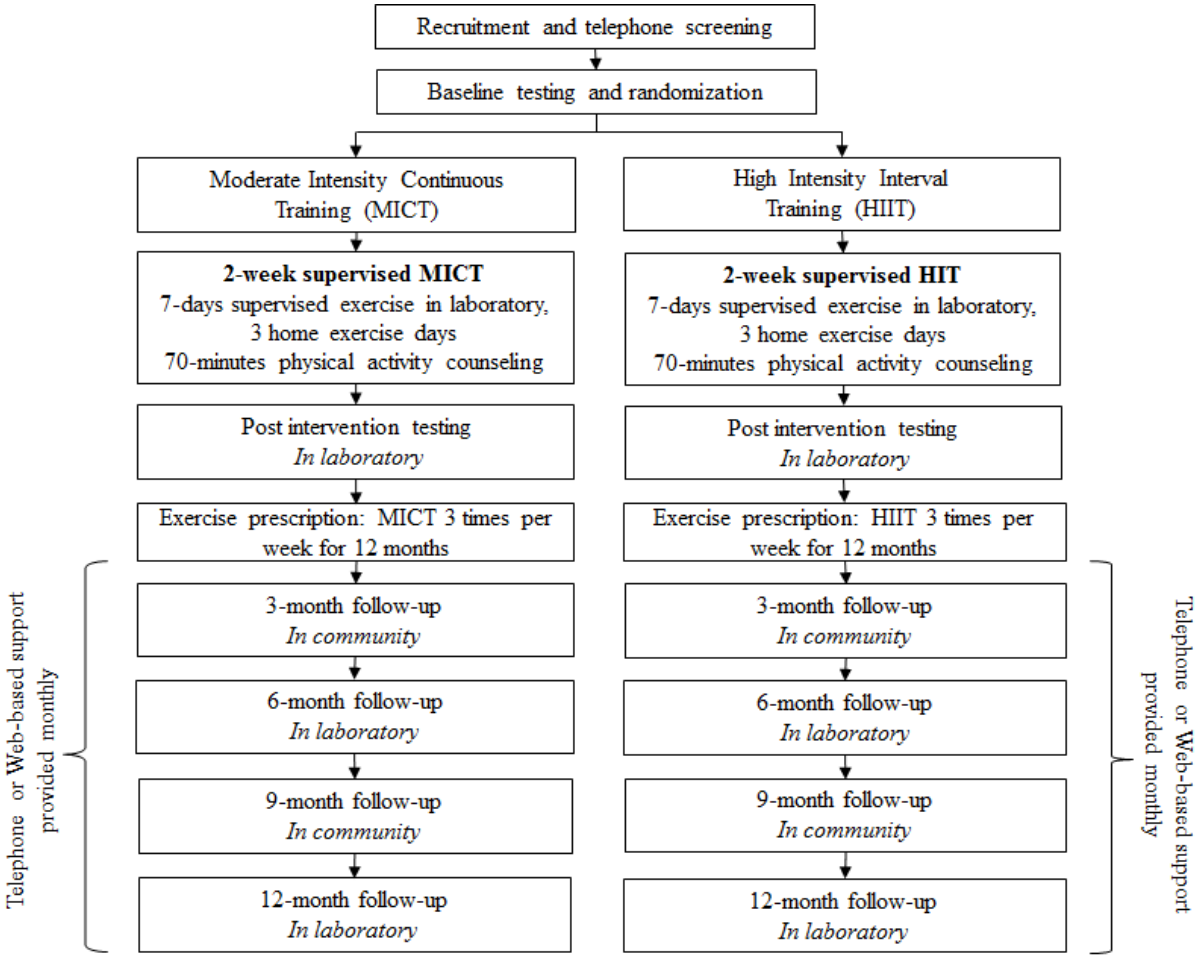
Study Design

Small Steps for Big Changes is a 2-arm, parallel group randomized controlled trial comparing adherence to HIIT with MICT in individuals at risk of T2D. This single-center trial will be conducted at The University of British Columbia, Okanagan Campus. The design of the study and flow of participants is described in Figure 1. Participants in both conditions will receive a 2-week supervised physical activity intervention consisting of engagement in their randomized exercise modality and brief, targeted counseling. The physical activity counseling will be identical for both conditions. Follow-up assessments will occur at 3, 6, 9, and 12 months. The trial will aim to recruit 100 participants. The supervised training will be conducted in waves (10 waves with approximately 10 participants per wave). All participants will begin supervised training on a Monday. Reporting of this trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials statement. Future reporting of the results of this trial will follow the Consolidated Standards of Reporting Trials guidelines [41].

Participants

The study sample will consist of adults aged between 30 years and 65 years; who are physically inactive (ie, engage in 2 or less bouts of moderate and/or vigorous aerobic exercise per week in the last 6 months, assessed using the Godin Leisure Time Physical Activity questionnaire [42]); have a body mass index (BMI) between 25 kg/m^2 and 40 kg/m^2; and are cleared to engage in vigorous exercise (via the Physical Activity Readiness Questionnaire for Everyone [PAR-Q+] or further clearance by physician, if needed [43]).

Figure 1. Flow of participants through the Small Steps for Big Changes program.



Recruitment and Screening

Participants will be recruited using posters administered in the local community, social media, newspaper advertisements, and word of mouth. Advertisements will invite inactive adults aged between 30 years and 65 years to contact the researchers about potential participation in a lifestyle change program, specifically designed to assist individuals who wish to become regular exercisers. A contact phone number and email address will be provided for individuals to contact the research team. Individuals who contact the research team will be able to ask questions regarding the program, and if wishing to proceed, will be scheduled for a previsit telephone screening interview. Telephone screening will take approximately 30 minutes during which the research coordinator will outline the time commitment of the study; record the participants' age, current medications, height, and weight (to calculate BMI); and administer verbally and record responses to the Godin Leisure Time Physical Activity questionnaire [42] and the PAR-Q+ [43]. Following completion of the initial screening questions, the research coordinator will inform the individual that he or she is (1) ineligible to participate in the program with reasons provided; (2) may be eligible, however, based on the results of the PAR-Q+ clearance and completion of the Physical Activity Readiness Medical Examination (ePARmed-X+) [43] will be required from the individual's family physician; or (3) may be eligible for the program and will be invited to the laboratory for final screening. Participants required to obtain medical clearance will be sent the ePARmed-X+ (electronically or via mail) and must have the form completed and signed by their physician. Potentially eligible individuals will be sent an information sheet containing study details and will be informed that final eligibility status will be shared following completion of a baseline assessment to confirm objective height, weight, and activity status.

Baseline Testing and Randomization

Baseline testing will last approximately 150 minutes. Participants will be provided with a detailed consent form and will be invited to ask any questions. After written consent is obtained, weight, height, and blood pressure will be taken and a 7-day physical activity recall interview [44] will be conducted to confirm eligibility.

Eligible individuals will be stratified based on sex and then randomly assigned to either the HIIT or MICT exercise conditions. An external statistician, who has no other involvement in the trial, will generate random allocation sequences, which will be linked to an interactive Web page. Permuted blocks of random size will be used. Once an individual is identified as eligible, the research coordinator will access the

password-protected Web page, and after entering requisite information on patient eligibility and sex, participants will be randomly allocated. Participants and researchers will be aware of group allocation. Following group assignment, participants will have a fasting blood sample taken, consume a 75 g glucose drink as part of a modified oral glucose tolerance test, complete several Web-based questionnaires, have a second blood sample taken 30 minutes following the glucose drink consumption, undergo a body composition scan, and complete a maximal cardiorespiratory fitness test to exhaustion on a cycle ergometer. At the end of the session, participants will be provided with an accelerometer to wear for 7 consecutive days, commencing the day after baseline testing. Participants will be shown how to wear the device and will be instructed to remove the device while sleeping or for water-based activities. In addition, instruction will be provided to remind participants how to correctly wear the accelerometer. Short message service (SMS) text messages or emails will be sent on days 1, 3, and 5 of monitoring to remind participants to wear the device (see Multimedia Appendix 1 for study measures).

A voluntary subsample of 8 to 10 participants per group will return to the laboratory 3 days after the preassessment for insertion of a continuous glucose monitor (CGM). The CGM will be worn for 2 consecutive days, and participants will be provided with a standardized diet. Participants will return after 2 days of wearing the CGM to have the CGM removed. These 2 additional visits to the laboratory will last approximately 30 minutes in total. No sample size calculation will be conducted as this aspect of the study represents an exploratory aim to determine if CGM can be used to detect changes in glucose control in this population.

Supervised Exercise Training

In this study, 10 days after completing baseline testing, eligible participants will begin the 2-week supervised exercise training. Participants in each condition will participate in 10 sessions of exercise performed over a 12-day period (ie, Monday to Friday over 2 weeks with Saturday and Sunday as rest days). Seven of these sessions will be supervised in the laboratory and will last approximately 30 to 60 minutes each, while 3 sessions will be conducted at home to foster independence and work through plausible barriers participants may encounter in the future. Each supervised exercise session will occur one-on-one with a counselor and will consist of an exercise component (ie, HIIT or MICT) and 10 minutes of counseling. Participants will be exposed to a variety of exercise formats within their given modality (ie, stationary cycling, treadmill walking, elliptical machine, and outside walking). For 4 of the 7 supervised sessions, participants will be able to self-select the exercise format to encourage autonomy. A total of 2 sessions will be performed on the cycle ergometer during which in-task affect and enjoyment will be assessed to more precisely control exercise intensity and control for the influence of exercise format on enjoyment. The exercise prescriptions for each condition will be progressive in nature (see Table 1) and matched for estimated external work.

Table 1. Two-week intervention exercise prescription.

High intensity interval training[a]	Training day/activity completed	Continuous moderate intensity training[b]
4 intervals	Day 1[c]	20 minutes
5 intervals	Day 2[d]	29 minutes
6 intervals	Day 3[e]	33 minutes
Home day, 6 intervals prescribed	Day 4[e]	Home day, 33 minutes prescribed
7 intervals	Day 5[e]	36 minutes
8 intervals	Day 6[e]	40 minutes
Home day, 8 intervals prescribed	Day 7[e]	Home day, 40 minutes prescribed
9 intervals	Day 8[e]	43 minutes
Home day, 9 intervals prescribed	Day 9[e]	Home day, 43 minutes prescribed
10 intervals	Day 10[c]	50 minutes

[a]One high intensity interval consists of 1 minute at ~80-90% VO_2 peak and one minute ~40% VO_2 peak.

[b]Moderate intensity continuous exercise consists of continuous exercise at ~45-55% VO_2 peak.

[c]Stationary bike.

[d]Outdoor walking (hills for HIIT, flat for MICT).

[e]Participant choice (includes stationary bike, treadmill, elliptical, outdoor walking).

High-Intensity Interval Training Protocol

HIIT involves sessions of 4 to 10 ×1-minute high-intensity intervals (cycling *sprints*, uphill treadmill walking, uphill outdoor walking, and elliptical machine) at approximately 80% to 90% peak oxygen uptake (VO_2 peak), interspersed with 1-minute rest periods at approximately 40% VO_2 peak. Results from the pilot study preceding this randomized controlled trial

demonstrated that individuals with prediabetes respond well to this protocol [30].

Moderate-Intensity Continuous Training Protocol

MICT involves sessions of 20 to 50 minutes continuous moderate-intensity exercise (cycling, treadmill walking, outdoor walking, and elliptical machine) at approximately 45% to 55% VO_2 peak. This prescription of MICT matches the progression of HIIT (percent increase over time) and modeled the exercise program that has been shown to prevent the progression of prediabetes to T2D (ie, primarily walking; [11]). An intensity of approximately 45% to 55% VO_2 peak, which approximates brisk walking [45,46], has been shown to improve cardiometabolic health in several large trials [47,48] and is commensurate with the level of intensity recommended by the American College of Sports Medicine [49] for inactive adults to promote exercise adherence.

Transition to Independent Exercise

The 2-week supervised exercise training program will incorporate 3 unsupervised sessions to enable participants to practice engaging in exercise independently. Following completion of the 2-week program, participants will be asked to engage in their randomized exercise protocol (ie, HIIT or MICT) a minimum of 3 times per week for the next 12 months. Specifically, participants in HIIT will be prescribed a 5-minute warm-up, 10 ×1-minute high-intensity intervals, and a 5-minute cooldown. Participants in MICT will be prescribed 50 minutes of moderate-intensity exercise.

Exercise Counseling

To assist participants with the transition to independent exercise and to promote long-term exercise adherence, participants in both conditions will receive a brief behavioral exercise counseling intervention built into the 2-week supervised training program. The counseling involves 10 minutes of one-on-one structured discussion at the end of each supervised exercise session, totaling 70 minutes over the 2 weeks. Participants will see the same counselor each session to bolster rapport. A detailed description of the BCTs used in the behavioral intervention and the social cognitive mechanisms they are hypothesized to target is reported elsewhere (Bourne et al, unpublished data). Participants will receive a worksheet for each of the 3 home-based sessions, each reviewing specific behavior change constructs.

In summary, the key aims of the behavioral exercise counseling are to:

1. Enhance confidence to perform the exercise (ie, task self-efficacy): providing instruction on how to perform the behavior, opportunities to practice engaging in exercise, helping participants identify physiological cues associated with the assigned exercise intensity, sharing the success stories of similar individuals, and providing positive support.
2. Increase confidence to self-manage exercise (ie, self-regulatory efficacy): providing opportunities to practice self-monitoring behavior, preplan exercise behavior, work through exercise barriers, and practice independent exercise.
3. Increase awareness of the psychological and physiological outcomes associated with exercise engagement (ie, outcome expectations): through education and drawing on the experiences of similar individuals and of the participant throughout the 2-week intervention.

The counseling will follow a semistructured format, targeting specific psychological and behavioral constructs each session, while allowing the participants to share their questions and concerns. The content of the program, tools, and materials to be used; session description; and the underlying theoretical constructs are presented in Multimedia Appendix 2.

Mobile Phone–Based Self-Monitoring Application

To promote exercise adherence after the 2-week intervention, participants will be provided with a self-monitoring mobile application (app; [50]). The counselor will create the participant's profile on the app and will show the participant how to navigate through the app on both a smartphone and a computer. Participants will be encouraged to monitor their exercise behavior daily (ie, record exercise into the app, hereon in referred to as *check-ins*) regardless of whether purposeful exercise was planned or completed that day. Participants will be permitted to record 4 nonexercise days within the app per week, coinciding with the prescribed 3 bouts of planned exercise for each week. Once all 4 *rest days* had been used, participants will record a *missed session* on days on which no exercise is completed.

Participants will be reminded to record their exercise behavior each day via an automated SMS text message sent from the app if they have not checked in by 9:00 pm. Participants will be informed that the counselor is able to view their exercise behavior through the counselor portal of the app. In the event of 3 consecutive missed check-ins, the participant will be contacted by the counselor via the app messaging function. During the 12-month follow-up period, the participant will be messaged monthly using the app messaging system on months with no scheduled follow-up appointments (months 1, 2, 4, 5, 7, 8, 10, and 11). These SMS text messages will target verbal persuasion, performance accomplishment, vicarious experience, awareness of physiological and affective cues, social support, self-monitoring, relapse prevention, and action planning.

Outcomes and Measures

A timeline for when each measure was assessed is provided in Multimedia Appendix 1.

Primary Outcomes

The primary outcome is cardiorespiratory fitness determined by measuring VO_2 peak at 6- and 12 months postrandomization. VO_2 peak will be assessed by a continuous incremental ramp maximal exercise test on an electronically braked cycle ergometer (Lode Excalibur, The Netherlands). Expired gas will be collected continuously by a metabolic cart (Parvomedics TrueOne 2400, Salt Lake City, Utah, USA) that is calibrated with gases of known concentration and a 3.0 L syringe before every test. The test begins with a 4-minute warmup at 30 Watts, after which Watts increase by 1 every 4 seconds (15 Watts per minute). Verbal encouragement will be provided to the

participant throughout the test. The test will be terminated upon volitional exhaustion or when revolutions per minute fall below 50. VO_2 peak is defined as the highest 30-second average for VO_2 (in L/min and mL/kg/min). Criteria for achieving VO_2 peak are (1) respiratory exchange ratio >1.15; (2) plateau in VO_2; (3) reaching age-predicted heart rate (HR) peak (220-age); and/or (4) volitional exhaustion. A Polar chest strap, which is integrated with the metabolic cart and cycle ergometer software (Lode Exercise Manager), will capture HR. HR peak and peak power output will be recorded as the highest values attained in the test. Cardiorespiratory fitness will be assessed at baseline and 6- and 12-month follow-up.

Secondary Outcomes

Physical Activity

Objectively measured purposeful MVPA adherence (ie, MVPA10+) will be assessed by triaxial accelerometry (Actigraph GT3X-BT, Actigraph, Pensacola, Florida, USA) at baseline and 3-, 6-, 9-, and 12-month follow-up. MVPA10+ is appropriate for measuring purposeful exercise [51] and provides a conservative estimate of exercise adherence. Participants will be instructed to wear the accelerometer on their right hip for 7 consecutive days at each measurement time point. Participants will be instructed to remove the accelerometer during sleep and for water-based activities. Accelerometers will be initialized and downloaded using ActiLife version 6.11. Epoch lengths will be specified at 5 seconds and will be summed as counts per minute. Nonwear time will be classified as 90 minutes of consecutive zeros, allowing for nonzero counts up to 2 minutes; if no counts are detected during the 30-minute counts before and after this interval [52], these data will be classified as nonwear time and excluded from analysis. Participants must have a total of ≥10 hours of valid wear time per day to be included in the analyses [53]. Our pilot work confirmed that recovery intervals during HIIT register as moderate-to-vigorous activity, not interruptions to physical activity. Freedson cut points [54] will be used to identify time spent in moderate (1952-5724 counts/min), vigorous (≥5725 counts/min), and MVPA (≥1952 counts/min) during wear time on valid wear days. Time spent in the various intensities will be averaged across valid wear days and multiplied by 7 to provide a weekly estimate of physical activity at each measurement time point. Purposeful exercise will be operationalized as minutes spent in MVPA10+ [54], in line with physical activity guidelines, which specify that bouts of physical activity should be accumulated in bouts of 10 minutes or more. Furthermore, given that participants in HIIT are prescribed 75 minutes of purposeful exercise per week (ie, 3×25-min HIIT sessions) and participants in MICT are prescribed 150 minutes per week (ie, 3×50-min MICT sessions) and that physical activity guidelines highlight the equivalency of 75 minutes of vigorous exercise and 150 minutes of moderate exercise, additional supplemental analyses will be conducted, whereby each vigorous minute of exercise within the identified MVPA10+ bouts will be credited as 2 minutes. This approach was carefully considered for the adherence measure and justified in the grant application for this trial. As such, this modified MVPA10+ outcome represents an appropriate measure of purposeful exercise [51] and allows for a direct assessment of adherence to HIIT or MICT.

Self-reported physical activity adherence will be assessed through an exercise log completed through the mobile application. Participants will be asked to record (1) whether exercise was complete, (2) type of exercise completed, (3) the duration of the exercise, (4) the number of intervals conducted (for the HIIT condition exclusively), and (5) how hard the session was (Rating of Perceived Exertion scale; [55]). The percentage adherence will be calculated (ie, number of exercise sessions divided by the number of prescribed sessions multiplied by 100% [56]).

Psychological Measures

Task self-efficacy, self-regulatory efficacy, concurrent self-regulatory efficacy, outcome expectations, and self-monitoring will be assessed at baseline, post intervention, and at 6- and 12-month follow-up (see Table 2 for specific details on study measures). Additional psychological variables that will be assessed include (1) exercise enjoyment measured at baseline, post intervention, and at 6- and 12-month follow-up [57]; (2) instrumental and affective attitudes measured at baseline, post intervention, and at 12-month follow-up (adapted from Conner et al [58]); and (3) affective state measured at baseline, post intervention, and at 12-month follow-up [59].

On training days 1, 6, and 10, counselors will ask participants to rate their in-task affect [60] and rating of perceived exertion [55] at the beginning (2.5%), middle (42.5%), and end (92.5%) of workout completion in both conditions (percentages indicate the proportion of workout completion to ensure this was matched across sessions of different lengths). In addition, participants will be asked to rate their exercise enjoyment halfway through the exercise session (50% of workout completion) in both conditions.

Anthropometric and Demographic Measures

Body mass, height (SECA, 700 SECA Hamburg Germany), waist circumference (measured at the level of the umbilicus), and blood pressure (measured manually using a sphygmomanometer) will be measured in the morning after an overnight fast at baseline, post intervention, and at 6- and 12-month follow-up using standard procedures. Information on ethnicity, household income, marital status, education level, medication history, and current smoking status will be collected at baseline.

Body Composition

Dual-energy x-ray absorptiometry (Hologic Discovery A) scans will be used to assess percentage body fat mass at baseline, post intervention, and at 12-month follow-up.

Biochemical Variables

A qualified and experienced phlebotomist will obtain a blood sample in the fasted state (≥8 hours overnight fast) and exactly 30 minutes following consumption of the 75 g glucose drink (Trutol, Fisher Scientific) from an antecubital vein. Samples will be placed on ice and processed within 30 minutes to obtain plasma via centrifugation for 15 minutes at 1550 g at 4°C.

Table 2. Description of psychological constructs assessed in the *Small Steps for Big Changes* program.

Outcome	Measure	Items	Exemplar question	Response options
Task self-efficacy	Study-specific. Created following recommendations made by Bandura [25] and McAuley and Mihalko [61]	4	How confident are you that you can perform 4-high intensity intervals OR perform 20-minutes of continuous moderate exercise (dependent on condition)	0% (not at all) to 100% (extremely confident)
Self-regulatory efficacy	Study-specific. Adapted from Shields and Brawley [62]	14	How confident are you that you can develop solutions to cope with time management challenges with respect to your exercise schedule?	0% (not at all) to 100% (extremely confident)
Concurrent self-regulatory efficacy	Study-specific. Adapted from Jung et al [19]	5	During a typical week, how confident are you in your ability to concurrently manage high-intensity interval training /continuous moderate intensity exercise amongst your other valued life goals? (dependent on condition)	0% (not at all) to 100% (extremely confident)
Outcome expectations: likelihood	Study-specific. Adapted from Locke et al [31]	23	How likely is it that each outcome in the list below will occur at least once in a typical week for the next four weeks as a result of engaging in high-intensity interval training/moderate intensity continuous training (dependent on condition) Lower risk of type 2 diabetes; Feel good about my physical appearance	1 (very unlikely) to 9 (very likely)
Outcome values	Study-specific. Adapted from Locke et al [31]	23	How much do you value attaining each outcome from the list below? Lower risk of type 2 diabetes; Feel good about my physical appearance	1 (little value to me) to 9 (great value to me)
Self-monitoring	Study-specific. Adapted from Hallam and Petosa [63] and Petosa [64]	19	In the past week I mentally kept track of my exercise activities	1 (never) to 5 (very often)
Affective and instrumental attitudes	Study-specific. Adapted from Connor et al [58]	13	For me, exercising three days per week would be...1 (useless) to 7 (useful)	1 to 7 (anchors vary depending on the question)
Affective state	The Positive and Negative Affect Schedule (PANAS; [59])	20	Read each item and then use the scale to indicate to what extent you have felt this way during the past few days (Interested, Distressed, Upset)	1 (very slightly or not at all) to 5 (extremely)
Enjoyment	Physical activity enjoyment scale (PACES; [57])	18	Please rate how you feel at the moment about the physical activity you have been doing...1 (I enjoy it) to 7 (I hate it)	1 to 7 (anchors vary depending on the question)
In-task affect	Feeling Scale [60]	1	When asked please tell me how you feel at that current moment using the scale below	+5 (very good) to −5 (very bad)
In-task rating of perceived exertion	10-point Category-Ratio Scale [55]	1	Using the scale provided please rate how hard you are currently working	0 (no exertion at all) to 10 (maximal exertion)
In-task exercise enjoyment	Study-specific	1	Using the scale provided please rate how much you are enjoying this exercise session	1 (note at all) to 7 (extremely)

Samples will be batch-analyzed in duplicate after storage at −80˚C. Plasma glucose will be assessed via the enzymatic hexokinase method using a commercial assay (Pointe Scientific) on a clinical chemistry analyzer (Chemwell 2910, Awareness Technologies). Insulin will be measured by enzyme-linked immunosorbent assay (Mercodia, Upsula, Sweden), as described previously [65]. Glucose (mmoL/L) and insulin (mU/L) values will be used to calculate homeostasis model assessment of insulin resistance using the Web-based Homeostasis Model Assessment-2 calculator, a validated method that is highly correlated (r=.88) with the hyperinsulinemic-euglycemic clamp [66] and is sensitive to change following exercise interventions [65,67,68]. Oral glucose disposition index will be used to assess beta-cell function and will be calculated based on the hyperbolic relationship between glucose-stimulated insulin secretion (change in plasma insulin divided by the change in plasma glucose from fasting to 30 minutes) and insulin sensitivity (1/fasting insulin, as described by Utzschneider et al [68]). The inflammatory marker C-reactive protein will also be assessed. Postintervention samples will be obtained approximately 48 hours following the last supervised training session and at 12-month follow-up.

Continuous Glucose Monitor

CGM will take place using the iPro 2 Professional CGM and Enlite sensor (Medtronic MiniMed, Northridge, CA) in a subsample of participants. The first 20 participants randomized in the trial will be invited to participate in the CGM assessment. The CGM records glucose values in a blinded fashion using a small microneedle inserted into the subcutaneous abdominal adipose tissue that is connected to a recorder that quantifies

interstitial glucose values every 5 minutes. Finger-stick blood glucose samples are taken 4 times per day and are analyzed by a software program (CareLink Pro) upon device removal and downloaded to create 24-hour blood glucose curves. CGM data will be analyzed for (1) average blood glucose, (2) 2-hour postprandial area under the glucose curve, (3) postmeal spikes, and (4) glycemic variability (mean amplitude of glycemic excursions and SD). Participants who wear a CGM will be provided a standardized diet (approximately 24 kcal/kg, approximately 60% carbohydrates, approximately 27% fat, and approximately 13% protein) to consume during the day before and on the day of each 24-hour monitoring period. CGM data will be collected for 24 hours at baseline and beginning approximately 24 hours after the last day of supervised training. To accurately interpret CGM data, each participant will consume the same meals at the same times of the day during each assessment period.

Participant Safety

The primary safety concerns for participants in this trial will be associated with completing the cardiorespiratory fitness test and increased physical activity in daily life. These concerns include cardiovascular and musculoskeletal events. All participants will be cleared for exercise using the PAR-Q+ [43], and if required, their family physician will be asked to assess the participants' readiness to engage in exercise and provide a completed ePARmed-X+ [43]. Participants that are not cleared for exercise by 1 of these 2 methods will be excluded from the study. During the cardiorespiratory fitness test, participant's blood pressure and HR will be monitored and the test will be terminated if blood pressure exceeds 220/120 mmHg or an abnormal response is recorded. The supervised exercise period is designed to gradually introduce participants to exercise by increasing the amount of physical activity performed each day. In addition, participants have the autonomy to choose their preferred exercise format (eg, walking and elliptical) for 7 of the 10 training days, further reducing the risk of musculoskeletal discomfort. Injuries sustained because of exercise will be reported. All training and supervising staff are first aid trained.

Intervention Fidelity

To promote the fidelity of intervention delivery and to ensure the underlying BCTs are administered as intended, a comprehensive 2-day counselor training workshop will be delivered by the principal investigator (an expert in BCTs). To augment the workshop, a standard operating procedure manual will guide intervention delivery for each day of the 2-week training program and for all follow-up face-to-face contact points (ie, 3-, 6-, 9-, and 12-months). The manual consists of detailed scripts and protocols for each exercise session, phone call, or app interaction. Counselors, who will be health psychology graduate students, will complete a checklist for each training day and follow-up session to ensure all key intervention components are administered. Checklists will align with information contained within the intervention scripts, for example, *reviewed and discussed barriers sheet completed by participant*. The 2-day training workshop covers theory and BCTs targeted in the intervention and is mandatory for all counselors. Each counselor will participate in role-play activities during the workshop that will be observed by the primary investigator, and feedback will be provided. Counselors will record intervention attendance, missed sessions, session time changes, or dropout for each participant throughout the intervention and follow-up.

During the follow-up phase, counselors will be provided with standardized monthly messages to send to each participant either using the app messaging system or via email in the months when no face-to-face contact was scheduled. Counselors will record the details of all contact with participants during this time.

Statistical Procedures

Sample Size

The a priori sample size was derived in relation to the primary outcome for this trial, cardiorespiratory fitness assessed at 6 and 12 months. To calculate the sample size, a pooled mean of 20.8 mL/kg/min and a SD of 4.0 mL/kg/min were used based on our previous pilot study [30]. At the time of study design, the meta-analyses of Weston et al [69] reported that supervised HIIT led to approximately twice (approximately 19%) the improvement in VO_2 peak as compared with MICT (approximately 10%) in participants with lifestyle-induced metabolic disease. We, therefore, used a 9% difference between HIIT and MICT as a meaningful exercise-induced increase in our population of interest, corresponding to a Cohen *d* effect size of 0.48 (or Cohen *f* of 0.24). Using these data, with a two-tailed alpha of .05 and 80% power, assuming a medium correlation among repeated measures of r=.5, it is calculated that 15 participants are required per group for a significant within-between interaction (calculated using G*Power v3.1; Department of Psychology, University of Duesseldorf).

However, given that the secondary outcome of exercise adherence typically produces greater measurement variability, the final sample size is determined to be powered for detecting a clinically relevant within-group increase in average daily MVPA assessed by an accelerometer. To calculate sample size, data from the Framingham Heart Study [51] and the Health Survey for England [70] were used. The Framingham data contain the most comprehensive cardiometabolic health measures matched with accelerometry-profiled physical activity in the world (N=2109, $mean_{age}$=47 years, and female=54.53% (1150/2109). Using these data, an increase in 10 minutes of MVPA per day is associated with a 15% reduction in cardiometabolic risk [51]. An increase in approximately 9 min MVPA per day has been shown to reduce progression of prediabetes to T2D [71]. Thus, we calculated sample size to detect a 10-minute increase in average MVPA per day as this amount of activity is linked with improved cardiometabolic health and prevention of T2D. Given that in the Framingham study, the Actical rather than the Actigraph accelerometer was used, additional data were needed from which to derive the mean and SD for MVPA. To this end, the Health Survey for England data were used, which reported an association between physical activity and cardiometabolic risk factors, with MVPA mean values of 12 minutes per day (SD 16). This mean value does not differ markedly from other mean daily MVPA values in either the Canadian Health Measures Survey [72] or National

Health and Nutrition Examination Survey [73]. To detect a difference of 10-minutes average MVPA per day within conditions, assuming a SD of 16, with 80% power at $P<.05$, 41 participants per group are required. A conservative loss to follow-up of approximately 20% is anticipated, and therefore, the trial aimed to recruit 50 participants per group (ie, 100 participants to be randomized).

Proposed Data Analyses

Preliminary analyses will be conducted to test for univariate and multivariate outliers and to test for normality. Data transformations will be conducted if required. Variance between the conditions in baseline outcome variables will be examined. Data will be analyzed on an intention-to-treat basis, with individuals retained within their randomized groups regardless of participation. All significance tests will be assessed at a 5% level of significance and effect sizes will be reported. Sensitivity analysis will be conducted to examine the impact of missing data. We will account for missing data by performing multiple imputation by chained equations to determine whether the results are impacted [74].

Mixed-effects regression with baseline as a covariate and 6- and 12-month outcomes as dependent variables will be used to examine differences in cardiorespiratory fitness between HIIT and MICT. Physical activity behavior assessed by accelerometer will be analyzed similarly but will include 3-, 6-, 9-, and 12-month time points. Mixed-effects regression using baseline and all other time points will be used to determine whether the treatments result in a significant change from baseline.

The mediating effects of task self-efficacy, self-regulatory efficacy, concurrent self-regulatory efficacy, outcome expectations, and self-monitoring will be examined using the INDIRECT macro developed by Preacher and Hayes [75]. The macro computes the following steps simultaneously: (1) regression coefficients for the impact of the intervention on the potential mediators; (2) the association between changes in the mediators and changes in the outcome variable; and (3) the total effects, direct effect, and indirect intervention effects. Bias-corrected bootstrapped 95% asymmetrical CIs will be computed for the indirect effect. Significant mediation will be established if the CIs do not include zero. Multiple mediation models will be computed for MVPA at 12-month follow-up and cardiorespiratory fitness at 12-month follow-up.

A series of mixed-effects regressions will be conducted to examine changes over time between groups in anthropometrics, body composition, biochemical markers, CGM, and additional psychological constructs.

Data Management and Quality Assurance

The administrative database (ie, participant information) and questionnaire data will be managed in-house. Random checks will be performed on the entered survey data against paper records. All errors will be logged and corrected. All physiological, anthropometric, and biochemical measures will be conducted in 1 laboratory with established quality assurance systems. All data will be stored in a locked laboratory on password-protected and encrypted computers. Paper records will be stored in a locked filing cabinet.

Retention

Maximizing retention is an important issue to fully understand exercise adherence rates over the 12-month follow-up. At recruitment, all laboratory visits and community visits will be outlined for the participants and the importance of follow-up testing emphasized regardless of exercise behavior. During the 2-week supervised intervention, participants will book the same appointment time for each day and will be sent all the dates and times by the counselor before day 1 of the intervention. Moreover, 2 of the follow-up appointments will be conducted within the local community at a location and time that suits the participant. It is anticipated that this will help reduce some of the burden on participants in attending a laboratory visit.

Ethics Approval and Consent to Participate

Ethical approval was provided by the University of British Columbia Clinical Research Ethics committee (H12-02268-A008), with informed consent obtained from all participants in the study.

Results

The project was funded in 2013 and enrollment began in July 2014. Data collection was complete in March 2017. Data analysis is currently underway, and the first results are expected to be submitted for publication in 2019.

Discussion

The *Small Steps for Big Changes* program will be the first randomized trial to examine the efficacy of low-volume HIIT compared with traditionally prescribed MICT as a means of increasing long-term physical activity behavior in individuals at elevated risk of T2D. The impact of HIIT on cardiorespiratory fitness, physical activity adherence, and psychosocial outcomes will be directly compared with current exercise recommendations for this population (ie, moderate-intensity continuous exercise).

The authors acknowledge potential limitations in the proposed methodology. Specifically, exercise studies suffer from potential selection bias, which could impact the generalizability of the results. Furthermore, the considerable number of outcome measures may limit an individual's willingness to participate. However, the number of outcome measures included in this study is similar to other exercise randomized controlled trials [76,77]. Generalizability of the findings may also be limited because of the study being conducted on a university campus, which may not reflect the environment of most individuals.

However, the findings from this study have the potential to make substantive contributions to understanding how different types of exercise protocol are tolerated and adhered to and the comparative health outcomes associated with these protocols. These findings could have significant implications for exercise recommendations provided for individuals at risk of diabetes.

In addition, this trial examines the effectiveness of a brief behavioral intervention designed to support the promotion of independent physical activity behavior through facilitation of self-regulatory strategies and efficacy beliefs. This intervention

brings together theory and evidence in a carefully constructed intervention that will have the opportunity to examine the causal pathways from cognitions to exercise adherence. Together, the results of this trial have the potential to impact future public health campaigns designed to increase physical activity with individuals at risk of T2D.

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Authors' Contributions

JEB participated in the design of the study and development of the intervention and drafted the manuscript. JPL and MEJ conceived the study and participated in the design of the study and the development of the intervention. MB and JB participated in the design of the study and the development of the intervention. JS participated in the design of the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Timeline for Small Steps for Big Changes schedule of enrolment, interventions, and assessments.

[PNG File, 199KB - resprot_v8i3e11226_app1.png]

Multimedia Appendix 2

Small Steps for Big Changes intervention outline.

[PDF File (Adobe PDF File), 49KB - resprot_v8i3e11226_app2.pdf]

Multimedia Appendix 3

Peer-reviewer report from the CIHR.

[PDF File (Adobe PDF File), 94KB - resprot_v8i3e11226_app3.pdf]

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Abbreviations

BCT: behavior change technique
BMI: body mass index
CGM: continuous glucose monitoring
DPP: Diabetes Prevention Program
DPPOS: Diabetes Prevention Program Outcome Study
ePARmed-X+: Physical Activity Readiness Medical Examination
HIIT: high-intensity interval training
HR: heart rate
MICT: moderate-intensity continuous training
MVPA: moderate-to-vigorous physical activity
MVPA10+: moderate-to-vigorous physical activity in bouts of ≥10 min
PAR-Q+: Physical Activity Readiness Questionnaire for Everyone
SCT: social cognitive theory
SMS: short message service
T2D: type 2 diabetes
VO_2peak: peak oxygen uptake

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Protocol

Reducing Retail Merchandising of Discretionary Food and Beverages in Remote Indigenous Community Stores: Protocol for a Randomized Controlled Trial

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Abstract

Background: Discretionary food and beverages (products high in saturated fat, added sugars, and salt) are detrimental to a healthy diet. Nevertheless, they provide 42% of total energy and account for 53% of food and beverage expenditure for remote living Aboriginal and Torres Strait Islander Australians, contributing to the excessive burden of chronic diseases experienced by this population group.

Objective: The aim of this study is to test an intervention to reduce sales of discretionary products, in collaboration with the Arnhem Land Progress Aboriginal Corporation (ALPA), which operates 25 stores in very remote Australia, by reducing their merchandising and substituting with core products in remote Australian communities.

Methods: We will use a community-level randomized controlled pragmatic trial design. Stores randomized to the intervention group will be supported by ALPA to reduce merchandising of 4 food categories (sugar, sugar-sweetened beverages, sweet biscuits, and confectionery) that together provide 64% of energy from discretionary foods and 87% of total free sugars in very remote community stores. The remaining stores (50% of total) will serve as controls and conduct business as usual. Electronic store sales data will be collected at baseline, 12-weeks intervention, and 24-weeks postintervention to objectively assess the primary outcome of percent change in purchases of free sugars (g/megajoule) and secondary business- and diet-related outcomes. Critical to ensuring translation to improved store policies and healthier diets in remote Indigenous Australia, we will conduct (1) an in-depth implementation evaluation to assess fidelity, (2) a customer intercept survey to investigate the relationship between customer characteristics and discretionary food purchasing, and (3) a qualitative study to identify policy supports for scale-up of health-enabling policy action in stores.

Results: As of August 2018, 20 stores consented to participate and were randomized to receive the intervention or continue usual business. The 12-week strategy ended in December 2018. The 24-week postintervention follow-up will occur in May 2019. Trial results are expected for 2019.

Conclusions: Novel pragmatic research approaches are needed to inform policy for healthy retail food environments. This research will greatly advance our understanding of how the retail food environment can be used to improve population-level diet in the remote Australian Aboriginal and Torres Strait Islander context and retail settings globally.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12618001588280; http://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375933 (Archived by WebCite at http://www.webcitation.org/76dbQEmwN)

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KEYWORDS

randomized controlled trial; indigenous population; food supply; diet

Introduction

Background

Aboriginal and Torres Strait Islander people residing in remote Australian communities bear a disproportionate burden of preventable chronic diseases [1]. Poor diet quality, including excessive intake of discretionary food and drinks, is a major contributor to preventable chronic diseases for all Australians [2]. Discretionary products are those that are not necessary for a healthy diet and are high in saturated fat, added sugars, and salt [3]. They are detrimental to a healthy diet as they displace more nutritious core (nondiscretionary) foods. Nevertheless, for the Aboriginal and Torres Strait Islander population living in remote Australian communities, discretionary products provide 42% of total energy [4] and account for 53% of food and beverage expenditure [5]. Reducing discretionary product intake is imperative to improving health in this population group.

The majority of food consumed in remote communities is purchased at the local community store [6]. Community stores, in most instances, belong to the community, which gives members the power to initiate and sustain community-level change. Optimizing the store environment as a health-enabling setting, in partnership with the community, represents a key strategy and opportunity to improve dietary quality and reduce preventable chronic disease burden.

We recently led the "stores healthy options project in remote indigenous communities (SHOP@RIC)" study, a large trial with 20 remote community stores to assess the impact of a price discount on purchasing [5]. It responded to concerns expressed by community Aboriginal leaders that high food prices of core items were driving a diet dominated by unhealthy foods and beverages as these provided cheap calories, tasted good, and were convenient and easy to store [7,8]. We found that a price discount on fruit and vegetables increased their purchase. However, any potential positive health gains, may have been negated because of the concomitant increase in the purchases of other foods including both core and discretionary products [9]. This may be explained by shoppers redirecting their produce savings toward those readily available and well-merchandised items. This evidence supports findings from a systematic review of grocery store interventions and the food price modeling literature, which conclude that discounts on healthy core food groups need to be accompanied by parallel pricing or strategies to reduce purchasing of discretionary products and encourage healthier food purchasing [10-12]. At the end of the SHOP@RIC trial, in a knowledge exchange meeting, retail leaders working with remote community stores and community store directors recommended that we collaborate to test how merchandising strategies could optimize the store environment to encourage healthier food purchasing.

Merchandising is the "activity of promoting the sale of goods, especially by their presentation in retail outlets," and it includes activities such as display techniques, free samples, pricing, shelf talkers, and other point-of-sale methods [13]. Merchandising utilizes the 4 elements of marketing management (ie, product, price, promotion, and place) to competitively position a product in the marketplace [14]. In this planned trial, we will use a pragmatic community-level randomized controlled trial to assess the impact on consumer purchasing and retail performance of a population-level intervention that targets discretionary products through reducing their merchandising in remote Aboriginal and Torres Strait Islander Australian community stores. We will target 4 product types (sugar per se, sugar-sweetened beverages, sweet biscuits, and confectionery) that were together shown to contribute 64% of the energy from discretionary product purchases and 87% of free sugars (free sugars include all sugars added to products plus sugars naturally present in honey, syrups, and fruit juices), using purchasing data from 20 remote community stores [5]. This is a novel approach; specifically targeting discretionary product purchases through modifying the store environment rather than solely focusing on increasing access to and promotion of core (healthier) food and beverages has rarely been a focus for public health interventions [15].

Our research will increase the understanding of merchandising as a factor influencing dietary behavior in consumer food environments [14,16], and one that, with appropriate support, is modifiable by retailers. We will conduct this research in collaboration with the Arnhem Land Progress Aboriginal Corporation (ALPA), one of the largest remote retail store associations and employers of Aboriginal and Torres Strait Islander people in Australia. This research will advance our

knowledge on the implementation and optimization of pragmatic retail food environment interventions to enhance population-level diet. It will translate directly into practice and policy through a policy analysis and the involvement of key stakeholders (including remote community leaders and remote community store directors) through evidence synthesis and knowledge exchange on policy options.

Objectives

Our study objectives are to:

1. assess the impact of reducing discretionary product merchandising on customer purchasing and retail business performance in remote Indigenous communities,
2. identify characteristics of customers associated with discretionary product purchasing, and
3. analyze and characterize the policy supports needed to scale-up nutrition evidence uptake in retail stores in remote Indigenous Australia.

This study tests the hypotheses that, over a 12-week intervention (and at 24-weeks postintervention), a strategy designed to reduce the merchandising of target discretionary products will reduce grams of free sugars per megajoule (MJ) energy (ie, sugars added to products plus sugars naturally present in honey, syrups, and fruit juices) in foods and drinks purchased through the community store (our primary outcome measure), and it will have positive impacts on secondary outcome measures relating to business performance and diet. This paper will describe the detailed protocol for study aims 1 and 2, and it excludes the policy analysis, aim 3.

Methods

Setting

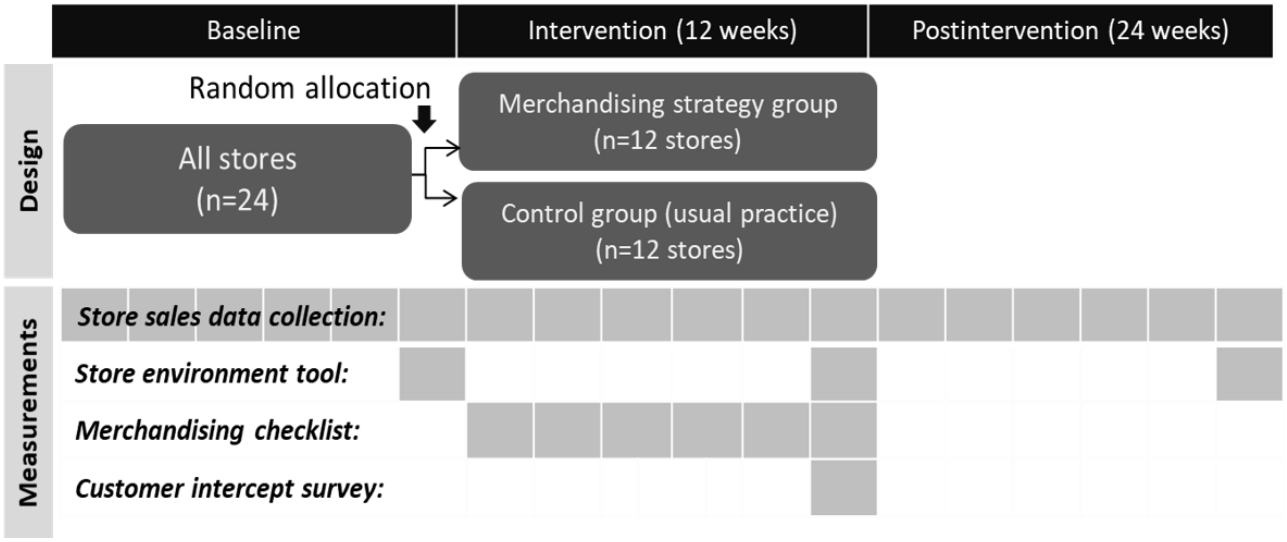
Aboriginal and Torres Strait Islander people represent 3.3% of the Australian population [17]. A total of 19% of Aboriginal and Torres Strait Islander people live in remote or very remote areas of Australia in small towns commonly referred to as communities and/or homelands. These communities vary in size with most having fewer than 1000 people. Remote and very remote areas in Australia are defined by an objective measure of relative access to services on the basis of geographic distance to service centers [18,19]. According to the socioeconomic index for areas, these communities are also considered to be socioeconomically disadvantaged on the basis of aggregated social and economic information collected through the national Australian census [20]. In remote and very remote Aboriginal and Torres Strait Islander communities, the most amount of food is acquired from the local community retail store. There are over 170 community food retail stores throughout Australia [21]. These are small- to medium-sized retail businesses [22], in many cases, owned by the community, and these are major employers of local Aboriginal and Torres Strait Islander people [23]. In the northern territory (NT), the Australian Government Department of Prime Minister and Cabinet (PM&C) is responsible for community store licensing legislation under the Stronger Futures in the NT Act 2012 [24]. Licensees are required to stock a satisfactory range of healthy and good quality food, drink, and grocery items and demonstrate reasonable steps to promote food nutrition and health products. Other aspects of a store's operations that may impact food security are also considered within the license.

ALPA is Australia's largest Indigenous corporation [25]. ALPA was formed in 1972 and has grown to be a large-sized corporation employing 1100 people. ALPA owns 7 stores in 6 communities in North East Arnhem Land, NT, where the community members are ALPA shareholders. In addition, ALPA, manages 13 stores in the NT and Queensland through its Australian Retail Consultancy arm that was set up in 2002. In 2013, it acquired the Island and Cape chain of 6 stores in Cape York and the Torres Strait Islands in North Queensland. It also operates businesses that aim to create local employment. ALPA has long recognized the importance of promoting health and nutrition in the communities it serves, and its food and nutrition policy first implemented in the early 1980s aims to increase the availability and affordability of nutritious foods and the understanding of health, good food, and nutrition among its customers [26]. For example, for over 30 years, ALPA has subsidized fruit and vegetables, and it now provides discounted 600 ml bottled water at Aus $1. In 2017, ALPA developed a front-of-store and end-of-aisle strategy to be a part of its nutrition policy that reduces merchandising of discretionary products. ALPA expressed its desire for this strategy to be rigorously evaluated. The Healthy Stores 2020 intervention was co-designed with ALPA, and it incorporates elements of the ALPA front-of-store and end-of-aisle strategy. Like ALPA, local store board directors in many remote Indigenous communities are increasingly receptive to considering strategies, in some cases, actively modifying the store environment, to discourage discretionary product purchases and encourage healthy food and drink purchases [27,28].

Design

We will use a community-level pragmatic randomized parallel group, 2-arm, superiority trial with a 1:1 allocation ratio design and a baseline, 12-week intervention period and 24-week postintervention period to assess the effect of the intervention on customer purchasing and store business performance measured objectively through store sales data (Figure 1). We will use a customer intercept survey to address our second aim of determining the characteristics of customers associated with discretionary product purchasing. An in-depth implementation evaluation will assess implementation fidelity (ie, intervention compliance) using a Merchandising Checklist administered fortnightly by phone with store managers and accompanying in-store photographs captured by store managers. A Store Environment Tool "Store Scout" (developed by Menzies School of Health Research) will be used to assess changes to the retail choice architecture and contextualize the results.

Figure 1. Study design schema.



Our intervention has been co-designed with ALPA, and it will reduce the merchandising of high sugar discretionary products and subsequent desirability of these products, while allowing for substitute merchandising of core foods. Our overarching aim is to reduce the purchasing of targeted discretionary items. Due to the unknown impact of the intervention on business outcomes including level of resources needed for full implementation, ALPA considered a 12-week intervention period as acceptable. We previously reported short-term (ie, less than 6 months) food price interventions to be effective when applied in stores and/or supermarkets [12]. For this study, we considered a 12-week intervention to be of adequate duration to demonstrate the impact assuming immediate customer response and implementation compliance. We found in a previous trial that a 24-week postintervention period allowed an assessment of longer-term intervention impact on store practice without losing the engagement of key stakeholders.

Theoretical Framework

The strategy is informed by a social ecological theory that poses that behavior is shaped by interaction between the individual and the environment [29]. Using this theory, we assert that specific factors in the retail food environment can incentivize and drive the excessive consumption of discretionary products. Therefore, to modify behavior, it is necessary to focus on modifying its determinants in the store food choice architecture rather than on individuals alone (eg, through customer education). We have drawn on consumer decision-making models to understand the use of merchandising practices by retailers [30-32]. These models generally consider food choice decisions as a 3-staged process of (1) product awareness, (2) interest or desire, and (3) the decision to buy or not. The merchandising techniques used by retailers aim to influence this process through increasing visibility (ie, awareness) and attraction (ie, interest or desire) of brands and products at point-of-sale to stimulate customers' purchases, especially impulse purchases, which can make up 46% or more of total purchases [31-33]. An impulse purchase is one that occurs without a previously recognized need for the item [30], and the likelihood of making an impulse purchase is influenced by both product characteristics (eg, hedonicity and price) and retailer variables (eg, price, promotion, and place) [30]. Discretionary products are highly palatable, often available in a ready-to-eat form and have high hedonic appeal (ie, elicit prompt pleasurable emotions). As consumers tend to forego long-term negative results for immediate gratification, discretionary products are commonly impulse purchases [31] as the mix of desirable product characteristics, along with merchandising, makes them extremely appealing. Our intervention has therefore been designed to reduce awareness and attraction of discretionary products while expanding the awareness and attraction of substitute core products. ALPA is responsible for strategy implementation through its store managers.

The implementation intervention logic is based on the Behavior Change Wheel [34] and is expected to affect store manager behavior in relation to maintenance of the strategy through the following 5 functions: (1) Persuasion (ALPA management communicating support for and importance of the study to induce positive feelings of store managers to stimulate action), (2) Incentivization (ALPA management communicating benefits of the study to store managers and creating an expectation of reward in terms of health benefit to the community and recognition of ALPA as a leader in healthy food retailing), (3) Training (implementation setup team imparting skills to store managers on how to maintain the strategy), (4) Environmental Restructuring (ALPA management providing hands-on assistance to store managers to set up the strategy; ALPA management and store managers supporting the strategy), and (5) Enablement (ALPA management and research team showing support for the strategy and assisting store managers with troubleshooting of issues that may arise during implementation).

Ethical approval has been granted by the combined NT Department of Health and Menzies School of Health Research Human Research Ethics Committee (ref: HREC-2018-3048) and the Far North Queensland Human Research Ethics Committee (ref: HREC/18/QCH/23-1211).

Eligibility and Recruitment

Recruitment of Stores

This research will be conducted in partnership with ALPA who, at the time of designing the study, managed 25 stores in 24 communities. The ALPA stores comprise 3 corporation types, as these are as follows: company owned stores (6 in Queensland), stores managed on behalf of Aboriginal store owners (12 in NT and 1 in Queensland), and member stores where community residents are the shareholders (6 in NT). Overall, 12 of these stores operate in communities where there is more than 1 store. All stores managed by ALPA will be eligible. Using stores managed by a single store association will help ensure uniform and high-level implementation fidelity. In the 1 community where there are 2 ALPA stores, both stores will be allocated together to intervention or control during randomization.

The recruitment process will commence with the study being first presented and discussed with the ALPA and the Island and Cape boards. These boards are able to give consent for the ALPA and Island and Cape owned stores. On approval from the ALPA board, contact will then be made with each of the stores in NT with a management agreement with ALPA and a meeting arranged with the respective store boards. A study story will be used to facilitate a face-to-face discussion with store board directors. This will be facilitated by ALPA personnel alone or together with a member or members of the research team. Local authority groups in each of the communities will be informed of the study via a letter describing the study purpose and indicating that the community store board will be invited to participate.

Randomization

Consenting stores will be allocated to intervention or control using random number ranking, Stata version 15, StataCorp LLC.

Blinding. Blinding of store allocation is not possible for store managers, ALPA personnel responsible for intervention implementation, research staff administering the intervention, or customers and other community members. This will not impact the data collected for the primary and secondary outcomes, as the store sales data used to measure intervention effect are objective electronic data. In addition, objective measures in the form of photographs will be used to assess implementation fidelity.

Intervention

Through our co-design approach with ALPA, the intervention (Table 1) builds on its new front-of-store and end-of-aisle strategy. It includes components that the ALPA nutritionist together with the ALPA merchandising and operations teams considered feasible and acceptable to trial from a business perspective and that the research team proposed to likely be the most effective.

A traffic light system based on the NT School Nutrition and Healthy Eating Guidelines [35] will be used to classify food types as healthy or less healthy, with discretionary food types flagged as red (less healthy).

Implementation

The ALPA General Manager of Retail Services and ALPA Nutritionist, who are both study investigators, will use a store task list, and they will use a drinks fridge planogram (physical layout diagram) developed by ALPA with input of the study investigators on proportion of unhealthier to healthier drinks, to communicate to store managers and their area managers about what is required. The task list will be developed on the basis of merchandising practice observed and photographed for each intervention store at baseline, specifically tailored on the basis of each store's unique premium high traffic areas such as counter, front- and end-of-aisles, and store entrance. The task lists will indicate the maximum number of shelf facings for sugar, sugar-sweetened beverages, sweet biscuits, and confectionery product categories, with a list of substitutable core food products to fill the space opened. Substitutable core products will be identified with ALPA and indicated to store managers in a 2-page reference guide. Fidelity to no price reductions on targeted products will be maintained from baseline, with no changes during the intervention period, via ALPA's standard pricing procedures. ALPA will lead the implementation of the intervention and will support the training of its store staff in implementation procedures for each of the intervention stores at start-up. The store will be relayed (ie, implementation of strategy) in consultation with store managers by members of the research team with an ALPA area manager or the ALPA nutritionist with an ALPA area manager. Store managers will use photographs of the newly relayed store to communicate stocking procedures to store staff for strategy maintenance. Thereafter, store managers will be responsible for maintaining the intervention with the support of their area managers. We expect some local adaptation of the intervention because of heterogeneity in the physical design of each store and input on implementation from store directors, but ALPA will aim for standardization of the intervention delivery across stores. Strict monitoring of intervention compliance will be conducted by the research team (see the Implementation Evaluation section below). Any nonadherence identified through monitoring will be communicated immediately to the responsible store manager to correct.

Table 1. Intervention components.

Targeted discretionary items (all red table sugar, sugar-sweetened beverages, sweet biscuits, and confectionery; price, promotions, and place)	Healthier alternatives (all green and amber items; price, promotions, and place)
1. No promotional activity[a] on discretionary products, including no price discounts, volume promotions (eg, 2 for 1 type offers), posters, shelf stripping, and fridge branding	—[b]
2. No misleading promotional activity (eg, fruit and vegetable fridge branding on a fridge containing confectionery, or no sugar shelf stripping on shelves with sugary drinks)	No misleading promotional activity (eg, fruit and vegetable fridge branding on a fridge containing confectionery, or no sugar shelf stripping on shelves with sugary drinks)
3. No visible availability at counter and high traffic areas[c] of discretionary products (eg, front-and end-of-aisle displays)	Substitute visible availability of core products
4. Reduced facings[d] (ie, number of identical products on a shelf)	Substitute facings of core products in the proximity of targeted product categories where the facings have been reduced
5. Reduced refrigerator space for targeted drinks[e]	Substitute refrigerator space for healthier drinks as follows: water, small units of unsweetened fruit juice, and artificially sweetened beverages
6. In stores with no non-Arnhem Land Progress Aboriginal Corporation competitor store in the community, no units more than 600 ml of targeted soft drinks permitted in refrigerators	—
7. Shelf stripping warning on target products and floor sticker indicating quantity of sugar in drinks	Floor sticker promoting water as the healthiest drink choice

[a]Price mark-downs with no signal of savings to the customer permitted on short-dated food and drink stock. Marked-down items not permitted in high traffic areas.

[b]Not applicable.

[c]Products considered at high risk of theft to remain at front of store, but in the least prominent location such as under the counter.

[d]Sweet biscuit facings reduced by half; table sugar facings reduced to 1 bay, no multipacks displayed, smaller units at eye level; and confectionery facings reduced by half and no increase in range permitted.

[e]Artificially sweetened drinks (diet drinks) were classified as amber, not red.

Control stores will be asked to continue usual store practice and told by ALPA that they will be supported to implement the Healthy Stores 2020 strategy at the study end if demonstrated to be effective.

Governance

Decisions relating to study design and protocol, ethics requirements, and research dissemination have been and will continue to be made by the research investigator group who meets monthly. Overall, 3 working groups will be established, comprising research investigators and key stakeholders to oversee and advise on development, implementation, and evaluation of the (1) merchandising strategy, (2) customer intercept survey, and (3) qualitative study to identify the policy supports for scale-up of health-enabling policy action in stores. A communication and research dissemination strategy approved by the research investigator group will govern internal and external stakeholder communication. This includes feedback of study findings and lessons learned at the end of the study to the ALPA and Island and Cape boards and participating communities.

Study Outcomes

Primary Outcome

The primary outcome is difference in free sugars (g/MJ) from baseline in intervention versus control stores derived from store sales data. Free sugars contributed 26% of total energy purchased from 20 community stores, more than double the World Health Organization recommendation of less than 10% of total energy intake [36]. Our outcome measures were informed by modeling the estimated impact of the intervention on both target product categories and nutrients, using 49 continuous weeks of nonintervention store sales data collected from 20 remote Indigenous communities who participated in the SHOP@RIC study.

Secondary Outcomes

We will assess the impact on store revenue as a secondary outcome. This measure was considered by ALPA as important in determining the impact on retail performance. A necessary outcome for ALPA is that revenue is maintained throughout the intervention. Retail measures useful in evaluating specific merchandising effects on business operations will be examined where data are available, including number of products purchased per transaction (basket size), number of unique transactions, and category share of store sales. We will also collect data on intervention costs, including costs associated with strategy material production, implementation, and evaluation.

Our use of store sales data captures all foods and drinks sold, enabling an assessment of total nutritional quality of purchases as well as exploring impact on specific product types. We will examine the impact on purchases of targeted discretionary products (table sugar, sugar-sweetened beverages, sweet biscuits, and confectionery), total discretionary products, and nontargeted products (eg, water, diet drinks, fruit, and vegetables). We will examine the impact on the nutritional content of all food and

drinks sold, including total energy, energy density, and nutrient density.

Implementation Evaluation

Merchandising Checklist

We will assess intervention implementation using a Merchandising Checklist and the Store Environment tool (Store Scout App). The Merchandising Checklist will capture the intervention activities. Store managers from control and intervention stores will be requested fortnightly during the 12-week intervention period to respond to a brief checklist of intervention components delivered by a member of the research team via phone, and they will be requested to provide photos of premium locations (hot spots for product displays, such as high traffic areas, defined for each store following baseline data collection) to verify degree of compliance with intervention components. Store managers will be asked to comment on observations about community-level incidents that they perceive may affect sales (eg, weather events or festivals). They will also be asked questions related to their perceptions of intervention implementation and effectiveness.

Store Environment Tool (Store Scout App)

Store Scout App (developed and piloted by our team in 2016 in 6 remote stores) assesses the overall store as a consumer environment (ie, the retail choice architecture), through measures of stocking and merchandising of 7 categories of food and drinks (including fruit and vegetables, drinks, snacks, meals and convenience food, breads and cereals, dairy products and eggs, and meat and seafood). We will train government and Aboriginal Community-Controlled Organization employed public health nutritionists to conduct assessments in control and intervention stores. The tool will be completed at the end of the baseline, intervention, and postintervention periods.

Customer Intercept Survey Substudy

In the final 2 weeks of the intervention, we will conduct customer intercept surveys (1080 unique customers; 45 per store) from control and intervention stores to identify the following:

1. Differences among customers in discretionary food and drink purchasing in intervention and control communities.
2. Customer characteristics that predict discretionary product purchases.
3. Proportion of customers who regularly purchase food and drinks from other food outlets in or outside of the community.

Using a structured close-ended question survey in electronic format (iSurvey) with standardized scripts, trained surveyors with support from store staff will interview customers after they complete their purchase. Surveyors will be scheduled to survey customers at store front (postshop) over a period of 6 hours (3×2 hour sessions over the course of the day) per day for up to 3 days, to capture a broad spectrum of customers and shopping purpose, planned or unplanned, each subject to different levels of impulse shopping propensity. We consulted with ALPA to ensure this is feasible on the basis of number of transactions per day. We anticipate surveys to take 5 to 10 min per customer.

Upon exiting the store, customers will be invited to provide their receipt (a photograph of the receipt will be recorded) and respond to a short-item questionnaire to gather information on characteristics of the customer (age range, gender, shopping alone versus with child or others, and impulse shopping propensity). Data on payment method (eg, cash or card) and food shopping frequency at other retail outlets will also be collected.

Data Collection

The data source for the primary and secondary outcome analysis will be weekly sales reports generated by ALPA for each store for the entirety of the study and sent electronically to the research team. These data will include product identifier (stock keeping unit or barcode), product description, quantity sold, and dollar value. Store products will be linked to nutrient data using a database that we have developed specifically for this purpose, which is mostly derived from the Australian Food, Supplement, and Nutrient Database [37], with discretionary food flagged from the Discretionary Food List developed by the Australian Bureau of Statistics [38]. We will use built-in, reliable data checking processes that we have used over the last decade in our research to assess and quantify the nutritional impact of sales.

Analyses

Effect of Intervention

Longitudinal data analysis models will be used on fortnightly store sales data aggregated from weekly sales. This will enable the effect of the intervention to be expressed as a relative change. Analyzing fortnightly data reduces variation because of income cycles, as observed in our previous analyses with sales data [6]. All models will include random effects for the stores and fixed effects for fortnight and intervention. Within-store residuals will be assumed to have an autoregressive structure of order 1. We will report effect sizes (and 95% CI) together with the associated *P* values.

Descriptive statistics will be used to describe contextual data. To assess implementation fidelity (as described in the implementation evaluation), a dichotomous variable of high or low fidelity will be derived from the repeat measures collected throughout the study in intervention and control stores using the Merchandising Checklist. Contextual and qualitative data will be analyzed to determine factors influencing implementation.

A store environment global score will be derived from use of the Store Scout App and compared across the 3 time periods. We will assess the degree to which the intervention has impacted the consumer environment and been sustained at 24 weeks postintervention in control and intervention stores.

Analyses will be conducted according to the intention to treat principle applied at store level; sensitivity analyses will be conducted looking at the stores' implementation fidelity. Statistical analyses will be performed using Stata version 15.

Customer-Level Response (Substudy)

Percent discretionary product to total food and beverage dollars (dependent variable) will be calculated for each receipt collected during the Customer Intercept survey. Associations between the dependent variable and dichotomous variables indicating exposure or no exposure to the intervention will be estimated using mixed-effects linear models. Effect of the intervention will be expressed in terms of percent difference relative to the control group adjusting for baseline differences in merchandising. Mixed models will include a random intercept for community to account for within community correlation (clustering effect). As this is a convenience sample of customers, the potential confounding effect of baseline exposure to merchandising of targeted products, age range, and gender will be explored by including these factors in the models. Store Scout will be conducted at baseline in control and intervention communities to provide a proxy of merchandising exposure at baseline. Multivariable linear mixed models (with random intercept for community) will be conducted to identify customer characteristics (eg, payment type) associated with purchase choice.

Sample Size

Primary Outcome Measurement

Our intervention targets products that collectively account for 87% of free sugars from all product purchases in remote communities. The effects of the strategy are likely to be seen from the beginning of the intervention period, and we expect that sales (gram weight) of targeted products will be reduced by approximately 10% and free sugars (g/MJ) by approximately 8% to 9% throughout the intervention; we will test if this is sustained postintervention. A mean effect size of a 10% reduction in targeted discretionary product categories purchased is based on Batis et al (2016) [39], where an 8% tax applied by the Mexican government on nonessential energy-dense foods resulted in low socioeconomic status households purchasing on average 10.2% less taxed foods than expected (−44 [−72, −16] g per capita per month). Using 20 weeks of data for 20 remote stores (SHOP@RIC data), we found a 95% CI for the relative change of free sugars (g/MJ) for 2 randomly chosen groups of 10 stores to have width ±3.6% approximately. This anticipated precision is excellent for detecting an anticipated effect of the primary outcome of approximately 8% to 9%. A corresponding power calculation is not necessary [40]; however, the proposed study would likely have approximately 90% power to detect a 6% reduction in the primary outcome (free sugars g/MJ).

Customer Response

Under the assumption of an intracluster correlation equal to 0.01 and a cluster size equal to 45 (on the basis of 24 communities), we calculated a sample size allowing a study design of 1.4. With a sample of 1080 customers, and assuming a relative SD of 40% for the outcome discretionary product dollars of total dollars, the study will have 80% power to detect an 8% difference (from 50% in the control group to 42% in the intervention group) in the discretionary product dollars and total dollars at an alpha of .05.

Results

As of August 2018, 20 stores consented to participate and were randomized to receive the intervention or continue usual practice. The 12-week strategy ended in December 2018. The 24-week postintervention follow-up will occur in May 2019. Results are expected for 2019.

Discussion

Principal Findings

There is strong evidence to show that merchandising is used to drive sales of discretionary foods [41]. The paucity of evidence on how to use merchandising techniques to reduce purchasing of discretionary products and nudge consumers toward healthier defaults is a large gap in our knowledge [42,43]. The limited available evidence suggests promise in reducing merchandising activity to restrict discretionary products and using merchandising activities to increase visibility and boost sales of targeted core foods [16]. Interest from retailers, including remote community store directors, to engage with researchers represents a unique and invaluable opportunity to address this evidence gap and cocreate knowledge. This trial will provide practical evidence needed to advance how public health can work with retailers to promote, implement, and evaluate health-enabling strategies in this private sector setting. As remote retailers' decisions directly impact population diet, generating this evidence through collaboration with retailers and other important knowledge users will ensure its viability.

The outcomes will indicate the level of effectiveness and feasibility of the proposed strategy and identify reasons for these outcomes. We will then build on these results to make recommendations for policy, if appropriate, or for the next research study, to identify effective and feasible healthy retailing interventions. The evidence from this study will directly inform the nutrition policy of ALPA and will indirectly influence policies of other retail organizations and community stores through the leadership and influence of ALPA in remote retailing and through the broader effort of the Commonwealth Department of PM&C, which is responsible for food security in remote Indigenous Australia.

Implications

Comprehensive multicomponent interventions are necessary to improve the quality of the customer food environment [44,45]. Our research will increase the health sector's understanding of merchandising as a critical factor influencing behavior, one that with appropriate support, can be implemented by retailers. It will also help improve other food environment interventions led by practitioners and academics worldwide, particularly those in other remote populations who experience similar health disparities. Indigenous Australians, especially those who live in remote locations, experience substantially more preventable chronic diseases compared with other Australians. Improving diet is imperative for closing the Indigenous health gap, and improving dietary intake can benefit the future health of generations to come. A key contributor to the adverse diet quality in this population is the alarmingly high intake of the

discretionary products that have proliferated the shelves in remote stores [28]. Food is predominantly sourced from community food retail stores, and many retail outlets operating in remote Australia are entirely community owned with store owners seeking in-store solutions to support healthier diets and combat diet-related diseases in a sustained way without negatively impacting on store sales. It is imperative that we work with retailers to provide high quality evidence to inform effective policy and practice for better health outcomes.

Conclusions

Examining the impact of modifying retail food environments for improved diet and health outcomes is a rapidly expanding research area worldwide [41]. Globally, our team is one of only several research teams who is actively investigating the role of retail food environments in population health. The bringing together of decision makers and practitioners in health and retail sectors including ALPA personnel, with investigators to lead this research, who are involved in food retail environment research in urban, rural, and remote contexts in Australia and Canada, will help lessen the current issue of methodological heterogeneity in the measurement of food environment exposures and outcomes [12,46]. This will enable enhanced generalizability of accumulated evidence on the impact of retail food environments on diet into the future.

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Authors' Contributions

JB, MF, EM, and CM conceived and all authors designed the study. All authors contributed to refinement of the study protocol and approved the final manuscript.

Conflicts of Interest

MF, EM, EM, AP, LMM, TW and CM declare that they have no competing interests. JB is a non-executive director of Outback Stores Pty Ltd and declares no other competing interests. KDS is an employee of the ALPA and declares no other competing interests.

Multimedia Appendix 1

Peer review from funding agency.

[PDF File (Adobe PDF File), 185KB - resprot_v8i3e12646_app1.pdf]

Multimedia Appendix 2

Authors response to peer review.

[PDF File (Adobe PDF File), 224KB - resprot_v8i3e12646_app2.pdf]

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Abbreviations

ALPA: Arnhem Land Progress Aboriginal Corporation

MJ: megajoule
NHMRC: National Health and Medical Research Council
NT: northern territory
PM&C: Prime Minister and Cabinet
SHOP@RIC: stores healthy options project in remote indigenous communities

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Protocol

Massive Open Online Courses (MOOC) Evaluation Methods: Protocol for a Systematic Review

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Abstract

Background: Massive open online courses (MOOCs) have increased in popularity in recent years. They target a wide variety of learners and use novel teaching approaches, yet often exhibit low completion rates (10%). It is important to evaluate MOOCs to determine their impact and effectiveness, but little is known at this point about the methodologies that should be used for evaluation.

Objective: The purpose of this paper is to provide a protocol for a systematic review on MOOC evaluation methods.

Methods: We will use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines for reporting this protocol. We developed a population, intervention, comparator, and outcome (PICO) framework to guide the search strategy, based on the overarching question, “What methods have been used to evaluate MOOCs?” The review will follow six stages: 1) literature search, 2) article selection, 3) data extraction, 4) quality appraisal, 5) data analysis, and 6) data synthesis.

Results: The systematic review is ongoing. We completed the data searches and data abstraction in October and November 2018. We are now analyzing the data and expect to complete the systematic review by March 2019.

Conclusions: This systematic review will provide a useful summary of the methods used for evaluation of MOOCs and the strengths and limitations of each approach. It will also identify gaps in the literature and areas for future work.

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KEYWORDS

online learning; e-learning, education; learning; education distance; computer-assisted instruction

Introduction

Massive open online courses (MOOCs) are rapidly becoming an established method of online and distance education, growing in prominence since the launch of the first MOOC in 2008. The idea of a course accessible by anyone with a computer with no fees or prerequisites for joining has caught the attention and imagination of many involved in e-learning, with MOOC being called the educational buzzword of 2012 [1]. Numerous MOOCs have been developed by top universities such as Harvard,

Stanford, and the Massachusetts Institute of Technology, giving additional gravitas to the field. MOOCs are accessible through multiple online platforms such as edX, Coursera, and FutureLearn. The possibility for anyone with a computer to participate in courses given by these universities and many other academic institutions has led to MOOCs being heralded as the democratization of education [2]. While traditional lectures are given to, at most, several hundred students, MOOCs have no participant limit and can potentially be given to tens of thousands of learners [3]. The scope of MOOCs is expanding beyond universities and into the workplace, with the flexible and self-directed nature of these courses making them highly transferable into the working environment. There is an increasing range of reasons for partaking in MOOCs, from mandatory university courses, to professional development, to self-interest [3].

While the MOOC field is new territory, the means of evaluating MOOCs is newer still and a gap in knowledge exists with regard to the methodologies which should be used for evaluation. The novel combination of teaching approaches used, including prerecorded videos, live discussion forums, peer-assessed assignments, and social media debate, warrant thorough investigation to enable providers to maximize participation and impact [4]. It is vital that appropriate methods are identified and available to determine the impact of these courses, a crucial but underresearched element. Aspects such as the effectiveness and quality of learning and impact of knowledge gained are vitally important in determining the strength of MOOCs as a learning tool, but there is not a substantial evidence base on methods for how these factors are measured or evaluated [5]. The longer-term impact of undertaking a MOOC must also be understood; at present there is little follow-up data gathered after the courses have concluded. This information is particularly needed when courses are designed to increase the knowledge or skills of a specific working population. Issues such as the almost universal low completion rates of MOOCs (ie, 10% or lower) are also in urgent need of addressing and improvements must be made to increase retention [6].

Although there have been recent reviews conducted on MOOCs [7-10], none have specifically focused on methods used for evaluation. With the heterogeneity of participants in MOOCs and the low retention rate [11], conducting effective evaluations of MOOCs is critical. To date, little work has been done in this area [12] and it has been highlighted as an area for future research [13]. Despite increasing research about MOOCs, there are limitations in reporting the methods and/or using valid and reliable measures in the studies [9]. Although it may not be advisable to develop a standard way to evaluate MOOCs due to their heterogeneity, a review on evaluation methods could help inform future evaluations on the current state of knowledge and the most reliable methods that can be used.

The purpose of this paper is to provide a protocol for a systematic review on MOOC evaluation methods. The systematic review is designed to identify all the relevant literature published thus far on methods of MOOC evaluation, extract methodologies and objectives, and synthesize these into a narrative describing the spectrum of methods available and recommendations for future research and practice.

Methods

Overview

We will follow elements of the Cochrane Handbook for Systematic Reviews for conducting the review [14] and will use Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) for reporting this protocol [15] (see Multimedia Appendix 1). To identify appropriate Medical Subject Headings (MeSH) and keywords, we will use the population, intervention, comparator, and outcome (PICO) framework to build the research question. We will follow six stages in this systematic review: (1) literature search, (2) article selection, (3) data extraction, (4) quality appraisal, (5) data analysis, and (6) data synthesis.

Literature Searches

Inclusion and Exclusion Criteria

Course evaluations can have many definitions. In this review, we will focus on the definition by Edwards, which states that evaluations focus on the experience of teachers and the students to assess and illustrate their *effectiveness* [16]. Therefore, we will only include studies that focus on the evaluation of MOOCs with reference to the course design, materials, or topics. The studies will be included only if they were evaluating the MOOC in general or features directly related to MOOCs, such as MOOC videos, MOOC discussion posts, and MOOC assessments. We developed the following PICO framework to guide the search strategy, based on the overarching question, “What methods have been used to evaluate MOOCs?”:

1. Population: the target population will include learners in any geographic area who have participated in MOOCs.
2. Intervention: the intervention will be *MOOC evaluation methods*. This is intended to be broad to include qualitative, quantitative, and mixed methods.
3. Comparator: studies do not need to include a comparator for inclusion in this systematic review.
4. Outcome: learner-focused outcomes such as attitudes, cognitive changes, learner satisfaction, etc, will be assessed.

This PICO was converted to a search strategy with the assistance of a medical librarian, as shown in Table 1.

Inclusion Criteria

We will include studies with a primary focus on MOOC evaluation and studies that have applied or reviewed MOOC evaluation methods: quantitative, qualitative, or mixed. Evaluation of MOOCs does not need to be the primary focus of the paper for inclusion in this systematic review.

Publication dates will be restricted from 2008 to 2018. The start date of 2008 was selected because MOOCs were introduced in 2008 [17]. Studies from any geographic location will be included.

Table 1. PICO[a] framework search strategy for MOOC[b] evaluation methods.

Search categories	Sample search terms to screen within electronic databases
Phenomenon of interest	MOOC* OR "massive open online course" OR coursera OR edX OR odl OR Udacity OR futurelearn
Intervention	Evaluat* OR measur* OR compar* OR analys* OR report* OR assess*
Comparator	Method*
Outcome	Knowledge OR "applicable knowledge" OR retent* OR impact OR quality OR improv* OR environment OR effect

[a]PICO: population, intervention, comparator, and outcome.

[b]MOOC: massive open online course.

Exclusion Criteria

We will restrict publications to the English language only. Studies will also be excluded if the primary focus is e-learning or blended learning, but not MOOCs.

We will search the following databases: (1) Scopus, (2) Education Resources Information Center (ERIC); (3) Institute of Electrical and Electronics Engineers (IEEE) Xplore, (4) Medline/PubMed, (5) Web of Science, and (6) British Education Index. To identify potentially relevant grey literature, we will also search Google Scholar and Google search engines. The search strategy for Scopus was developed in consultation with a medical librarian. The search strategy was adjusted for the rest of the databases based on the keywords of each database. The complete search strategy is included in Multimedia Appendix 2. Search results will be imported into EndNote and duplicates removed.

Screening and Article Selection

All records identified from the software searches will be recorded in a software management program, EndNote X8.2 (Clarivate Analytics). EndNote will also be used to remove any duplicates. Two independent reviewers will screen the title and abstract of all identified studies against the eligibility criteria. The full text of the identified studies will then be reviewed and assessed for eligibility. Disagreements will be resolved by discussion or by consultation with a third reviewer, if required.

Once the final list of studies is determined, the references for each included article will be searched to identify additional studies that should be considered for inclusion.

A PRISMA flow diagram will be created to document the selection process and reasons for article exclusions to ensure repeatability of the search results. This will include (1) Identification: records identified through database searching, additional records identified through other sources, and records after duplicates removed; (2) Screening (by title and abstract): including the number of records screened and records excluded; (3) Eligibility: full-text articles assessed for eligibility and full-text articles excluded, with reasons; and (4) Included: studies included in qualitative synthesis.

Data Extraction

The full text of each manuscript will be reviewed and data extracted with data points as defined in Table 2. The first reviewer will complete the data abstraction table for each of the included studies; this form will then be reviewed by the second reviewer. We have kept the data extraction table fields in the free form because we have anticipated that there will be high heterogeneity between studies, which can limit the use of predetermined fields. However, we were able to create predetermined fields for the data collection method and evaluation method fields of the table (see Table 2) based on initial reading of MOOC evaluations. Subvariables related to the comparator may be added to the data extraction sheet based on the available information, such as comparator type and comparison data analysis method.

Quality Appraisal

We will assess the quality of the included studies by conducting a risk of bias assessment. If there are any randomized controlled trials included, we will use the Cochrane Collaboration risk of bias tool [18]. Otherwise, for observational cohort and cross-sectional studies, we will use the National Institutes of Health-National Heart, Lung, and Blood Institute quality assessment tool [19]. The quality of the included studies will be recorded in a table for publication.

Data Analysis

We do not expect to be able to conduct a meta-analysis due to the anticipated heterogeneity of studies. We will therefore summarize the data by conducting a descriptive analysis. To commence the analysis, we will compare the studies based on the evaluation method—quantitative, qualitative, or mixed methods—and data collection methods. We will include information on the evaluation methods, size of the groups of learners, characteristics of the learners, and description of the evaluation outcomes.

Data Synthesis

We will also provide a narrative synthesis of the included studies. We will summarize the findings and present a table of the main results from all included papers. These will be supported by a narrative addressing the process as well as any rationale and challenges at each stage. These results will summarize and describe the MOOC evaluation methods, but also identify gaps and highlight areas where further research would be useful.

Table 2. Data extraction table.

Article information	Data extracted
General information	Article title
	Author name(s)
	Publication date
	Country of origin
Study characteristics	Study aims and rationale
	Study research question(s)
	Theoretical underpinning
Methods	Research design
	Outcome measure(s)
	Data collection method (yes/no)
	Survey: precourse survey, postcourse survey, other survey
	Interview
	Learning management system data
	Discussion posts
	Quizzes: pretest, posttest, other test, quiz
	Data analysis model/method
	Main data analysis method
	Secondary data analysis method
Intervention (evaluation method)	Type of learner(s)
	Evaluation method: quantitative, qualitative, mixed methods
	Group size
Outcome measures	Learner-focused outcomes (eg, knowledge, skills, and attitude/behavior)
	Other outcomes (eg, cost-effectiveness and other)
Comparator details	(If applicable)

Results

The systematic review is ongoing. We completed the data searches and data abstraction in October and November 2018. We are now analyzing the data and expect to complete the systematic review by March 2019. We will submit the findings for publication and peer review.

Discussion

This systematic review will provide a *systematic and transparent* review of the literature in order to better understand the strengths and weaknesses of methods currently used to evaluate various aspects of MOOCs. The key implications drawn from the synthesized data will help to inform future evaluation work. In this section, any researcher assumptions will be discussed, as well as conclusiveness of the data; strengths, weaknesses, and limitations of the systematic review; gaps in the current literature; and possibilities for future research.

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Authors' Contributions

EM conceived the study topic and oversaw drafting. KF prepared the first draft of the protocol. AA reviewed and amended the second draft of the protocol. All authors reviewed and edited the first draft of the protocol. AA and EM responded to peer-review feedback. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

PRISMA-P 2015 Checklist.

[PDF File (Adobe PDF File), 109KB - resprot_v8i3e12087_app1.pdf]

Multimedia Appendix 2

Full search strategy.

[PDF File (Adobe PDF File), 68KB - resprot_v8i3e12087_app2.pdf]

Multimedia Appendix 3

Peer-reviewer report from EIT Health.

[PDF File (Adobe PDF File), 298KB - resprot_v8i3e12087_app3.pdf]

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Abbreviations

EIT: European Institute of Innovation and Technology
ERIC: Education Resources Information Center
IEEE: Institute of Electrical and Electronics Engineers
MeSH: Medical Subject Headings
MOOC: massive open online course
PICO: population, intervention, comparator, and outcome
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

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Protocol

Digital Education for the Management of Chronic Wounds in Health Care Professionals: Protocol for a Systematic Review by the Digital Health Education Collaboration

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Abstract

Background: Digital education is “the act of teaching and learning by means of digital technologies.” Digital education comprises a wide range of interventions that can be broadly divided into offline digital education, online digital education, digital game-based learning, massive open online courses (MOOCs), psychomotor skills trainers, virtual reality environments, virtual patient simulations, and m-learning. Chronic wounds pose an immense economic and psychosocial burden to patients and the health care system, as caring for them require highly specialized personnel. Current training strategies face significant barriers, such as lack of time due to work commitments, distance from provider centers, and costs. Therefore, there is an increased need to synthesize evidence on the effectiveness of digital education interventions on chronic wounds management in health care professionals.

Objective: Our main objective is to assess the effectiveness of digital education as a stand-alone approach or as part of a blended-learning approach in improving pre- and postregistration health care professionals’ knowledge, attitudes, practical skills, and behavior in the management of chronic wounds, as well as their satisfaction with the intervention. Secondary objectives are to evaluate patient-related outcomes, cost-effectiveness of the interventions, and any unfavorable or undesirable outcomes that may arise.

Methods: This systematic review will follow the methodology as described in the Cochrane Handbook for Systematic Reviews of Interventions. As our systematic review is one of a series of reviews on digital education for health professionals’ education, we will use a previously developed search strategy. This search includes the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library), MEDLINE (Ovid), Embase (Ovid), Web of Science, the Educational Resource Information Centre (ERIC) (Ovid), PsycINFO (Ovid), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO), the ProQuest Dissertation and Theses database, and trial registries. Databases will be searched for studies published from January 1990 to August 2018. Two independent reviewers will screen the library for included studies. We will describe the screening process using a flowchart as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We will extract the data using a previously developed, structured data extraction form. Included studies will be quality-assessed using the Risk of Bias tool from Cochrane. We will narratively summarize the data and, if possible, we will conduct a meta-analysis. We will use Cochrane’s RevMan 5.3 software for data analysis.

Results: We have completed the screening of titles and abstracts for this systematic review and are currently selecting papers against our inclusion and exclusion criteria through full-text revision. We are expecting to complete our review by the end of April 2019.

Conclusions: This systematic review will provide an in-depth analysis of digital education strategies to train health care providers in the management of chronic wounds. We consider this topic particularly relevant given the current challenges facing health care systems worldwide, including shortages of skilled personnel and a steep increase in the population of older adults as a result of a prolonged life expectancy.

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KEYWORDS

distance education; digital education; e-learning; continuous medical education; health professions; health personnel; leg ulcers; pressure ulcers; systematic review

Introduction

Since the beginning of the 21st century, advances in telecommunications and the Internet, as well as increased access to computers and other digital devices, accelerated the uptake of digital learning. In health care, digital education is a well-accepted methodology of teaching in undergraduate studies, as well as a means to deliver continuous professional education to busy health care providers [1,2].

Digital education is "the act of teaching and learning by means of digital technologies" [3]. This is an overarching definition that encompasses a variety of educational approaches, concepts, methods, and technologies that are constantly evolving. Digital education can be classified according to the teaching methods, specifications of the technology, or modality of digital education. It can also be delivered as a stand-alone instructional method or as a blended-learning approach, combining elements of digital education with traditional, face-to-face learning [3]. Digital education comprises a wide range of interventions that can be broadly divided into the following [4-6]:

1. Offline and computer-based digital education (ie, offline digital education)
2. Online and local area network (LAN)-based digital education (ie, online digital education)
3. Digital game-based learning
4. Massive open online courses (MOOCs)
5. Psychomotor skills trainers, virtual reality environments, and virtual patient simulations
6. Mobile learning (m-learning)

Offline computer-based digital education refers to applications that do not require an Internet connection to deliver the learning activities, such as CD-ROMs, USB sticks, or material that was previously downloaded from a networked connection but does not require it for the learning activity [5]. Online digital education, also known as Web-based or LAN-based digital education, requires an active network connection to be delivered and it includes tutorials, discussions, or live conferencing, among other formats [7,8]. Digital game-based learning applies gaming principles and mechanics to create engaging learning activities to improve learners' attitudes, motivation, and knowledge [5]. MOOCs are courses offered online to large numbers of participants, independently of their location and entry qualifications [9]. Psychomotor skills trainers, virtual reality environments, and virtual patient simulations are different approaches offering a first-person active learning experience. Psychomotor skills trainers are used to develop fine motor coordination skills and techniques, while virtual reality environments and virtual patient simulators are computer-generated depictions of a given environment or a patient clinical case, respectively [5]. Lastly, m-learning refers to any digital education intervention that utilizes mobile devices to deliver educational content [5].

Several characteristics of digital education are believed to improve knowledge, including flexibility to access study materials at a convenient place and time, interactive lessons that can be repeated according to the learners' needs, and the availability of practice exercises with feedback to improve understanding [7,10-12]. Another characteristic that may be especially valuable for health care is the opportunity to provide lessons with standardized content that could help to produce globally accepted health care professionals [13]. These attributes make digital education particularly well-suited to deliver continuous medical education (CME) programs to professionals after entering the workforce. CME programs convey significant advantages to the skills and knowledge of health care providers, who generally understand their benefits and are willing to engage in these programs [14] despite facing significant barriers, such as lack of time due to work commitments, distance from educational centers, and costs [15,16].

Access to CME programs is particularly relevant to train professionals involved in the management of complex conditions, such us chronic wounds. Chronic wounds are wounds that "fail to proceed through an orderly and timely process to produce anatomic and functional integrity" [17]. They affect about 1% of the population, primarily the elderly, and are associated with a considerable reduction in the quality of life of affected patients [18]. Chronic wounds management requires intensive use of resources and personnel, particularly specialized nurses, increasing the economic burden on already overstretched health systems [19,20]. A key barrier to effective wound care appears to be a lack of interest in quality chronic wound care shown by health care professionals, a situation that

can only be improved with revised, evidence-based wound care education [20]. A 2005 review by Flanagan et al on the barriers of implementation of evidence-based best practice in wound care highlighted the need for continuous education of nursing personnel, to overcome barriers to learning and develop critical skills [21].

Considering the immense economic and psychosocial burden of chronic wounds [19,22,23], we believe that a systematic evaluation of the effectiveness of digital education interventions to deliver learning programs on chronic wound management is required. A number of systematic reviews, including several already published or submitted by our group, have evaluated the effects of digital education interventions on different aspects of health professions' education [4-6,24-36]. Nevertheless, to date, we have not encountered other literature or systematic reviews evaluating the effect of digital education interventions to train health care professionals on management of chronic wounds. Therefore, in this systematic review we will attempt to summarize the literature evaluating the use of digital education interventions to improve the management of chronic wounds by health care professionals.

The objective of this systematic review is to assess the effectiveness of digital education for chronic wounds management as a stand-alone approach or as part of a blended-learning approach in pre- and postregistration health care professionals.

Methods

We will follow the Cochrane guidelines to conduct this systematic review [37]. A detailed summary of the methods we will use in this review were reported in a previous paper [3]. This protocol was registered with PROSPERO on October 9, 2018 (registration ID: CRD42018109971).

Criteria to Select Studies to be Included in the Review

Our systematic review will include clinical trials in which any category of digital education intervention was utilized to train health care professionals in chronic wound management. The following study designs will be included: randomized controlled trials (RCTs), cluster RCTs, and quasi-RCTs. Cross-over trials will be excluded due to high risk of contamination as a result of carry-on effect. We will include eligible papers published in any language and in any type of publication, including research articles, abstracts, and conference proceedings.

The populations included in this review will include the following: (1) preregistration students pursuing a degree in any health care-related field, in a university or tertiary institution recognized by relevant governmental or professional bodies or (2) postregistration health care professionals, as referred by the Health and Welfare chapter of the International Standard Classification of Education: Fields of education and training 2013 (ISCED-F 2013) [38]. The health care-related professions eligible for the review include the following: medicine, nursing and midwifery, medical diagnostic and treatment technology, and therapy and rehabilitation. If a study presents data on more than one professional group or includes pre- and postregistration participants, it will be included if they report the results for each subgroup separately. Studies presenting a mixed-group analysis will be excluded. The included studies should present any of the comparisons that are listed in Textbox 1.

Outcome Measures

Primary Outcomes

Aligned with previous systematic reviews on digital education interventions from our group, we will evaluate the following primary outcomes:

1. *Learners' postintervention knowledge*, defined as the objective evaluation of learners' conceptual understanding, using validated or nonvalidated instruments, such as multiple-choice questionnaires or other kinds of questionnaires. If multiple posttest assessments were conducted, we will use the first posttest assessment in the analysis. Subsequent posttest assessments (ie, knowledge retention) will be used in sensitivity analysis (see Data Synthesis section below).
2. *Learners' postintervention skills*, defined as the learners' ability to execute a procedure or technique (ie, management of chronic wounds, in this review) taught to them, assessed using any validated or nonvalidated instrument (eg, number of mistakes made, or time spent in the task).
3. *Learners' postintervention attitude*, defined as the learners' perceptions about the intervention and about patients and colleagues, in relation to acquiring new knowledge or skills. We will measure them using any validated or nonvalidated instrument as reported in the primary study.
4. *Learners' postintervention satisfaction*, defined as learners' levels of expectation and enjoyment toward the intervention, assessed using validated or nonvalidated instruments.
5. *Learners' postintervention behavior change*, defined as any change in the way learners modify their practice or the way they interact with patients, measured using any validated or nonvalidated instrument.

Textbox 1. Comparisons that should be present in included studies.

- Any digital education intervention versus traditional learning
- Any digital education intervention versus blended-learning intervention
- Any digital education intervention versus another digital education intervention
- Any digital education intervention versus no intervention
- Any blended-learning intervention versus traditional learning
- Any blended-learning intervention versus no intervention

Secondary Outcomes

We will evaluate the following secondary outcomes:

1. *Patient-related outcomes*, as reported in the primary studies, will be assessed only in studies involving postregistration health care professionals using any validated or nonvalidated instruments.
2. *Cost and cost-effectiveness* of implementing the digital education interventions.
3. *Adverse effects of the digital education intervention*, including dropouts, isolation, and effects of isolation on the learners' mental well-being (eg, depression and anxiety) and other adverse effects as reported in the primary studies.

Identification of Studies

This systematic review is one in a series of systematic reviews our group is conducting to assess the use of digital education modalities for pre- and postregistration health professionals' education and training. Each review of the series addresses a different aspect of digital education, including categories (ie, online, offline, virtual reality, etc) [24,25,27,28,30,31], specific pathologies [26,29,32], or learning theories [33,34]. This systematic review will evaluate the use of digital education interventions for chronic wound management training. We will therefore utilize the same literature search as other reviews already completed or under development. The search strategy includes the databases listed in Textbox 2.

All databases were searched for studies published from January 1990 to August 2018 without any language restriction. We selected the year 1990 as the starting date of our search, since computer usage was limited to basic functions before that time. The search strategy was developed for MEDLINE and was later adapted to the other databases. Multimedia Appendix 1 presents the MEDLINE search strategy. We also searched the International Clinical Trials Registry Platform Search Portal and the Current Controlled Trials metaRegister of Controlled Trials for unpublished clinical trials to try to mitigate publication bias. Finally, we will examine the reference lists of all included studies and relevant systematic reviews, as well as perform a hand search of relevant journals. In the event that data retrieved from the published studies is incomplete or missing, we plan to contact the study authors to request clarification. The search results from all databases have been imported into a single EndNote X8.1 (Clarivate) library and duplicate records were removed.

Two authors will work in parallel to screen titles and abstracts to identify studies for full-text revision. The full-text versions of selected articles will be retrieved and assessed by two reviewers working independently. Reviewers' individual results at each step of the screening process will be compared; disagreements will be settled between them or through an arbiter if an agreement cannot be reached. The steps of the screening process will be presented in a flow diagram according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [39], including the reasons for exclusion of papers at the full-text screening stage.

Data Extraction and Quality Assessment

Two reviewers, working independently, will extract the data for all included studies using a Microsoft Excel prepiloted, standardized data recording form used by the group in other digital education systematic reviews. The information to be extracted includes the following: study design and participants' demographics, type of digital education intervention, method and device used to deliver the intervention, and type of content (eg, images, text or video, and reported outcomes). Disagreements between the authors will be resolved through consensus or consultation with a third review author, considered the arbiter.

The methodological quality of included papers will be assessed in parallel by two authors using the *Risk of Bias* tool from Cochrane [40]. We will assess the following domains: random sequence generation; allocation sequence concealment; blinding of outcome assessment; completeness of outcome data; selective outcome reporting; and other sources of bias such as baseline imbalance, inappropriate administration of an intervention, or contamination. We will not assess blinding of participants or personnel, as the nature of the intervention precludes blinding. If we include cluster RCTs, the assessment will include the following: recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomized trials. Each parameter will be classified as high, low, or unclear risk of bias, using the words *yes*, *no*, or *unclear* and the colors red, green, and yellow, respectively. We will report the results using a risk-of-bias table or summary as per the Cochrane Handbook for Systematic Reviews of Interventions [41].

Textbox 2. Databases included in the search strategy.

- MEDLINE (Ovid)
- Cochrane Central Register of Controlled Trials (CENTRAL; Cochrane Library)
- Embase (Ovid)
- Web of Science
- Educational Resource Information Centre (ERIC; EBSCO)
- PsycINFO (EBSCO)
- Cumulative Index of Nursing and Allied Health Literature (CINAHL; EBSCO)
- ProQuest Dissertation and Theses database

Statistical Analysis

We will use Cochrane's RevMan 5.3, the software used for preparing and maintaining Cochrane Reviews, to analyze the data. To estimate the effect size of the digital education interventions in the primary study, we will first calculate the mean difference and 95% CI if the results are reported as a continuous variable. We will calculate the risk ratio and 95% CI when the study reports the outcome as a dichotomous variable. If the same outcome is reported by more than one study using different measurement tools, we will recalculate mean differences into standardized mean differences. In the event that an RCT presents more than one intervention arm, the relevant digital education arm will be compared with the least-active control arm. If cluster RCTs are included in this review, we will aim to obtain data at the student level. If that is not possible, we will first establish if the original analysis had been adjusted for the effects of clustering and, if so, we will extract and use the reported estimates. Otherwise, we will check for unit of analysis errors and we will attempt to reanalyze the data using the appropriate unit of analysis and account for the intraclass correlation coefficients [42].

When a primary study is missing relevant outcome data, we will attempt to obtain the information by contacting the study authors. If a response is not obtained, we will report it accordingly. We will not impute any missing outcome data. We will, whenever possible, conduct analyses on an intention-to-treat basis.

Assessment of Reporting Biases

If the systematic review includes more than 10 studies, we will assess publication bias through a qualitative analysis of the characteristics of included studies using a funnel plot and regression weighted by the inverse of the pooled variance [43].

Data Synthesis

If the characteristics of the included studies allow, we will attempt to perform a meta-analysis. To proceed to the analysis, we will group the articles according to study design and type of intervention. We will categorize the studies' outcomes as per Miller's classification of clinical competence [44] to assess learners' knowledge and skills in accordance to the type of assessment utilized (eg, if an outcome reported as *skill* is assessed by a knowledge test, we will consider the outcome as knowledge), independently of the teaching method. Leaners' attitudes will be divided into cognitive, behavioral, or affective attitudes and analyzed independently [45]. Learners' satisfaction will be reported in a narrative synthesis.

Before attempting the meta-analysis, we will assess if it is feasible by evaluating the included studies for methodological and statistical heterogeneity. We will assess the characteristics of the forest plot and calculate the I^2 statistic [37]. If we observe substantial heterogeneity (ie, I^2 greater than 0.5), we will explore its causes by conducting subgroup analysis. If extensive clinical or methodological heterogeneity is identified, we will not report a meta-analysis, but will instead use a narrative synthesis.

If a meta-analysis is possible, we will use a random-effects model, as it provides a more conservative estimate of effect and it is the preferred method when there is moderate heterogeneity. We will perform separate analyses for interventions among pre- and postregistration health care professionals. We will include the intention-to-treat analysis of the results in the meta-analysis.

To examine the impact of bias on study outcomes and in the results of the meta-analysis, we plan to perform sensitivity analyses. We will exclude studies according to the criteria in Textbox 3.

If the data allow, we plan to conduct subgroup analyses, stratifying the data as described in Textbox 4.

Textbox 3. Criteria to exclude studies for sensitivity analysis.

- High risk-of-bias studies, as per our assessment using Cochrane's Risk of Bias tool; we plan to meta-analyze the data, excluding high risk-of-bias studies, to examine the strength of the results
- Small studies with less than 30 participants in each study arm
- Source of funding as follows:
- Studies funded exclusively through industry sponsorship
- Studies funded through public and industry sponsorship that includes the free provision of study materials
- Studies not funded by industry sponsorship, including publicly funded studies and studies that did not provide free materials, or when the funding was not described or was unclear
- Studies comparing more than one digital education or blended-learning intervention to traditional learning; in this case, a sensitivity analysis will be performed to assess the impact of each intervention on the measure of effect

Textbox 4. Stratification of data for subgroup analyses.

- Type of digital education intervention
- Chronic wound type: vascular ulcers (ie, venous ulcers and arterial insufficiency ulcers), diabetic foot ulcers, and pressure ulcers
- Registration stage: preregistration students and postregistration professionals
- Type of student or professional group, as per the International Standard Classification of Education: Fields of education and training 2013 (ISCED-F 2013) [38]
- Quartiles of adherence and time spent on the intervention, reported as a percentage
- Countries' income—low- and middle-income countries versus high-income countries—according to the World Bank's classification

Reporting of Results

We will produce a narrative synthesis of results, even if a meta-analysis is not possible. The report will include a *Summary of Findings* table following the Cochrane Handbook for Systematic Reviews of Interventions [41]. The table will outline the main outcomes for each included study and, if a meta-analysis is possible, the table will present the results for each of the primary outcomes, as well as potential adverse effects, if they were reported by the primary studies.

Results

We have completed the screening of titles and abstracts for this systematic review and are currently selecting papers against our inclusion and exclusion criteria through full-text revision. We are expecting to complete our review by the end of April 2019.

Discussion

Digital technologies are increasingly used to deliver learning programs to pre- and postregistration health care professionals. Evidence from systematic reviews have shown that these programs are at least as effective as traditional learning in improving learners' outcomes [46,47]. Digital learning offers a suitable alternative to deliver CME programs to health care professionals that may not be able to access them otherwise, due to work load, distance from learning centers, or costs [16]. This, in turn, may increase the uptake of these programs and potentially improve the quality of care. There is a wealth of evidence supporting continuous training to health care providers, particularly nursing personnel, in the management of chronic wounds [48-50]. As the global population ages, the burden of chronic wounds will continue to increase, making it crucial to ensure health care providers caring for these patients are properly trained and are following established, research-based practices.

Our systematic review will use stringent methodology to review the available literature and aim for an informed conclusion on the value of providing technology-enhanced education programs to enhance the quality of chronic wound management.

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Authors' Contributions

LTC conceived of the idea for the review. LM, NJYY, ZQT, KDOM, and BMK wrote the protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1

MEDLINE search strategy.

[PDF File (Adobe PDF File), 121KB - resprot_v8i3e12488_app1.pdf]

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Abbreviations

CENTRAL: Cochrane Central Register of Controlled Trials
CINAHL: Cumulative Index of Nursing and Allied Health Literature
CME: continuous medical education
ERIC: Educational Resource Information Centre
ISCED-F 2013: International Standard Classification of Education: Fields of education and training 2013
LAN: local area network
MOOC: massive open online course
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial

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Protocol

Smartphone-Delivered Peer Physical Activity Counseling Program for Individuals With Spinal Cord Injury: Protocol for Development and Pilot Evaluation

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Abstract

Background: Leisure-time physical activity (LTPA) is a critical component of a healthy lifestyle for individuals with spinal cord injury (SCI). However, most individuals are not sufficiently active to accrue health benefits. The Active Living Lifestyles program for individuals with SCI who use manual wheelchairs (ALLWheel) targets important psychological factors that are associated with LTPA uptake and adherence while overcoming some barriers associated with participation restrictions.

Objective: The goal of the paper is to describe the protocol for the development and evaluation of the ALLWheel program for individuals with SCI who use manual wheelchairs.

Methods: The first three stages of the Medical Research Council framework for developing and evaluating complex interventions (ie, preclinical, modeling, exploratory) are described. The preclinical phase will consist of scoping and systematic reviews and review of theory. The intervention will be modeled by expert opinions and consensus through focus groups and Delphi surveys with individuals with SCI, clinicians, and community partners. Finally, the feasibility and potential influence of the ALLWheel program on LTPA and psychological outcomes will be evaluated.

Results: This project is funded by the Craig H Neilsen Foundation, the Fonds de Recherche du Québec–Santé, and the Canadian Disability Participation Project and is currently underway.

Conclusions: Using peer trainers and mobile phone technology may help to cultivate autonomy-supportive environments that also enhance self-efficacy. Following a framework for developing and evaluating a novel intervention that includes input from stakeholders at all stages will ensure the final product (ie, a replicable intervention) is desirable to knowledge users and ready for evaluation in a randomized controlled trial. If effective, the ALLWheel program has the potential to reach a large number of individuals with SCI to promote LTPA uptake and adherence.

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KEYWORDS

smartphone; mobile phone; behavior change; digital peer training; leisure-time physical activity; spinal cord injury; Medical Research Council framework

Introduction

Leisure-Time Physical Activity Is Critical for Individuals With Spinal Cord Injury

Spinal cord injury (SCI) is associated with various sequelae, including respiratory disease, heart disease, diabetes, osteoporosis, overuse injuries, sexual disorders, pressure ulcers, chronic pain, fatigue, and depression [1,2]. Furthermore, the increased risk of sedentariness that often results from reduced mobility after SCI (eg, sitting in a wheelchair) can trigger a chain of negative physiological and psychological events that exacerbate secondary health conditions [3].

Participation in leisure-time physical activity (LTPA) can have a profound impact on health and quality of life after SCI. From a physiological perspective, findings from two systematic reviews confirm that participation in LTPA improves physical capacity, muscular strength, and respiratory function [4] and lowers risk factors associated with endocrine metabolic disease (eg, heart disease, osteoporosis, diabetes) [5]. Evidence from three systematic reviews suggests that participation in regular LTPA can positively influence psychosocial factors, including motivation, quality of life, and overall well-being [6-8].

Participation in LTPA is critical for individuals with SCI [8], especially those who use wheelchairs [9]. Even moderate amounts of LTPA may optimize functioning and slow the spiraling effects of deconditioning that are associated with SCI [10]. It is promising that many individuals with SCI have high LTPA intentions [11]. However, it is concerning that most are not active enough to accrue the health benefits. The results of two surveys with 73 and 965 individuals with SCI highlight this problem, reporting that 45% to 50% of respondents did not participate in any LTPA at all [11,12]. Therefore, the medical community is being encouraged to consider LTPA as a critical outcome that needs to be monitored for individuals with SCI [13].

Approaches to Community-Based Leisure-Time Physical Activity for Individuals With Spinal Cord Injury

Compared to the general population, individuals with SCI find it more difficult to start and adhere to LTPA regimes due to physical, environmental, and psychological barriers [13-16]. Transportation and physical health were the most commonly reported barriers [17]. Several approaches have been shown to be feasible and successful for overcoming the barriers and improving LTPA among individuals with SCI in the community, including home visits [18], telephone-delivered programs [19-22], online support [23], and gamification and virtual reality [24,25]. However, many existing approaches lack a strong grounding in behavior change theory [23] and thus may miss important psychological factors that are known to influence LTPA behavior over the long term. Telephone-delivered interventions represent one approach with a strong theoretical foundation that has been shown to sustain LTPA intentions over time [19,20]. Moreover, telephones have been reported as the preferred method of intervention delivery among individuals with SCI [26].

While telephone counseling presents a promising strategy for promoting LTPA among adults with SCI, direct and continuous contact has been reported to be important for enhancing effectiveness and adherence [27]. Therefore, LTPA programs for individuals with SCI should maintain the advantages of telephone delivery to overcome some of the barriers to LTPA but also integrate face-to-face contact.

Psychological Factors Influencing Leisure-Time Physical Activity Behavior

There are important psychological factors that influence LTPA uptake, adherence, and retention that need to be considered including autonomy support, motivation, and self-efficacy [28]. Self-determination theory provides a framework for understanding the motivations that may influence change in LTPA behavior [29] and has been effectively applied in the development of LTPA interventions [30]. Self-determination theory posits that through the satisfaction of autonomy, competence, and relatedness [31], autonomous motivation (ie, engaging in an activity for the value, importance, or enjoyment of the behavior) is increased and subsequently drives behavior change and maintenance [32]. Perceived competence, a similar construct to self-efficacy (ie, an individual's belief in his or her ability to accomplish a specific task [33]), has been shown to be a key determinant in eliciting LTPA behavior change [32]. In fact, self-efficacy is one of the most salient factors predicting uptake and maintenance of LTPA [34,35].

Peers are particularly useful role models after SCI, as they can help to establish a meaningful social network through shared life experiences, relatedness, and management of similar conditions [36-38]. Intervention delivery by peers can provide a source of personal contact (eg, face-to-face contact), which has been shown to increase LTPA and satisfaction with participation among individuals with SCI [18,39,40]. Although peers represent an influential approach to enhance self-efficacy and motivation for LTPA, existing programs have not fully incorporated the use of the power of SCI peers [39,40].

Mobile Technology and Social Media

Mobile technology (ie, smartphones and tablets) are becoming ubiquitous and may afford greater accessibility and convenience for the SCI population to participate in LTPA interventions [41,42]. Advancements and access to mobile technology may also extend the reach and effectiveness of telephone-delivered interventions. For instance, social networking available through smartphones and tablets may offer increased methods for achieving personal contact (eg, contact with peer groups) and may improve solutions to the timely delivery of LTPA interventions for individuals with SCI [43]. Importantly, the use of mobile technology and social media to deliver LTPA

interventions can allow for various methods of contact depending on participant preferences (eg, voice and video calls, text messaging).

Smartphones represent an affordable, portable, and novel approach using modern technology that may provide a useful medium for integrating important psychological variables (supportive environment, motivation, self-efficacy) while providing remote access to an LTPA intervention that is designed specifically for individuals with SCI. Integrating peers to deliver the LTPA program adds an important social element that may further enhance motivation and self-efficacy. However, given that 33% to 50% of individuals with SCI may not be able to use mobile technology [44], an LTPA program delivered by peers through social networking may offer alternate ways to access the program, including from desktop and laptop computers, which could accommodate various needs.

The aim of this paper is to describe the protocol for the development and evaluation of a theory-informed Active Living Lifestyles program for individuals with SCI who use a manual wheelchair (ALLWheel). In its early conceptualization, the name of the program was the Smartphone-Delivered Peer Physical Activity Counseling (SPPAC) program. Given the evolution of the program, the name ALLWheel will be used in all future evaluation and dissemination.

Methods

Guiding Framework

The Medical Research Council methodological framework was applied to design the protocol for the development and evaluation of the ALLWheel program [45]. The Medical Research Council framework describes five distinct phases: preclinical or theoretical (phase I), modeling (phase II), exploratory (phase III), randomized controlled trial (RCT) (phase IV), and long-term implementation (phase V) [45]. Figure 1 illustrates the Medical Research Council framework, highlighting phases I to III.

Phase I: Preclinical and Theory

Objective Ia

The objectives of this study are to summarize the impact of existing LTPA programs in Canada, identify existing gaps in programming for individuals with SCI, and make recommendations to address some of the gaps.

Design

Scoping reviews provide a form of knowledge synthesis that addresses an exploratory research question to map key concepts, summarize evidence, and identify gaps in research [46].

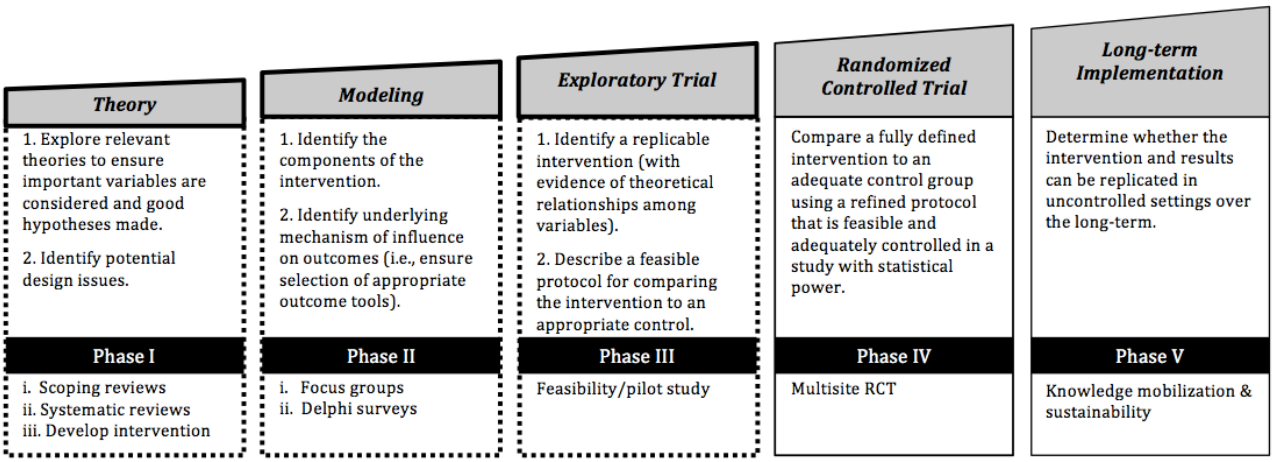
Procedure

Three experts in SCI and LTPA will follow a 6-step approach: identification of the research question, identification of relevant articles, article selection, evidence extraction, synthesizing and summarizing the data, and consultation with stakeholders [47]. The review will consist of (1) a systematic search of the scientific literature (ie, electronic databases including PubMed/MEDLINE, PsycINFO, CINAHL) using key words for spinal cord injury, physical activity, mobility, and community and (2) a Google search based on the authors' knowledge of existing programs and the abovementioned keywords. All scientific and grey literature pertinent to the objective will be considered. Findings from this scoping review will be used to design a subsequent systematic review (objective Ib) and to develop a focus group schedule (objective IIa) [48].

Objective Ib

The primary objective of this study is to determine the effectiveness of existing programs on LTPA among individuals with SCI who use manual wheelchairs. Secondary objectives include summarizing details related to program content, delivery methods, integration, and facilitators and barriers and discussing the potential of a mobile phone and peer-led LTPA program for overcoming some of the barriers reported among individuals with SCI.

Figure 1. Illustration of the processes for the development and evaluation of the ALLWheel program according to the Medical Research Council framework. RCT: randomized controlled trial.



Design

A systematic review will be done according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement guidelines (prisma-statement.org) [49,50].

Procedure

Original searches will be conducted by two independent researchers using online databases (PubMed/MEDLINE, CINAHL, PsycINFO, Embase, SPORTDiscus). Reference lists of selected studies and relevant review articles will be hand searched. The search strategy and study selection criteria will be developed according to the Participant, Intervention, Comparison, and Outcomes guidelines as described in the Cochrane Handbook for Systematic Reviews [51]. Accordingly, keywords will include terms relevant to Participant (spinal cord injury, manual wheelchairs), Intervention (LTPA, physical activity, self-determination theory, social cognitive theory, behavior change), Comparison (randomized controlled trial, quasi-experimental), and Outcomes (physical activity, participation, motivation, self-efficacy). Studies that fit the Cochrane guidelines and are written in English will be included in the review.

Two reviewers will independently rate the titles, abstracts, and full texts and select articles for inclusion. If consensus is not reached regarding inclusion criteria, a third reviewer will be consulted. The same two reviewers will assess methodological quality of randomized controlled trials using the Physical Therapy Evidence Database [52] and of pre-post studies using the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group [53]. Relevant data (mean differences in LTPA from pre- to immediately post-intervention) will be extracted to meet the primary objective. If feasible, a meta-analysis will be conducted. To meet the secondary objective, details about the program content, delivery methods, facilitators and barriers, and other pertinent information will be extracted and organized according to the two theoretical frameworks (ie, self-determination theory [29,33] and social cognitive theory [33]) that guide this research. Findings from this review will be used to design the prototype for a new LTPA intervention and develop discussion points for the focus group schedule.

Phase II: Modeling

Objective IIa

The first objective in the modeling phase is to gain expert input about the initial prototype of a novel LTPA program.

Design

A qualitative study design will be used.

Participant Recruitment

Purposive sampling will be used to recruit 10 to 15 experts (ie, individuals with SCI, health care professionals, and community partners that specialize in SCI) to participate in a focus group. Involving key stakeholders has been shown to improve intervention development and outcome selection [54]. Health care professionals will be kinesiologists, occupational therapists, and physiotherapists who have at least 5 years' experience working with the SCI population or at least 5 years of experience with LTPA interventions for persons with SCI. Individuals with SCI will be eligible to participate if they are aged 18 years and older, live in the community, have a traumatic or nontraumatic SCI (tetraplegia or paraplegia), use a manual wheelchair as their primary means of mobility, and are one or more years post-SCI [55]. Participants will be identified through existing community partners (eg, Adaptavie, Viomax, and Spinal Cord Injury British Columbia) and clinical partners (eg, outpatient rehabilitation programs at each site) that are the knowledge users of the ALLWheel program. Institutional ethics guidelines will be followed and informed consent will be obtained.

Procedure

Based on the findings from phase I, a concept version of the ALLWheel program including intervention content and smartphone apps (eg, voice calls, text messaging, videoconference, social media) will be provided to participants before the focus group. Participants will also receive an open-ended questionnaire to complete prior to the focus group where they will be asked to provide descriptive information about appropriateness of the ALLWheel intervention, suggestions for changes to content or delivery method, missing content, and potential concerns. Responses from the questionnaires will be used to guide the discussion during the focus groups. The focus group guide will be developed according to the Interview Protocol Refinement framework such that questions will align with the study objectives, questions will be organized to create an inquiry-based conversation, and the protocol will be reviewed and piloted among the research team [56]. A moderator and a research assistant will open the discussion with a brief description of results from the questionnaire and facilitate a brainstorming activity to determine potential modifications to the ALLWheel intervention protocol. Two focus groups will be conducted (each with 6 to 8 knowledge users who will be individuals with SCI, members of community groups, and clinicians) over 90 minutes and will be audiorecorded.

Data Analysis

Summary statistics will be used to describe the sample. Audiorecordings from the focus groups will be transcribed verbatim and analyzed using NVivo qualitative data analysis version 10 software (QSR International Pty Ltd). Content analysis will be done to identify recommendations for modifications to intervention delivery method or content, additional content to be included, and appropriateness of outcome measurement and determine if other general changes are necessary. Two to three individuals will perform a directed content analysis by repeatedly reviewing and organizing the data and extracting meaningful units into major themes and subthemes. Themes and subthemes will be discussed and agreed upon by the research team, and findings will be presented to the subjects in the form of Delphi surveys to obtain consensus.

Objective IIb

The second objective of the modeling phase is to achieve consensus from experts on a novel LTPA program.

Design

The Delphi method is a widely accepted and useful research approach for intervention development in the absence of sufficient evidence from experimental studies [57]. A group of experts provide insight on the topic through sequential questioning (ie, in multiple rounds) until consensus is obtained among the group [58,59]. In this way, the Delphi method will provide useful insight about an LTPA intervention that uses peers and smartphone technology for individuals with SCI who use manual wheelchairs.

Participant Recruitment

The same individuals who participated in the focus groups will form an expert panel and complete the Delphi surveys.

Procedure

Using an iterative process, participants will complete written questionnaires in multiple rounds to achieve consensus on the ALLWheel intervention structure and content [60]. In the first Delphi round, the ALLWheel intervention will be presented and experts will be asked to provide anonymous feedback. Details of the ALLWheel intervention will be described (eg, components to be included, useful motivational strategies, preferred program delivery methods, critical considerations) using definitive statements, and participants will rate their level of agreement or importance using Likert scales (eg, strongly agree to strongly disagree; not at all important to very important). Participants will then be asked for additional suggestions for improvement using open-ended questions. Subsequent Delphi rounds will be administered until 70% consensus is achieved [57]. The final step will consist of an expert meeting to integrate findings from the Delphi survey (eg, components to include/exclude, delivery methods preferred, critical motivation strategies) to generate a concept version of the ALLWheel program [57].

Phase III: Exploratory Trial

Objective IIIa

The first exploratory objective is to evaluate the feasibility of the ALLWheel study protocol for indicators of process, resources, management and treatment effect.

Objective IIIb

The second exploratory objective is to evaluate the influence of ALLWheel on objective LTPA (actigraphy).

Objective IIIc

The third exploratory objective is to evaluate the influence of ALLWheel on subjective LTPA, barriers to LTPA, motivation, psychological needs satisfaction, and satisfaction with participation.

Objective IIId

The fourth exploratory objective is to explore potential mediating and moderating relationships between LTPA and sociodemographic factors, epidemiological variables, and all secondary outcomes.

Design

A three-site, pre-post feasibility study will be done.

Participant Recruitment

A convenience sample of 12 community-dwelling individuals living with SCI will be recruited through community partners (eg, Adaptavie, Viomax, and Spinal Cord Injury British Columbia) and clinical partners (eg, outpatient rehabilitation programs at each site) that are the knowledge users of the ALLWheel program and who will be involved in the development and refinement of the program. According to Hertzog [61], 10 to 15 participants may be adequate to detect feasibility in a pilot study. Since the primary purpose of this study is to assess feasibility of the ALLWheel protocol for a future clinical trial, from a pragmatic perspective of future recruitment in a relatively small population, a smaller sample size is justifiable. Participants will be between 18 and 65 years old, live in the community, have had an SCI for 1 or more years [55], use a manual wheelchair as their primary means of mobility, be able to self-propel a manual wheelchair for at least 100 meters; not currently be meeting the physical activity recommendations [62], and be cognitively able to engage in the ALLWheel intervention (Mini-Mental State Exam score ≥25) [63]. Individuals will be excluded if they anticipate a health condition or procedure that contraindicates training, have a degenerative condition that is expected to progress quickly, or are concurrently or planning to take part in another LTPA intervention over the period of the study. Participants will be screened using the Physical Activity Readiness Questionnaire and e-PARmed-X+ [64]. Institutional ethics guidelines will be followed at each of the three sites, and participants will provide informed consent.

Procedure

Preferred duration and delivery methods for the ALLWheel intervention will be explored in phase II. However, for the purposes of study planning and budgeting, the intervention length (ie, 6 months) and number of contacts with participants (ie, 14) will be based on the findings of an effective telephone-counseling intervention for improving LTPA for individuals with SCI [19]. Program sessions will be customized to individual LTPA goals, and spouses/partners may be integrated into the ALLWheel program if desired by participants. For the proposed study, a physically active peer coach who has had an SCI for at least 5 years will deliver the ALLWheel intervention. The peer coach will receive comprehensive training through a 2- to 3-day workshop administered by study investigators.

Outcome Measures

All assessments will be administered by trained testers at each site who will be trained in a 3-hour workshop facilitated by study investigators (KB, EL).

Descriptive characteristics and sociodemographic information that are known to influence LTPA among individuals with SCI will be collected at baseline (T1) including age, sex, marital status, income, level of SCI, medications, psychological well-being, and social support [9,65-67]. Depression and anxiety will be assessed using the 14-item Hospital Anxiety and Depression Score [68,69], and social support will be assessed using the 6-item Interpersonal Support Evaluation List [70,71].

Feasibility Indicators

Feasibility indicators related to process, resources, management, and treatment will be collected throughout study [72]. A description of feasibility indicators, how they will be measured, and the parameters for success are described in Multimedia Appendix 1. Testers at each site will administer all outcome measures at baseline (T1), postintervention (T2), and 3 months postintervention (T3). The selected outcomes are reflective of important theoretical variables known to influence LTPA uptake, adherence, and retention. Additional outcomes may be identified during phases I and II.

Actigraphy

The primary outcome, LTPA, will be measured objectively using actigraphy, a noninvasive method of monitoring human activity using a small and lightweight accelerometry-based activity monitor (Actigraph GT3X+, ActiGraph LLC) that can be worn on the body of the wheelchair user and on the wheelchair without impeding movement [73]. The monitor contains an accelerometer that is sensitive to motion in all directions, and data are stored in the monitor as activity counts [74]. Time between sampling units (epochs) will be set at 15 seconds, allowing the greatest sensitivity for low-intensity activity [74]. Concurrent validity and reliability have been established [75,76]. Further validation for the use of actigraphy to distinguish between low and moderate intensities of LTPA among individual manual wheelchair users, including manual wheelchair users with SCI, is available elsewhere [77].

Upon completion of all secondary outcomes (subjective self-reports) at each time point, the tester will provide participants with 2 actigraphs (one will be positioned on the rear wheel of the manual wheelchair in a waterproof enclosure; the other will be worn on the nondominant arm). Participants will be asked to wear the actigraph at all times over a 7-day period except during sleep, bathing, or swimming. Participants will record the time the actigraph was put on and taken off using a log. The tester will obtain the actigraph and log from the participant at the end of the 7-day period. Only data from the days in which the actigraphs are worn for at least 13 hours per day will be included in the analysis [78]. Data will be converted to mean activity counts per hour (ie, bouts per hour).

Secondary outcomes reflect the proposed theoretical impacts of the ALLWheel intervention (ie, the relationship between LTPA behavior) and psychological determinants of behavior change (eg, motivation, autonomy support, and satisfaction of psychological need for LTPA). The secondary outcomes will help to discern a clinically important impact of the ALLWheel intervention.

Leisure-Time Physical Activity Questionnaire

Self-reported LTPA behavior will be measured using the 7-day Leisure-Time Physical Activity Questionnaire for adults with SCI [79]. Since actigraphy may not capture the intensity of some activities (eg, weightlifting) and they cannot be worn while swimming, participants will also be asked to recall the frequency (number of bouts) and duration (minutes per bout) of light, moderate, and heavy intensity LTPA over the past 7 days. Acceptable test-retest reliability and construct validity have been documented among adults with SCI [80,81].

Treatment Self-Regulation Questionnaire

Motivation to participate in LTPA will be evaluated using the 15-item Treatment Self-Regulation Questionnaire [82], which is designed to measure the degree of autonomous self-regulation to participate in healthy behaviors. Reasons for engaging in or changing health behaviors are scored using a 7-point Likert scale ranging from 1 (not true at all) to 7 (very true). Three subscales assess 6 forms of motivation, including autonomous regulation (identified, integrated, and intrinsic motivations), controlled regulation (external and introjected motivations), and amotivation. The questionnaire has been validated for assessing motivation for engaging in exercise [83]. Since the purpose of this study is to assess participation in physical activity that one engages in during their free time, wording for *exercise* will be changed to LTPA.

Leisure-Time Barrier Self-Efficacy Scale

Self-efficacy to overcome salient barriers to LTPA participation (eg, transportation problems, bad weather, pain, fatigue) will be assessed using a 6-item Leisure-Time Barrier Self-Efficacy Scale. The scale has been used in previous research with SCI [84-86] with evidence of high reliability and validity [84] and acceptable internal consistency [81].

Psychological Need Satisfaction in Exercise Scale

Satisfaction of the psychological needs for LTPA will be assessed using the Psychological Need Satisfaction in Exercise Scale [87]. Participants are asked to rate 18 items that reflect how a person may feel during physical activity using a 6-point Likert scale. A mean score will be calculated for autonomy, competence, and relatedness.

Wheelchair Outcome Measure

The Wheelchair Outcome Measure is a semistructured interview that allows participants to select important wheelchair-oriented participation goals. Participants are asked to identify 2 to 5 goals and evaluate their current satisfaction with participation in each goal (on a scale from 0 to 10). Participation goals are incorporated into the intervention. The instrument demonstrates good reliability and validity in use among individuals with SCI and older adults [88,89].

Data Analysis

Analyses will consider study feasibility indicators and primary and secondary outcomes. Means and standard deviations (continuous variables) and frequencies and proportions (categorical variables) will be used to summarize all data. Feasibility outcomes (objective IIIa) will be treated as binary, with *success* indicating the protocol is sufficiently robust to move forward with an RCT with only small or no adaptation required and *revise* indicating a need for changes before proceeding (see Multimedia Appendix 1). Controlling for confounding and within-subject changes from baseline to postintervention and from baseline to follow-up in LTPA behavior will be determined using paired sample *t* tests (or nonparametric equivalent) (objective IIIb). Paired sample *t* tests will be used to evaluate within-subject change scores from

baseline to postintervention and from baseline to follow-up for self-reported LTPA, motivation, LTPA barrier self-efficacy, autonomy support, satisfaction of the psychological needs for LTPA, satisfaction with participation in meaningful activities, and controlling for confounding (objective IIIc). Exploratory analyses (objective IIId) will be conducted to investigate the strength and direction of the relationships between sociodemographic and epidemiological factors and primary and secondary outcomes, looking for moderate to strong relationships [90].

Results

This project is funded by the Craig H Neilsen Foundation, the Fonds de Recherche du Québec–Santé, and the Canadian Disability Participation Project. Approval has been obtained from the university research ethics boards at all sites for all phases of the study. Phase I scoping and systematic reviews have been completed, and manuscript preparation is underway. Phase II focus groups and Delphi surveys are near completion, and manuscript preparation is underway. Phase III pilot and feasibility evaluation is currently underway. All study staff have been hired and trained at all sites, and recruitment and data collection are ongoing. Four peer trainers have been recruited and trained, and recruitment for phase III was completed in September 2018.

Discussion

Principal Findings

The ALLWheel intervention presents an innovative approach to targeting change in LTPA for individuals with SCI. Guided by the tenets of two behavior change theories (ie, self-determination theory and social cognitive theory), conception of ALLWheel will integrate important psychological precursors to LTPA including autonomy, relatedness, competence/self-efficacy, and motivation [29-33]. Furthermore, development of the ALLWheel intervention and study protocol will follow the Medical Research Council framework for developing and evaluating complex interventions [45], which will ensure that ALLWheel is evidence-based. Development of the ALLWheel program will also involve knowledge users (eg, individuals with SCI, community organizations, clinicians) throughout all aspects of development, evaluation, and implementation, ensuring an integrated approach to knowledge translation. Finally, a feasibility evaluation will allow for refinement of the intervention and iterations of the protocol to maximize its impact.

Although the LTPA needs of individuals with SCI are not fully understood, there is reason to believe that including peers in intervention delivery may have benefits [39]. Furthermore, a program delivered using a smartphone has the potential to overcome many existing barriers to LTPA for individuals with SCI and allows for integration of an important face-to-face component (ie, through video-conferencing). The application of digital peer training (ie, digital person-to-person training facilitated by a peer using smartphone technology [91]) could maintain the benefits of telephone-delivered interventions (eg, increased geographic reach [19-21]), incorporate human support (ie, an important predictor of effect and adherence of behavior change interventions [91]), ensure individually tailored programs, and facilitate the implementation of important psychological factors [31-33]. Evaluating outcomes of autonomy, motivation, and self-efficacy will allow for exploration of theorized relationship between psychological factors and LTPA, which will provide crucial information for refinement of the intervention before conducting a larger RCT.

Including expert stakeholders (ie, individuals with SCI, clinicians, and community partners) in the development of a theory-based ALLWheel intervention is an integral component of this research program [54]. Obtaining consensus from our stakeholders and knowledge users will ensure that we develop a comprehensive LTPA intervention that is desirable to the people for whom it is intended. Evaluating the feasibility of the intervention in pre-post study design will allow for feedback from the stakeholders and modifications before implementing a larger more expensive effectiveness trial.

ALLWheel has potential for large geographic reach to individuals of various ages, and determining the feasibility of administering the program in English and French may lead to translation in other commonly used languages in Canada. Future studies can estimate cost effectiveness, measure long-term retention, and assess impact on the known health benefits.

Limitations

Larger multisite clinical trials are required to establish evidence that informs effective behavior change strategies for individuals with SCI. However, a 3-year development and feasibility study is a critical and prudent process to follow before designing a large and expensive multisite RCT. Developing a pilot and testing the intervention according to the Medical Research Council framework will help to ensure that the intervention is evidence-based and the protocol and intervention are feasible to administer. While the generalizability of ALLWheel is limited to individuals with SCI at this point, it is possible that digital peer training may provide a useful strategy for delivering LTPA programs to a broader population of wheelchair users and even the general population.

Conclusion

Using peer coaches and smartphone technology may help to cultivate autonomy supportive environments that also enhance self-efficacy. Following a framework for developing and evaluating a novel intervention that includes input from stakeholders at all stages will ensure the final product (ie, a replicable intervention) is desirable to knowledge users and ready for evaluation in an RCT. If effective, the ALLWheel program has the potential to reach a large number of individuals with SCI to promote LTPA uptake and adherence.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Description of feasibility indicators and parameters for the success of the Smartphone-Delivered Peer Physical Activity Counseling intervention and study protocol.

[PDF File (Adobe PDF File), 79KB - resprot_v8i3e10798_app1.pdf]

Multimedia Appendix 2

Peer-reviewer report from the Craig H Neilsen Foundation.

[PDF File (Adobe PDF File), 400KB - resprot_v8i3e10798_app2.pdf]

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Abbreviations

ALLWheel: Active Living Lifestyles for Individuals Who Use Wheelchairs
LTPA: leisure-time physical activity
RCT: randomized controlled trial
SCI: spinal cord injury
SPPAC: Smartphone-Delivered Peer Physical Activity Counseling

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Protocol

Structural Transformation to Attain Responsible BIOSciences (STARBIOS2): Protocol for a Horizon 2020 Funded European Multicenter Project to Promote Responsible Research and Innovation

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Abstract

Background: Promoting Responsible Research and Innovation (RRI) is a major strategy of the “Science with and for Society” work program of the European Union’s Horizon 2020 Framework Programme for Research and Innovation. RRI aims to achieve a better alignment of research and innovation with the values, needs, and expectations of society. The RRI strategy includes the

"keys" of public engagement, open access, gender, ethics, and science education. The Structural Transformation to Attain Responsible BIOSciences (STARBIOS2) project promotes RRI in 6 European research institutions and universities from Bulgaria, Germany, Italy, Slovenia, Poland, and the United Kingdom, in partnership with a further 6 institutions from Brazil, Denmark, Italy, South Africa, Sweden, and the United States.

Objective: The project aims to attain RRI structural change in 6 European institutions by implementing action plans (APs) and developing APs for 3 non-European institutions active in the field of biosciences; use the implementation of APs as a learning process with a view to developing a set of guidelines on the implementation of RRI; and develop a sustainable model for RRI in biosciences.

Methods: The project comprises interrelated research and implementation designed to achieve the aforementioned specific objectives. The project is organized into 6 core work packages and 5 supporting work packages. The core work packages deal with the implementation of institutional APs in 6 European institutions based on the structural change activation model. The supporting work packages include technical assistance, learning process on RRI-oriented structural change, monitoring and assessment, communication and dissemination, and project management.

Results: The project is funded by Horizon 2020 and will run for 4 years (May 2016-April 2020). As of June 2018, the initial phase has been completed. The participating institutions have developed and approved APs and commenced their implementation. An observation tool has been launched by the Technical Assistance Team to collect information from the implementation of APs; the Evaluation & Assessment team has started monitoring the advancement of the project. As part of the communication and dissemination strategy, a project website, a Facebook page, and a Twitter account have been launched and are updated periodically. The International Scientific Advisory Committee has been formed to advise on the reporting and dissemination of the project's results.

Conclusions: In the short term, we anticipate that the project will have a considerable impact on the organizational processes and structures, improving the RRI uptake in the participating institutions. In the medium term, we expect to make RRI-oriented organizational change scalable across Europe by developing guidelines on RRI implementation and an RRI model in biosciences. In the long term, we expect that the project would help increase the ability of research institutions to make discoveries and innovations in better alignment with societal needs and values.

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KEYWORDS

action plans; ethics; gender; guidelines; Horizon 2020; institutional change; model for RRI in biosciences; open access; patient involvement; public engagement; responsible research and innovation; structural change; science education; science with and for Society

Introduction

The misalignment of research and innovation with society could negatively affect the European Research Area in a number of ways [1]. First, European research and innovation could become unable to address the key problems that European society is facing and therefore, to contribute to "achieving objectives of sustainable development (consisting of economic, social, as well as environmental aspects)" [2]. Second, European research and innovation could become unable to exploit its potential in terms of innovation and commercial impacts and consequently, less competitive in the global market. Third, European research and innovation could become socially isolated, ethically contested, and not supported by citizens, public authorities, and economic players, with negative consequences for the availability of public research funds and private investments [3,4].

Fundamentally, what is at stake is the capacity of European research to be relevant and effective in societal and economic terms. In response, promoting Responsible Research and Innovation (RRI) is a major strategy of the "Science with and for Society" work program of the European Union's Horizon 2020 Framework Programme for Research and Innovation [5].

The term "Responsible Research and Innovation", while increasingly popular over the past decade [6-10], is conceptually underdeveloped and inconsistently applied [11]. According to the European Commission (EC), the RRI approach should be a key part of the research and innovation process and should be established as a collective, inclusive, and system-wide approach. In practice, RRI is implemented by the EC as a package that includes multiple actors and public engagement in research and innovation, enabling easier access to scientific results, the take-up of gender and ethics in the content and process of research and innovation, and both formal and informal science education [12].

In the literature, RRI is viewed as an "umbrella term" comprising a series of theoretical approaches and methods, and cutting across different sectors. As such, a wide range of stakeholders are involved in the RRI governance, which can be characterized as a patchwork of different and sometimes shared responsibilities. Most of the analyzed studies aim to contribute to the development of RRI in a specific discipline or area of research, drawing attention to the sedimented nature of the concept [13].

The aim of the Structural Transformation to Attain Responsible BIOSciences (STARBIOS2) project funded by the European

Union's Horizon 2020 research and innovation program (grant agreement No 709517) is to contribute to the advancement of the RRI strategy underpinning Horizon 2020. The specific objectives of the project are to attain RRI structural change in 6 European institutions through the implementation of action plans (APs) and to develop APs for 3 non-European institutions active in the field of biosciences; to use the implementation of APs as a learning process to develop a set of guidelines on the implementation of RRI; and to develop a sustainable model for RRI in biosciences

The STARBIOS2 project has been designed and is currently being carried out to promote RRI in 6 European institutions from Bulgaria, Germany, Italy, Slovenia, Poland, and the United Kingdom in partnership with a further 6 institutions from Brazil, Denmark, Italy, South Africa, Sweden, and the United States. The project is coordinated by the University of Rome Tor Vergata.

Methods

Theoretical Approach

The conceptual framework underpinning STARBIOS2 includes 4 major thematic elements, which are the interpretation of RRI; the relevance of RRI to the bioscience research sector; the interpretation of structural change; and the activation of structural change processes in research institutions and universities.

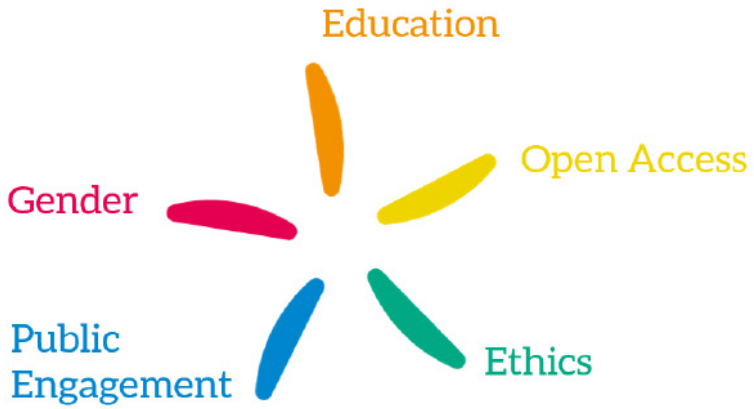
The Interpretation of Responsible Research and Innovation

In the context of this project, RRI is interpreted as an overarching policy strategy to radically increase the intensity and quality of the interactions between the European Research Area and European society. RRI aims to achieve a better alignment of research and innovation with the values, needs, and expectations of society [14]. At the level of research institutions, RRI activates structural processes able to profoundly modify their culture, values, rules, and procedures in 5 key areas (Figure 1):

- *Public engagement*: promoting the engagement of all societal actors—including researchers, citizens, policy makers, persons involved in business and industry, school children, and teachers—with the research and innovation process
- *Gender*: improving the excellence of scientific research, advancing gender equality within research institutions, as well as within the design and content of research and innovation
- *Education*: enhancing current educational strategies to provide future researchers and other societal actors with new capacities for taking responsibility in the research and innovation process and attracting children and youth to science, technology, engineering, mathematics, and medicine
- *Open Access*: making research and innovation transparent, free of charge, and easily accessible online, without restriction
- *Ethics*: ensuring that research and innovation respects fundamental rights and ethical standards, and shifting the view of research ethics away from a process of constraint, to one of supporting high-quality research results.

Although interest in some of the RRI issues, especially gender equality, ethics, and public engagement, is not new at European, national, and institutional levels, the novelty of the STARBIOS2 project is in bringing together the 5 keys of RRI in a unique strategy supported by a robust governance framework. Another important feature that differentiates STARBIOS2 from other RRI projects is the multicenter application of RRI in the field of biosciences. Another important differentiating feature of STARBIOS2 is the attempt to produce sustainable structural changes in the participating institutions.

Figure 1. Five keys of Responsible Research and Innovation as depicted in the Structural Transformation to Attain Responsible BIOSciences logo.



Relevance of Responsible Research and Innovation to the Bioscience Research Sector

While RRI aims to increase the intensity and quality of interactions between research and society in general, such interactions vary according to the research sector. Different research sectors have developed specific ways and methods for interacting with society with respect to the specific sectorial scientific, economic, and social challenges being faced [15], the societal players involved and their demands for engagement, communication styles, relationships with industry and, broadly, intensity of and tools for interaction with society. Furthermore, the uptake of RRI markedly impacts the contents and methods of research and innovation, which vary from sector to sector. Moreover, different disciplinary communities tend to interpret RRI according to their specific contexts, and attempts have already been made to develop RRI models tailored to specific research sectors. STARBIOS2 focuses on one specific research sector, biosciences, which can be understood in a broad sense to include biomedicine, biology, system biology, biochemistry, nature conservation, and biotechnology sciences [16]. The STARBIOS2 approach to RRI is relevant to address the diverse and complex challenges that arise in biosciences, including challenges related to public awareness of epidemics and vaccines, social responsibility for global nutrition, open access to big data, etc. Furthermore, the STARBIOS2 approach to RRI encourages collaboration across disciplinary boundaries and regions, as well as between scientific and nonscientific communities. This type of collaboration is increasingly required to deal with novel bioscience concepts such as the exposome, that is, all the biological, environmental, and social exposures relevant to an individual's health.

The Interpretation of Structural Change

In the context of the EC research policy environment, structural change refers to profound modifications of universities and research organizations [17] to pursue definite policy objectives. The concept of structural change is akin to the concept of institutional transformation [18] as both are based on the assumption that, in some cases or under given circumstances, the pursuit of new objectives requires pervasive, intensive, and far-reaching changes of the fundamental organizational processes, setup, and values [19]. Based on the experience of gender equality policies in science and technology [20-26], structural change is often characterized by 4 main features:

- *Irreversibility*: induced transformations are so rooted in the institution that they cannot be easily reversed (eg, by a simple leadership turnover or budget cuts)
- *Comprehensiveness*: a modification of the organizational life, affecting cultural and cognitive attitudes of staff and leaders, daily behaviors and practices, communication patterns [27], as well as procedures, rules, standards, and organizational structure
- *Inclusiveness*: structural change, as a collective effort, has to involve all players and stakeholders within the involved institutional or organizational unit, from leadership to students; therefore, both top-down and bottom-up processes are to be activated and coordinated
- *Contextualization*: even though problems and situations can be highly recursive and widespread, their mix is unique; this creates a need to contextualize structural change, for example, devising strategies and tools that are specifically tailored to the institution or unit

The Activation of Structural Change Processes in Research Institutions

Structural change will be activated through the design and implementation of institutional APs based on the iterative model adapted from the EC-funded project STAGES [28] (Figure 2).

The building blocks of the structural change activation model are as follows:

- *Core team*: In each research institution involved in the project, a core team is established to be in charge of the AP implementation. This core team is a source of new agency oriented to activate structural change processes [29-31] toward RRI within the department and the institution as a whole.
- *Context analysis*: One of the first actions of the core team is to analyze the context for the development and implementation of the AP. The context analysis considers multiple aspects, including previous experience within the department and the research institution in the key areas of RRI; the actors to be involved, their attitudes and orientations toward RRI, as well as their willingness to cooperate in the implementation of the AP; and the existing norms, organizational arrangements, and procedures applied in the management of each of the 5 RRI areas.
- *Detailed AP*: Based on the general AP included in the project's description of work and in the light of the context analysis, the core team develops a detailed AP.
- *Agency mobilization*: The core team is engaged with other influential individuals, groups, or networks already oriented toward or willing to promote RRI to enlarging the team and mobilizing them on RRI.
- *Negotiation processes*: Any action activates a negotiation process. Usually, negotiations related to consensus building or leadership on RRI involve multiple dimensions, including the interpretive dimension, which involves the interpretation of the situation within the organization, the symbolic dimension, which includes the visibility and recognition of RRI and its components, the institutional dimension, which pertains to the actual modification of the institutional structure, and the operational dimension, which translates decisions, goodwill, and declarations into action.
- *Structural impacts and reactions*: Negotiation processes are expected to have structural impacts on the institutions involved. Initial structural impacts will serve as the foundation upon which the rest will be built. At the same time, structurally negative reactions may also occur, changing the context or requiring modifications to the AP.
- *Self-reflexivity*: The core team is required to be self-reflective, that is, well aware of objectives, obstacles, timelines, opportunities, facilitating factors, and risks.
- *Technical assistance and monitoring and assessment*: The design and implementation of institutional APs is supported

through technical assistance and monitoring and assessment activity provided by 2 partners.

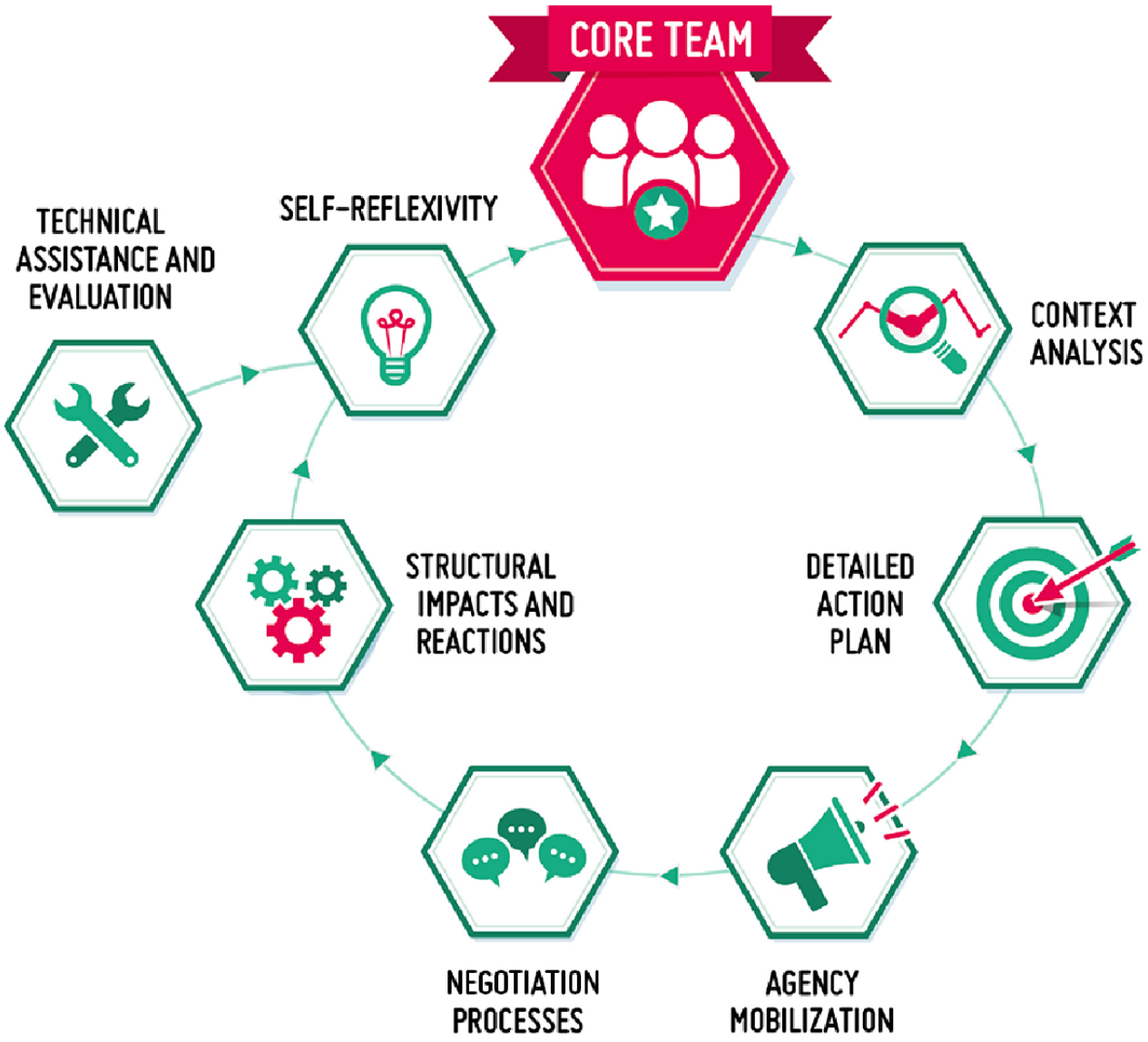
This model describes the nature of the AP implementation phase. In biosciences and other contexts characterized by high levels of uncertainty, innovation, and social complexity, project implementation processes rarely assume a linear trajectory. Rather, they tend to be nonlinear, characterized by stops and starts, sudden progress and setbacks, unplanned solutions, and deviations from the original plan. As a corollary, the implementation phase will require proactivity, flexibility, and the capacity to react rapidly to unexpected situations.

Project Partners

The STARBIOS2 project has been designed and is currently being carried out in 6 European institutions as follows: The Department of Biology, University of Rome Tor Vergata, Rome, Italy; the National Institute for Health Research Oxford Biomedical Research Centre, University of Oxford and Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; the Department of Biodiversity, University of Primorska, Koper, Slovenia; The Institute of Science Education, University of Bremen, Bremen, Germany; the Agrobioinstitute, Sofia, Bulgaria; and the Intercollegiate Faculty of Biotechnology University of Gdańsk and Medical University of Gdańsk, Gdańsk, Poland.

In the context of the global significance of RRI, the STARBIOS2 project is carried out in partnership with 6 additional institutions worldwide.

Figure 2. A structural change activation model adapted from the European Commission-funded project STAGES.



The three partners play roles in developing their own APs and the learning and sharing of RRI implementation experience and best practice beyond Europe are The International Centre for Genetic Engineering and Biotechnology, Cape Town, South Africa, The Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, and The University of Maryland, Baltimore, MD, United States.

Another 3 partners have responsibilities for providing the project consortium with the following contributions:

- The Laboratory of Citizenship Sciences, Rome, Italy (responsible for technical assistance)
- The Danish Centre for Studies in Research and Research Policy, Aarhus University, Aarhus, Denmark (responsible for monitoring and assessment)
- The Centre for Research Ethics & Bioethics, Uppsala University, Sweden (responsible for communication and dissemination; in 2018, this partner replaced Sparks & Co [France], which oversaw the communication activities in the first phase of the project).

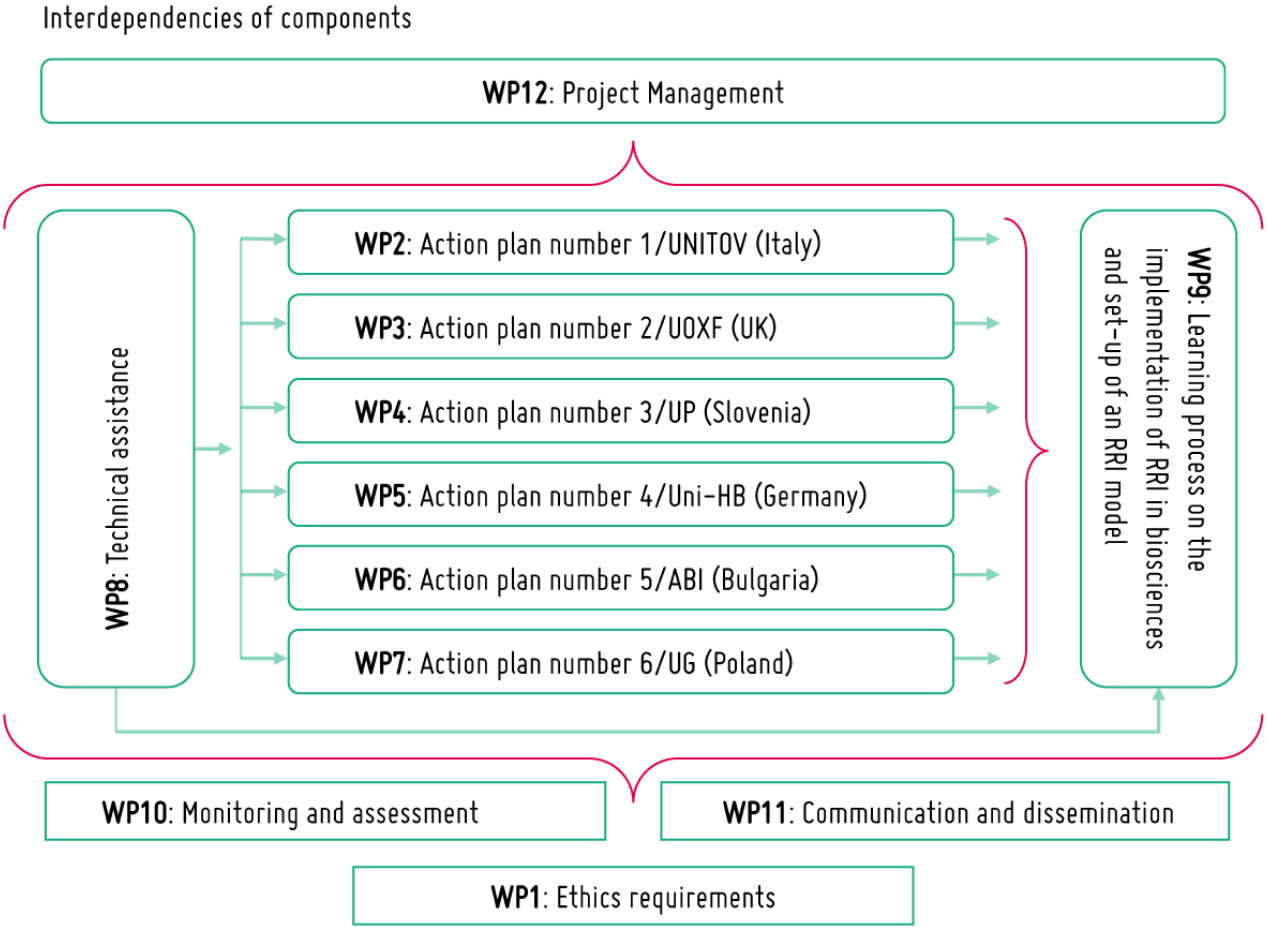
Project Structure

The project is organized into 6 core work packages dealing with the implementation of institutional APs based on the structural change activation model and others supporting work packages (Figure 3).

The work packages related to the 6 APs have in common the methodology illustrated above, and the fact that they deal with all 5 keys of RRI; these work packages, however, differ in the fact that they are designed to meet different local needs and operate in different political, cultural, and scientific contexts.

While each partner is responsible for the delivery of their specific APs, services, and learning activities related to the work packages, the overall project management is based on the principle of coresponsibility. Coresponsibility enables equal participation of consortium members in key decisions over the course of the project and underpins the composition of the Steering Committee, which includes representatives of all partners. The Project Coordinator presides over the Steering Committee and coordinates the project at the executive and scientific levels. A lead organization has been identified for every work package. In close cooperation with work package leaders, the Project Coordinator and their staff monitor the execution of the project, including risk analysis and adjustments to the original plan of activities. In addition to the internal controls that the Steering Committee has for the scientific and technical quality of the activities, the project also has an International Scientific Advisory Committee, an independent body providing external oversight of the scientific quality of the main outputs of the project.

Figure 3. The project organization and management. RRI: Responsible Research and Innovation; UNITOV: University of Rome Tor Vergata; UOXF: University of Oxford; UP: University of Primorska; Uni-HB: University of Bremen; ABI: Agrobioinstitute; UG: University of Gdańsk; UK: United Kingdom; WP: work package.



Technical Assistance and Evaluation

This specific project work package aims to provide continuous support to the partners involved in the implementation of the project APs through technical assistance activities in all phases of the project. These activities are expected to help drive the APs successfully from the detailed design phase to completion and ensure that the implementation of each AP can benefit from other RRI experiences in bioscience worldwide. Technical assistance is carried out through regular consultations via Skype, on-site visits, email correspondence, meeting on specific thematic issues with one or more AP teams, and mutual learning sessions during the Steering Committee meetings.

Different types of technical assistance include horizon scanning and structured presentation of materials, scientific texts, manuals, video, and events relevant for the different keys areas of RRI; self-reflection activities; horizontal exchanges among teams; facilitation of contact with external experts on specific issues foreseen within the different APs; promotion of contact between the experts inside the consortium; administrative and technical advice on financial and reporting issues; suggestions for tools to be used or adopted for carrying out specific activities; and support in designing and setting up specific actions.

Monitoring and Assessment

Working in cooperation with the Technical Assistance Team, the Monitoring and Assessment Work Package aims to examine and assess the process and progress toward the objectives of the project, provide input on the quality of the project activities, and assess the achievement of planned objectives and impacts, in acknowledgment and adaptation to the project nature [32]. Specific monitoring and assessment activities include the following:

- Transversal: cooperation with all other partners, facilitation of knowledge exchange, and technical assistance;
- Communication: identification of needs and potential beneficial activities, inducing critical self-reflection; and
- Balancing an internal or external role: a critical friend, overseeing the flow of the APs, mapping progress, and enabling timely intervention.

Development of the Guidelines and Model

RRI APs at STARBIOS2 institutions serve as “laboratories” of structural change; they will allow us to carry out guided observations and develop learning processes related to the implementation of RRI. Therefore, the project will allow us to learn lessons on how to foster a process of structural change oriented toward RRI in the bioscience sector. The authors will synthesize these lessons in a set of guidelines on the implementation of RRI within bioscience research organizations and develop a model for the diffusion of such activities in the bioscience sector. These activities will be carried out following a participatory approach.

The guidelines will contain recommendations for initiatives to promote structural change within research organizations aimed at promoting RRI. The model, on the other hand, will be focused on the general characteristics of RRI for a research organization within the bioscience sector.

The following activities are planned: information-gathering (through technical assistance and monitoring, literature review, and exchanges with other projects on RRI); analysis of existing RRI models; second-tier analysis of the STARBIOS2 APs; drafting of the guidelines provisional version; validation and final version of the guidelines; development and validation of a model for implementing RRI in the biosciences structure; drafting of a strategic document for a sustainable RRI model for biosciences; training program on RRI in biosciences with the involvement of STARBIOS2 international partners; and development of RRI APs by our partner institutions from South Africa, Brazil, and the United States.

Interconnections Between Activities

All project activities are interconnected with each other into 3 major components, where the outcomes of each preceding component serve as preconditions to the outcomes of each subsequent component:

- The implementation of the 6 APs (together with the related support, technical assistance, and monitoring activities) is directly intended to produce structural changes in the institutions involved.
- The development of the learning process is dependent upon the attainment of structural changes through the implementation of the APs, as well as comparisons between the experiences of implementing various APs.
- The development of the model on RRI for biosciences and the guidelines is, in turn, intrinsically dependent on the outcomes of the learning process.

In the long term, it is expected that the model and the guidelines developed and disseminated as part of this project will help to increase the ability of research institutions to make discoveries and innovations in better alignment with societal needs and values.

Communication and Dissemination

The results of this project will be communicated and disseminated through the professional networks of the partner institutions, conferences, workshops, peer-reviewed journals, trade publications, and mass media. To increase transparency and broaden outreach, research news and multimedia will also be published online on the project website, social networks, and social media.

Ethics

As part of the current European Union’s Horizon 2020 research and innovation program (grant agreement No. 709517), all partners completed the required ethics self-assessment and confirmed that all activities raising ethical issues would comply with applicable international, European, and national law; formally, all publicly funded bioscience institutions should require that. Ethics approval will be sought from the relevant Research Ethics Committees and host institutions at the appropriate time prior to commencing individual research components of projects involving human participants or personal

data. Ethical breaches should be punishable by the loss of public research funding and often by civil law suits.

Results

The project runs for 4 years from May 2016 to April 2020. As of June 2018, the initial phase has been completed. The 6 APs have been approved by the partners and are ongoing. All management, support, and advisory structures have been activated, and are working on a regular basis. A specific approach for mutual learning has been developed and discussed with all the AP Teams. The work on the development of a set of guidelines on the implementation of RRI and a model for RRI in biosciences has commenced and is currently at an early stage. An International Scientific Advisory Committee has been formed to advise on the reporting and dissemination of the project's results. As part of the communication and dissemination strategy, a project website [33] a Facebook page, and a Twitter account [34] have been launched and are updated periodically.

In addition, an ongoing observation tool has been launched; this observation tool, managed mainly by the Technical Assistance Team, will enable the collection of information from AP activities, which will be useful for the elaboration of guidelines and model. Aspects to be taken into consideration, in the development of the guidelines and model include the following: the mobilization of the actors and their agency within the process of implementing RRI-oriented initiatives and projects; the barriers encountered during the implementation of RRI-oriented initiatives and projects; the negotiation in which the actors are engaged in during the promotion of RRI; the structural impacts and reactions produced by the RRI promotion process; how self-reflection is carried out by the actors involved; and how context impacts research organizations and the promotion of RRI.

The substantive phase of the project is currently in full progress. The first substantive results include the following:

- The launch under the aegis of the United Nations Educational, Scientific and Cultural Organization Interdisciplinary Chair in Biotechnology and Bioethics of a university course on "Wellness, food and sustainable development"; the launch of an Observatory on gender to raise awareness on how gender models affect research activity and to modify organizational models (University of Rome Tor Vergata)
- The adoption of an Open Access Policy by the University Senate; the promotion of courses and theses about career development for women researchers; and the inclusion of RRI in the XXIV Biotechnology Summer School as a "pilot" experience toward the establishment of a teaching course in the educational curricula (University of Gdańsk)
- The creation of a Code of Conduct for Biosciences and its implementation into the syllabus of 3 courses; the adoption of gender among the quality indicators for the self-assessment of the activities implemented by different university departments (University of Primorska, Koper)
- The establishment of a Plant Biotechnology Information Centre aimed at promoting societal engagement and science communication around emerging research, ethical, and societal issues and the establishment of contacts with public institutions and nongovernmental organizations (Agrobioinstitute, Sofia)
- The elaboration of educational methods and tools to promote the awareness of RRI in different target groups (students, researchers, school classes, teachers, and citizens) and the development of an RRI mission statement at faculty level (University of Bremen)
- The evaluation and promotion of the use of sex and gender as key variables in biomedical research; the facilitation of knowledge exchange about open access among researchers and practitioners via presentations, digital strategies, and policy consultations (University of Oxford and Oxford University Hospitals NHS Foundation Trust).

Discussion

The authors anticipate that the project will have a significant impact on the organizational processes and structures of the institutions involved through the uptake of RRI. The authors expect to make RRI-oriented organizational change scalable across Europe through the development of a set of guidelines on the implementation of RRI and a model for RRI in biosciences. In the long term, the authors expect that the project will help increase the ability of research institutions to make discoveries and innovations in better alignment with societal needs and values. Potential risks within the delivery and impact of the project include the complexity of the project, which might affect the planned timeline for the delivery of the project, unexpected responses to changes in organizational culture, procedures, and structures, and the management of the involvement of a large number of stakeholders during various phases of the project. These potential risks are being addressed by the adoption of a context-specific approach to the implementation of project APs in different contexts, adequate stakeholder engagement, constant communication among the partners, periodic monitoring and assessment of the project delivery against its objectives, and continuous technical assistance throughout all phases of the project provided by one of the partners. Cooperation with international partners allows the learning and sharing of RRI implementation experience and best practice beyond Europe.

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Authors' Contributions

This paper is based on a funded grant proposal, which was conceived and developed collaboratively, among others, by the following coauthors: VC, AD, CM, LE, EB, DD, LZ, EKS, KPB, DE, MS, and LCJrA. CM, VC, DM, and PVO drafted this paper based on the funded grant proposal and the activities carried out in the early stages of the project. All other coauthors participated in the project implementation, contributed to data collection, and critically reviewed the manuscript for important intellectual content.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Evaluation Summary Report Coordination and support actions.

[PDF File (Adobe PDF File), 96KB - resprot_v8i3e11745_app1.pdf]

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Abbreviations

AP: action plan
EC: European Commission
RRI: Responsible Research and Innovation
STARBIOS2: Structural Transformation to Attain Responsible BIOSciences

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Protocol

Protocol for Investigating the Technical Efficiency of District Hospitals in the Public Health Sector of KwaZulu-Natal, South Africa

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Abstract

Background: The central objective of policy makers and health managers is efficiency in the delivery of health care. With frequent reports of global economic crises, there is a need to continuously measure the performance of various sectors of the health care system. This can inform the decision-making process toward allocating scarce resources with the aim of maximizing output.

Objective: The aim of this study is to determine the technical efficiency (TE) of public sector district hospitals in the province of KwaZulu-Natal, South Africa to provide information that will assist in policy formulation that may further assist in more efficient resource allocation decisions.

Methods: This is a health system research based on a quantitative research approach. All 38 public district hospitals in the 11 municipalities of the province will be included in this study. The data for the study will include inputs from hospitals' operations that contribute toward subsequent outputs. The input data will include information such as the number of health professionals (doctors, nurses, and other personnel) and number of hospital beds, whereas the output data will include information such as outpatient visits and number of admissions or discharge. Other data categories to be included will be determined by data availability and will be uniform for all facilities. Data for each facility for a 3-year period from 2014 to 2017 will be obtained from databases of the district health information, basic accounting, and personnel salary systems. On the basis of the data obtained, a model will be developed that can be used to assess how TE of public districts hospitals may be improved. TE will be determined using Data Envelopment Analysis, and factors influencing efficiency will be computed using StataCorp statistical package.

Results: As of February 2019, the study is at the data collection, data input, and analysis stages. The results are expected to be available from the second quarter of 2019.

Conclusions: Findings from this study can add to tools available to policy makers, health planners, and managers in making decisions about resource allocation in health care systems. Moreover, these findings will be disseminated electronically and in print.

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KEYWORDS

technical efficiency; district hospitals; data envelopment analysis

Introduction

Background

The health of a nation is the wealth of the nation is a popular saying. Thus, the health sector of any country is critical to social and economic development that links productivity to the quality of health care. According to the Millennium Development Goal (MDG) report of 2015, most sub-Saharan African countries failed to achieve the health-related targets set by the United Nations [1]. The health-related goals of MDG include reducing child mortality, improving maternal health, and combating HIV/AIDS, malaria, and other diseases, which represent the major health challenges in South Africa (SA) and other sub-Saharan African countries [1]. There is a need to continuously monitor the efficiency of health care facilities, especially the district hospitals, which offer generalist services and support the basic primary health care service. One of the goals of the newly introduced 2030 agenda of the United Nations known as *Sustainable Development Goals* is ensuring healthy living and promoting well-being for all ages [2]. Consequently, periodic monitoring of health care service delivery at health facilities is necessary.

Sub-Saharan Africa accounts for 11% of the world's population, yet it bears 24% of the global disease burden and allocates less than 1% of global health expenditure [3]. In this region, there is also a severe shortage of trained medical personnel, with just 3% of the world's health workers deployed in sub-Saharan Africa [3]. Reports have shown that sub-Saharan African countries are faced with a heavy burden of both communicable and noncommunicable diseases [1,3]. Unfortunately, most of these countries (especially areas with the greatest health care needs) lack adequate information for health planners to better understand and address problems related to equitable distribution of health care services. A report shows that the region of sub-Saharan Africa spent an average of 6.1% of its total gross domestic product (GDP) on health, far less than the 9.5% of GDP that countries of the Organization for Economic Co-operation and Development (OECD) spend on health [4]. However, SA on the other hand spends 8.8% of its GDP on health, which is higher than the health-related expenditure of most other sub-Saharan African countries and closer to OECD countries [4].

The mission of the SA National Department of Health (DoH) is to improve the health status of the population through prevention and health promotion [5] and also to consistently improve the health care delivery system by focusing on access, equity, efficiency, quality, and sustainability [5]. In 1994, the democratically elected government inherited a fragmented health system that was characterized by inequitable access, distribution, and financing [6]. In an attempt to redress the imbalances of the past, the DoH embarked on reforms as articulated in the white paper on transformation of the health system [6]. To improve the health status, the government, through the DoH, adopted the district health system as the operational vehicle to deliver comprehensive primary health care, of which district hospitals are an integral part. The district hospital plays a pivotal role in supporting the primary health care, and it is also the gatekeeper to more specialist care at provincial and tertiary hospitals [6].

The central objective of policy makers and health managers is to ensure efficiency in the delivery of health care [7]. For this reason, there is a growing interest in the measurement of inputs, activities, and outcomes of health systems. This is because of an increase in the cost of health care, increased demand for public accountability, and improved capabilities for measuring system performance. Where high levels of technical inefficiency exist, there is a significant concomitant waste of available resources. Even though efficiency occupies a central role in health policy, much of the attention of policy makers, donors, and health care researchers has been on health sector reforms and the mobilization of additional resources to redress inequalities in access to health care [8]. Given the level at which resources are being mobilized for health care services, it is important to investigate the efficiency with which these resources are used.

Hospitals are known to absorb the greatest proportion of the total health expenditure in most sub-Saharan African countries, estimated at over 45% to 69% of government health sector expenditure [9,10]. The SA health care system comprises a large public health sector that consumes around half of the 9% of the total expenditure and is collectively higher than 5% of the GDP recommended by the World Health Organization [11]. Despite the high expenditure, the country's health outcomes are poor in comparison with other similar middle-income countries, reflecting inequity in health care in the country [11]. The public hospital sector accounted for a very high proportion (80.9%) of the total health expenditure in 2016 and 2017. More than half (54.6%) of the total hospital expenditure in 2016 and 2017 was consumed by district hospitals [12]. As hospitals are increasingly consuming more health care resources, there is a need to determine if the increase is accompanied by increase in service provision.

Therefore, it is important to evaluate the efficiency of hospitals, as failure to do so will compromise efforts toward redressing inequities and access to health care. Improving the efficiency of hospitals is central to the overall improvement of health system performance as it will enable the redistribution of potential resources to ensure equity, accessibility, and the delivery of sustainable quality care.

Aim and Objectives

The overarching aim of this study is to determine the technical efficiency (TE) of public sector district hospitals in the province of KwaZulu-Natal (KZN), SA to provide analysis to inform policy formulation that may enable more efficient resource allocation decisions. The following objectives are identified to address the aim of the study. Firstly, to assess different approaches toward measuring TE of health facilities using a systematic review. Secondly, to determine the TE level of the selected district hospitals. Thirdly, to estimate the adjustment needed to make inefficient facilities more efficient. Fourthly, to identify factors that influence the performance and efficiency of these hospitals. Fifthly to compare the TE of rural district hospitals to those in urban areas. Finally, to develop a model

and framework to provide recommendations for improving efficiency of SA district hospitals.

Methods

Overview

KZN is the second most populous province in SA with a total population of above 10 million, comprising more than 85% black Africans. It is the largest province located at the southeastern part of the country, comprising 11 districts and 52 municipalities, which are a mix of urban, semi-urban, and rural areas. It is bordered on the east by the Indian Ocean and other parts by 3 other provinces and 3 other Southern African countries: Mozambique, Swaziland, and Lesotho [13].

There are 3 categories of hospitals in the country: the district, regional, and tertiary (provincial tertiary and national central) hospitals. District hospitals account for 64% of public hospitals in the country. It is the first level of referral, and it provides generalist health care where various outpatient and inpatient services are offered. District hospitals have between 50 and 600 beds, a 24-hour emergency service, and an operating theater. Specialists from different clinical services provide a range of diagnostic, therapeutic, and rehabilitative services [14].

Sample Size and Sampling Strategy

The sample size for this study will be all 38 public district health hospitals (DH) in KZN in the 11 municipalities of the province listed in Table 1. Any DH without available/retrievable data from the national database will be excluded from the study.

Study Design

This is a health system research based on a quantitative research approach to determine the TE of district hospitals in the KZN province using Data Envelopment Analysis (DEA). DEA was first introduced by Charness et al in 1978 for measuring the relative efficiency of organizations such as hospitals and schools [15]. DEA (a nonparametric method) defines efficiency as the ratio of the weighted sum of outputs of an organization to its weighted sum of inputs. It is particularly useful in public sector organizations (eg, health facilities) that lack the profit maximization motive and employ multiple-input and multiple-output production processes [15].

DEA uses linear programming techniques to compute the efficiency scores. Facilities that are technically efficient have a score of 1 or 100%, whereas inefficient hospitals have efficiency scores of less than one (ie, less than 100%) [15]. Efficiency of an organization is measured relative to an observed best practice within a set. This indicates that the benchmark against which to compare the efficiency of a district hospital is determined by the group of hospitals in the study and not a value fixed by hospitals outside of the group [16].

Some of the positive characteristics of DEA are that it can handle multiple-input and multiple-output models, it does not require an assumption of a functional form relating inputs to outputs, the facilities are directly compared against a peer or combination of peers, and finally, input and output variables can have different measuring units [16]. The theoretical framework for this study is as shown in Figure 1.

Data Types to Be Explored

The required data for this study will relate to direct services provided to patients at district hospitals and the inputs employed by the health facility to generate services and outputs, which reflect the general scope of the facility's health care activities.

Improved health status is the ultimate output of hospitals or the health system at large. However, because of difficulties in accurately measuring improvements in health status, hospital output is measured by an array of intermediate health services that are surrogate markers of changes in health status. The selection of inputs and outputs for a DEA study requires careful thought as the distribution of efficiency is likely to be affected by the definition of outputs and the number of inputs and outputs included [17].

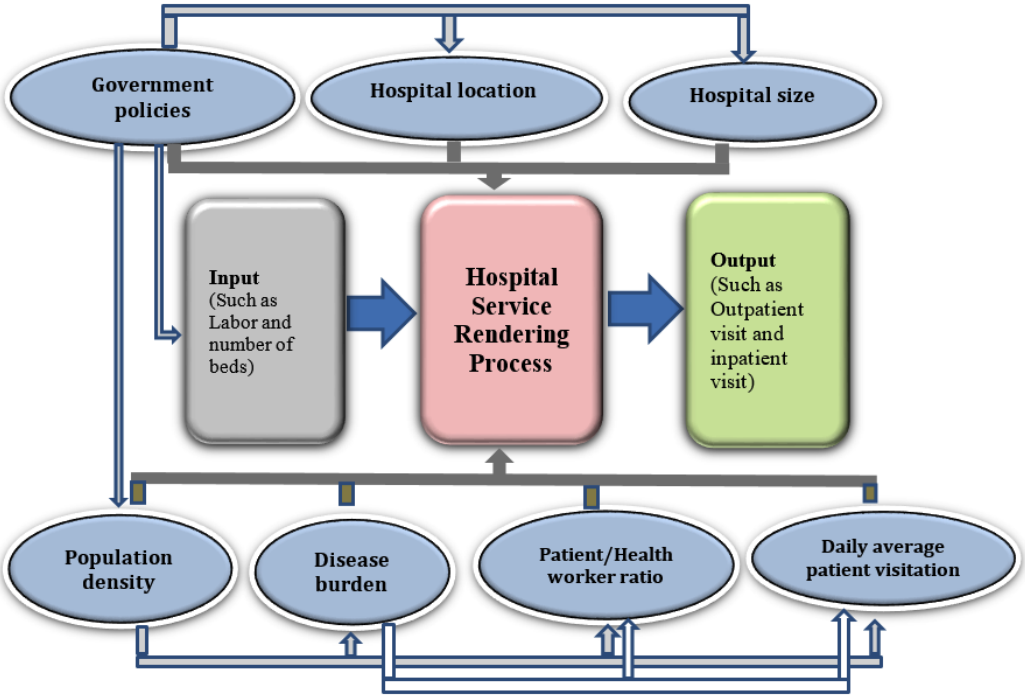
There are 2 major views toward defining and measuring the output of health care organizations [18]: first, *the process approach* asserts that the output of a health care organization comprises services provided by the different units such as the radiology, laboratory procedures, patient days, etc. Second, *the outcomes approach* regards the above processes only as intermediate steps leading to the desired change in a patient's health status, that is, output should be measured in terms of the end result or outcome, that is, improved health [18]. Though the generally agreed opinion is to measure health care output through improvement in service quantity and quality of life, it is easier to measure and define services rendered than changes in health status [16]. Health is multidimensional and is affected significantly by a host of other socioeconomic factors. Thus, output is measured as a range of intermediate outputs (health services) that purportedly improve health status. Therefore, the choice of data selection will be made on the basis of data availability and the input and output variables used in previous health care efficiency studies in Africa.

Inputs in hospital production are classified as labor, capital, and supplies. In most studies, the number of hospital beds is a proxy for capital. Thus, in this study, the input variables will focus on the number of health care professionals (doctors, nurses, and other personnel) and the actual number of hospital beds. More focus will be based on health professionals who are directly linked with health care provision. Information on the hospital expenditure within the periods under study will also be retrieved. On the other hand, hospital outputs for the DEA model will be identified from the district health information system (DHIS) database. This will include information such as admissions, outpatient visits, inpatient days, and number of admissions/discharges. Data type to be included will be determined by data availability, and it will be uniform for all facilities.

Table 1. List of district hospitals in KwaZulu-Natal, by municipality.

Municipality	District hospitals
Amajuba	Niemeyer Memorial Hospital
eThekwini	Osindisweni Hospital
	St Mary's Hospital
	Wentworth Hospital
Harry Gwala	Christ the King Hospital
	EG Usher Mem Hospital
	Rietvlei Hospital
	St Apollinaris Hospital
iLembe	Montebello Hospital
	Umphumulo Hospital
	Untunjambili Hospital
Ugu	GJ Crooke's Hospital
	Murchison Hospital
	St Andrew's Hospital
uMgungundlovu	Appelsbosch Hospital
	Northdale Hospital
Umkhanyakude	Bethesda Hospital
	Hlabisa Hospital
	Manguzi Hospital
	Mosvold Hospital
	Mseleni Hospital
Umzinyathi	C Johnson Mem Hospital
	Church of Scotland Hospital
	Dundee Hospital
	Greytown Hospital
Uthukela	Emmaus Hospital
	Estcourt Hospital
Uthungulu	C Booth Hospital
	Ekhombe Hospital
	Eshowe Hospital
	KwaMagwaza Hospital
	Mbongolwane Hospital
	Nkandla Hospital
Zululand	Benedictine Hospital
	Ceza Hosp
	Itshelejuba Hosp
	Nkonjeni Hosp
	Vryheid Hosp

Figure 1. A theoretical framework for hospital technical efficiency (designed by the researchers).



Data Collection Technique

The data collection technique for this study will be a consecutive sampling of all the district hospitals in the province as they occur in the national health database. On the basis of data availability, input and output data for a 3-year period between 2014 and 2017 will be retrieved. Nonfinancial input and output data will be obtained from the DHIS database and financial data (input data) will be obtained from the basic accounting system and policy on the personnel salary system, with permission from the KZN provincial DoH.

However, to obtain information on the likely factors that affect the performance of hospitals, some sets of information, which are not directly linked to delivery of health care services such as population density, disease burden, facility location, patient/health workers ratio, and daily average patient visitation, as contained in the database, will be retrieved.

Measures to Ensure a Scientifically Rigorous/Trustworthy Study

This will be done by making sure that selection for both input and output variables will be guided by previous health care efficiency studies and data availability within the database. The variables that will be chosen will be adequate to cover the general activities at the district health facilities. Data validity and reliability check will be done by randomly visiting some of the district hospitals for discrepancy check and data confirmation.

Proposed Data Analysis

The data obtained for the stated variables will be entered in Microsoft excel spreadsheets. As this study includes identifying the sources and magnitude of possible inefficiency in the health care system, it demands the use of DEA. TE analysis will be carried out using the DEA software package. The combination of the efficiency measurement system and open-source DEA software programs will be used in computing the DEA efficiency scores.

Each facility represents a decision-making unit (DMU), which is also sometimes referred to as data management unit in DEA. The DEA program requires that the data should be listed by observation, that is, each row for a DMU. The input and output variables will be listed in the column.

The frontier against which the TE of all hospitals is measured is defined by those hospitals in the group with a TE score of 100%. The hospitals producing on the efficient frontier define the best practice and thus could be regarded as role models. For each inefficient hospital, the DEA model has identified efficient hospitals that could be used as comparators [16]. The inefficient hospitals are expected to learn from their efficient peers by observing their production process [16].

Correlation and regression analysis will be computed to determine factors influencing efficiency using StataCorp statistical package.

Data Management and Storage Plan

The data obtained and entered in Microsoft excel spreadsheets will be stored in a back-up hard drive and in a protected cloud storage for safe and easy retrieval in the future. Data will be kept confidential during the study and in secure storage for 2 years after study completion. All personal data and details will be deleted, and no identifying information will be published.

Data Envelopment Analysis Model for Estimating Technical Efficiency

Charness et al proposed a constant return to scale for the DEA linear programming model, which stated that an increase in input should result in a proportionate increase in output [15]. The model is illustrated in Figure 2.

Figure 2. Data envelopment analysis model proposed by Charness et al.

$$Max\ h_0 = \sum_{r=1}^{s} u_r y_{rjo}$$

Subject to:

$$\sum_{i=1}^{m} v_i x_{ijo} = 1$$

$$\sum_{r=1}^{s} u_r y_{rjo} - \sum_{i=1}^{m} v_i x_{ijo} \leq 0, \quad j = 1, \ldots, n.$$

$$u_r, v_i \geq 0$$

Where:

Y_{rj}=amount of output r from hospital j

X_{ij}=amount of input i to hospital j

U_r=weight given to output r

V_i=weight given to input i

n=number of hospitals

s=number of outputs

m=number of inputs

Ethics Approval and Consent to Participate

Ethical approval was obtained from the Ethics Committees of the University of KwaZulu-Natal (HSS/0805/017D) and KwaZulu-Natal DoH (HRKM301/17). As this study did not directly involve human participants, instead of participants consent, permission to access the provincial health database was sought from the KZN health district manager.

Results

As of February 2019, the study is at the data collection, data input, and analysis stages. The study timeline in Table 2 illustrates that the results are expected to be available from the second quarter of 2019.

Table 2. Proposed study timeline where Q indicates quarter.

Year	2017			2018				2019			
Task	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Preparation of detailed research proposal and ethical approval	✓[a]	✓	✓								
Systematic and literature reviews			✓	✓	✓	✓	✓	✓			
Field work/data collection					✓	✓	✓	✓			
Data input/data analysis							✓	✓	✓		
Dissemination of study findings									✓	✓	✓

[a]✓: period of activity.

Discussion

It is vital to assess the TE of district and other hospitals to be able to utilize the available resources optimally and expedite the move toward achieving health and development goals. Findings from this study can add to the tools available to policy makers, health planners, and managers in making decisions about resource allocation in the health care system.

Dissemination of Study Findings

The aim of this study is to add to the tools available to policy makers, health planners, and managers in making decisions about the allocation of limited health care resources with the aim of maximizing the output from the health care system.

Findings of this research will be made available through publications in internationally peer reviewed journals and presentations at both local and international conferences. This will create information access for policy makers, health planners, and managers in making decisions about the allocation of health care resources with the aim of maximizing the output from the health care system. Moreover, the report of findings will be made available to KZN DoH.

Strengths and Limitations of the Study

Multiple hospital inputs and outputs will be used in computing efficiency as against the usual efficiency measurement through direct single input and output relationship. Due to time and cost constraints, the study could not cover all provinces in the country and as such, findings from this study may not be considered fully representative of the overall national situation. Limitations related to DEA approach can also have an effect on the study. These include the following: (1) Inability to compare the TE with district hospitals from other provinces in SA as DEA measures the efficiency relative to the best practices within hospitals in a sample group, (2) the result is sensitive to

measurement error, that is, an outlier because of an inflated hospital input or output can significantly reduce the efficiency of other hospitals.

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Authors' Contributions

The authors conceptualized the design of the study. TKB produced the first draft. IM revised the draft and contributed to the final draft. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DEA: Data Envelopment Analysis
DH: District hospitals
DHIS: District health information system
DMU: Decision-making unit
DoH: Department of Health
GDP: Gross domestic product
KZN: KwaZulu-Natal
MDG: Millennium Development Goal
OECD: Organization for Economic Co-operation and Development
SA: South Africa
TE: Technical efficiency

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Policy Proposal

Using Blockchain to Create Transaction Identity for Persons Experiencing Homelessness in America: Policy Proposal

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Abstract

More than 500,000 people experience homelessness in America each day. Local and federal solutions to the problem have had limited success because of the fragmentation of services and lack of valid and timely information. Billions of dollars spent to provide reliable, timely, and actionable information in health care have exposed the difficulty of establishing such a system using the prevalent information technology solutions. However, relying on successful examples of the use of blockchain to help refugee populations and poor farmers internationally, we have partnered to propose an innovative solution to this problem using the case of people experiencing homelessness in Austin, Texas. This paper aims to describe one of the first applications of blockchain technology for addressing homelessness in the United States by creating a digital identity for people experiencing homelessness and engaging emergency medical services and clinical providers. The authors argue that a lack of documentation to prove personal identity and the inability to access own records are major hurdles for empowering persons experiencing homelessness to be resilient and overcome the life challenges they face. Furthermore, it is argued that this lack of information causes misdiagnosis, duplication, and fragmentation in service delivery, which can be potentially addressed by blockchain technology. Further planning for creating a program on the ground with additional funding will demonstrate the results of using blockchain technology to establish digital identity for persons experiencing homelessness.

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KEYWORDS

affordable housing; Austin; blockchain; distributed ledger; emergency medical services; health information; homelessness; interoperability; transaction identity

Introduction

Over 500,000 people in America suffer from homelessness every night [1]; of these, 37% are children, 8% are veterans, and 48% are disabled. As cities across the United States face the ever-visible unsheltered population of homeless on its streets, the solutions are mostly about throwing more money and resources to address the symptoms rather than the underlying causes. Austin, Texas, is one of the fastest growing cities in the United States [2]. Although it faces similar issues of homelessness as any other city, it has the opportunity to test a disruptive technology, like blockchain, to develop a more effective and efficient solution to this chronic problem. This paper aims to describe the concept of how such technology innovation may work and to explain the solution proposed by a collaboration of city leaders, health and social service agencies, technology experts, and population health researchers.

The Homelessness Challenge

There is a general concern about homelessness in America owing to a growing shortage of affordable rental housing and a simultaneous increase in poverty. Income inequality and institutional discrimination exacerbate the situation. The National Coalition for the Homeless lists poverty, lack of

affordable housing, job loss, lack of health care, mental illness, substance abuse, and domestic violence as leading factors for homelessness. The report "Discrimination and Economic Profiling among the Homeless of Washington DC" 2014 showed the experiences of individuals living in homelessness and the discrimination they face. Reportedly, 42% are African American, 31% are non-Hispanic white people, and 24% are Latino people [3].

The situation of homelessness in Austin is quite grim (Table 1). On any single day, >2000 people experience homelessness in Austin. Annual figures range from 7000 counted homeless to >12,000 estimated people. Of those accounted for, only one-third sleep in a shelter every night, while a quarter sleep on the street sidewalk or a doorway, 16% sleep in a park, 13% sleep in a vehicle, and 9% sleep under bridges and in abandoned buildings. A census of persons experiencing homelessness showed that 80% are unemployed or have no earned income, 60% report a problem with drugs or alcohol in their lifetime, and 45% have a current mental health problem [4].

In addition, persons experiencing homelessness in Austin face many health challenges, which lead to overutilization of more expensive services like emergency departments and hospitalizations. This inefficiency adds to the overall cost of providing health care in the city and increases the burden on taxpayers. Of note, 60% of the homeless surveyed in Austin in 2015 had a drug or alcohol problem at some point in their lifetime, and 38% reported having been treated for it recently. Moreover, 48% suffered from mental health issues, and most of them had an ongoing issue that resulted in hospitalization. About 25% suffered from a chronic condition; one in five people reported a history of hepatitis C infection, and one in four people had a history of heat stroke or exhaustion [4].

Furthermore, the homeless are high users of health services, with >62% reported being in the emergency room in the past 6 months. Notably, 40% had used an ambulance to go to a hospital, and almost one-third had been hospitalized. Many used the hospital as their main point of access to get care. It is estimated that these high users of services cost the taxpayers about US $222,000 per person annually only for hospital care, emergency room visits, and emergency medical services transport [4].

Table 1. Profile of homeless in Austin and Travis County [3,4.

Demographics	Homeless in the county (n=7100 as per HMIS[a] census 2015), %	General population in the county (n=1,226,000 as per US Census Bureau 2016), %
Age (years)		
0-17	9	23
18-24	5	10
25-44	33	36
45-64	40	23
≥65	3	8
Race or ethnicity		
African American	42	8
Non-Hispanic white	31	50
Latino	24	34
Other	3	8

[a]HMIS: homeless management information systems.

The Underlying Causes of Homelessness

If providing affordable public housing and timely health care costs only a fraction of the cost incurred by public resources for a homeless person ($40,000 vs $222,000 per person annually) [4], the programmatic intervention to reduce homelessness seems straightforward. However, the existing social, health, and economic benefit systems in the public sector have limitations on how they may effectively help individuals who experience homelessness. Most policy solutions for homelessness focus on developing affordable housing units, employment assistance, or medical care programs, and few provide an integrated approach for delivering these services [5]. The public programs are usually organized around administrative departments in the city or county government rather than around the needs of individuals. If the solution is to be developed from a person-centered approach, then one of the key challenges of implementation is the system's inability to accurately collect, share, and verify information about the person experiencing homelessness. In the absence of verifiable information, the services are fragmented and an individual is unable to apply and benefit from any of the available services without going through multiple, duplicative, and bureaucratic requirements [5]. Such inefficiency is an unnecessary burden on the budgets of service providers and on the taxpayers who fund such public programs.

As far as information sharing is concerned, we may learn from our national experience in health information technology. Meaningful information sharing of patient data for delivery of health services has turned out to be a nontrivial task [6]. This is a problem of not only the poor and uninsured patients only,

but those with college education, employer-based health insurance, and above-median household incomes also suffer the consequences of the lack of information sharing in health care and social services. Billions of dollars spent on interoperability and "meaningful use" of health information technology systems have not been able to improve effective health care data sharing [7,8]. Whether it is owing to lack of incentives, structural problems of the system, or limited access to personal information by patients, it is unlikely that the required level of seamless information sharing in health will be achieved in the near future. The federal health information technology policy in the past 10 years clearly shows that while more resources can help in digitizing medical records, success in the effective use of the information cannot be accomplished with incomplete and marginal solutions [9,10]; it requires fixing the structural deficiencies of the health system. If the past is any indication of the future of health system transformation, it will be a long time before these structural issues around information sharing, patient empowerment, and value-based incentives will be resolved. Therefore, it can be argued that achieving information sharing through a person-centered approach to homelessness by using traditional information technology strategies is not likely to deliver results.

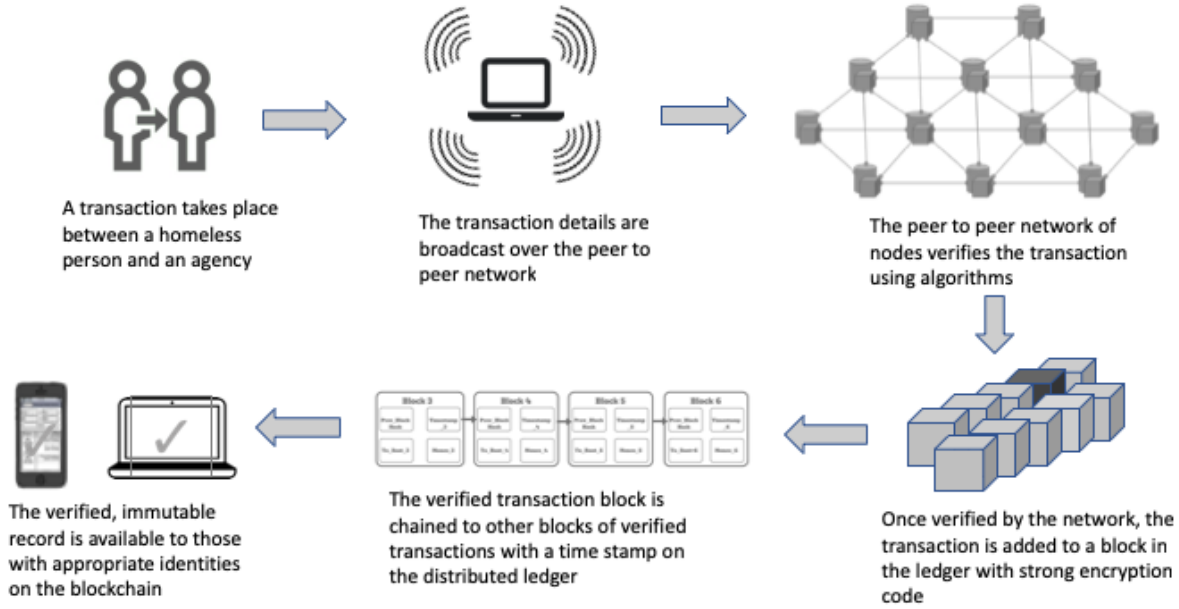
In contrast to the US experience in health information technology, there are some examples of innovative solutions that have been successfully applied to address the information-sharing problem in health and social systems outside the United States. International programs in resource-constrained economies may help us gain useful insights because they are generated in an environment of poverty and lack of resources [11,12]. The use of information and communication technologies to deliver health and other social services has been innovative and quite successful in many developing countries. The ubiquitous availability of internet connectivity and a new way of managing information and trust using blockchain technology seem to provide better hope for integrating information about an individual from different sources and solving the problems with information sharing described above [13-15].

Blockchain Technology's Promise

Blockchain technology has been touted to disrupt social and economic systems in society like the internet did [16,17]. Recent spikes in the value of bitcoin cryptocurrency is only a glimpse of how the market is gauging its potential in the future [18,19]. However, despite the hype about bitcoin and other cryptocurrencies, the often overlooked fact is that the real value of this experience lies in its underlying technology—blockchain based on distributed ledger technology (DLT). Blockchain can be described in many technical ways; yet, the simplest nontechnical definition is technology that uses DLT as a distributed data network, whereby all parties in a transaction get a secured and immutable copy of that transaction [20,21]. Figure 1 presents a simplified explanation of the DLT.

Blockchain technology is a new way of managing information, assets, and identity. It uses secure, immutable, append-only, timestamped content that is distributed over a network, which makes it almost impossible to hack [22]. The reason it is being hailed as such a disruptive technology is because it (1) takes out the intermediaries in transactions by creating a trust network among users; (2) promises a future that is truly based on distributed architecture without large central databases; (3) takes back control of an individual's data from other organizations and businesses and gives it to the individual; (4) makes all data highly liquid and portable, making geographical and political boundaries irrelevant; and (5) stores every transaction in multiple locations and minimizes hacking or fear of loss of data.

Figure 1. A simplified version of how Blockchain's distributed ledger works.



Application of Blockchain Internationally

Lack of "transaction identity" is a concept that provides a possible explanation of how people in poverty, refugees, or homeless people are prevented from breaking the cycle of being a beneficiary of available support services by public and private agencies. "Transaction identity" is defined as a collection of key aspects and relevant interactions that build a person's history and standing in society [23].

There are many examples of how the underlying technology of distributed ledgers in blockchain is being used internationally to solve the issues of transaction identity in poorer countries (Textbox 1; Figure 1). These projects rely on DLT developed for international humanitarian programs. The unique aspect of this implementation is that it deploys DLT or blockchain without any link to cryptocurrencies, like bitcoin, thereby avoiding some of the most notorious use cases of this technology. The DLT-based platform has been a mobile-friendly, affordable, and effective way to help refugees in the Middle East, poor farmers in South America, and HIV patients in Africa to establish their transaction identities, connect them to their records, and actively participate in global economic and social systems [24].

These global examples of the use of blockchain technology to address humanitarian use cases without exposing the vulnerable populations to cryptocurrency volatility and data-hacking risks may help in understanding the relevance of DLT to homelessness in America. One unique application of blockchain technology is to provide end-to-end visibility and proof of delivery of pharmaceutical products in developing countries in partnership with a global pharmaceutical company. For instance, an international supply chain problem is that of pilferage in pharmaceutical aid to places where tracking is difficult, and the aid is delivered to those who are not connected to global identity systems. When blockchain identities are generated for the commodities being shipped through intermediary suppliers in the global system and eventual beneficiaries, the immutability and distributed ledger entries prevent any fraud or reporting errors. Furthermore, the system tracks delivery to individuals whose identities are verifiable on the blockchain platform [25].

Another example is that of microenterprise solutions to pay farmers in Latin America by creating an economic identity of farmers on a blockchain platform [26]. Farmers usually do not have bank accounts and hence have to rely on middlemen to get paid for their harvests. This puts farmers at the mercy of intermediaries who maximize their profits by negotiating minimum payments for the produce from these farmers. By removing the need of intermediaries and helping create an economic identity of these farmers who can now sell their produce directly to buyers and get paid directly through mobile payments, the blockchain technology improves the economic condition of farmers and brings them into a global economy.

The exciting feature of these international examples is that all they need is a mobile phone or internet connectivity to help marginalized community members in resource-poor environments to establish and take control of their identity without the need of an intermediary. In addition, their identity allows them to link their disparate economic and social data through blockchain technology into an immutable and verifiable global information system. The examples above can be extrapolated to any other sector where information and data need to be shared, such as health, education, financial assistance, or microenterprise loans. It is therefore not a stretch of the imagination to consider the same DLT platform, which has been applied to refugees and farmers, to be used to connect social and health data of those experiencing homelessness in Austin.

Textbox 1. Example of how the underlying technology of distributed ledgers in blockchain is being used internationally to solve the issues of transaction identity in poorer countries.

Blockchain application is live in multiple countries in the following use cases:

1. Last mile transparency and traceability in supply chains for farmers to end a form of modern-day slavery
2. Education and health records access and ownership for refugees and migrant workers
3. Enabling gender equality for women farmers via access to better financial inclusion

Austin Blockchain Project for the Homeless

A practical way to understand the application of the DLT platform using blockchain, described above, is to take the case of a person experiencing homelessness on the streets of Austin. Persons experiencing homelessness in Austin today, unfortunately, have a very disjointed and often error-prone experience when it comes to health care [27].

This process is quite familiar to anyone who works in health care, or for that matter, in any other social service sector (Textbox 2). Persons experiencing homelessness in Austin receive services from multiple agencies that keep their beneficiaries' records in their organization's information silos [28]. Neither the person nor anyone outside each agency has the ability to access relevant information and coordinate the needs of the person experiencing homelessness in any systematic fashion.

Almost every major city is working on improving this system of data sharing for people experiencing homelessness, and many have created homeless management information systems (HMIS) [29]. Although it is an important part of the data ecosystem for persons experiencing homelessness, the HMIS may only allow better case management and tracking but may not ensure coordination of services and involvement of the beneficiaries of services. If each encounter and transaction of a person experiencing homelessness is recorded, validated, shared, and available in one place, we can solve the problem of information sharing, coordination, and validation of identity

(Textbox 3). The development of a blockchain platform as a system to capture these transactions may be achieved in a fraction of the time it will take to build an interoperable information system with interfaces among disparate systems. Furthermore, the blockchain system will be a truly person-centered, distributed, and authenticated information system that is, otherwise, extremely difficult and costly to develop under traditional information system designs.

Textbox 2. A basic flow of the reality that people experiencing homelessness face every day.

1. A person experiencing homelessness in Austin downtown has a medical or mental health event that requires care.
2. 911 is called, and Austin emergency medical services (EMS) picks up the person.
3. Not having any record for this person's prior health conditions, EMS takes the person to the local emergency department.
4. There is no historical information about the person in the hospital's record as well because there is no driver's license or government-issued identity available.
5. As the person experiencing homelessness is cared for in the emergency department, the lack of prior medical history puts the patient at risk for receiving wrong medications, misdiagnosis, and duplicative testing/imaging.
6. When discharged after treatment, the person cannot understand or recall all the transactions and treatments that occurred during the hospital visit; this information is also not shared with anyone outside the emergency department.
7. A few days or weeks later, Austin EMS is again asked to pick up the same person from the street to a different hospital in the city that is not linked to the first hospital.
8. The same process is repeated, with even more chances of duplication, error, and overtreatment; yet, the patient still possesses no details of this encounter and no one outside the second hospital emergency department has that information for future use.

Textbox 3. Steps required to change this system using traditional technology solutions.

1. Changing the processes to capture and store data in a standardized way, so it can make sense to those outside the immediate care provider.
2. Developing linkages, usually technical pathways, to send and receive data from different data systems.
3. Understanding and mapping how data are stored in different organizations and what their terms mean (semantic interoperability).
4. Agreeing on protocols for sharing information at a technical level.
5. Creating a data governance structure, so data are used for the purposes they were shared by individuals. In many cases, a person's consent is required to share information, which needs a separate consent management strategy.
6. At every step, there is a workflow change that is to be managed, and people who are affected by it need to be convinced of the need for change. Sometimes, further training is required to implement these changes.
7. The system of data sharing has to be tested and constantly validated, as new information may overwrite previously stored data, causing new discrepancies across different data systems.

Austin's Innovation Using Blockchain Technology

The city of Austin and the Dell Medical School's Population Health Department have partnered to test a blockchain data-sharing approach in Austin to coordinate services for those experiencing homelessness. As an academic institution, the Dell Medical School has a unique mission to improve the health of the community by creating a vital and inclusive ecosystem [30]. As a 21st-century medical school in a tier 1 research university, the Dell Medical School is geared to provide disruptive solutions to persistent health problems, and homelessness is one of them.

The idea is to begin by building trust relationships with a select number of people living on the streets of Austin. The program will use a DLT-based platform to create profiles for persons experiencing homelessness, using biometric features. This allows individuals to have direct access to all transactions that are recorded on the platform through any interaction in the system while also allowing each agency to access that record with permission of individuals (Textbox 4). The solution does not rely or restrict itself to any specific platform because all the information will be on a blockchain ledger and available with the consent of an individual. Simultaneously, the service providers can create their profile or accounts on the DLT platform as well. This will include a clinical site, emergency medical services, and a local homeless coalition organization. As a person experiencing homelessness touches any of these agencies, they exchange the encounter on a ledger that is shared between their accounts (the service provider and the client).

There will be a secured, immutable identity created for every individual in the program. This identity will allow persons to access their health data and details of the health encounter without violating any Health Insurance Portability and Accountability Act of 1996 rules. Next time the same person comes back for services or goes to another agency, the same process is repeated. As the number of these encounters increase, a copy of the transaction or encounter is recorded on the ledger that is on the person's account and available to that person at any place or any time. For example, when this person goes to the emergency department of a new hospital, the providers can see the history of encounters with other health care providers

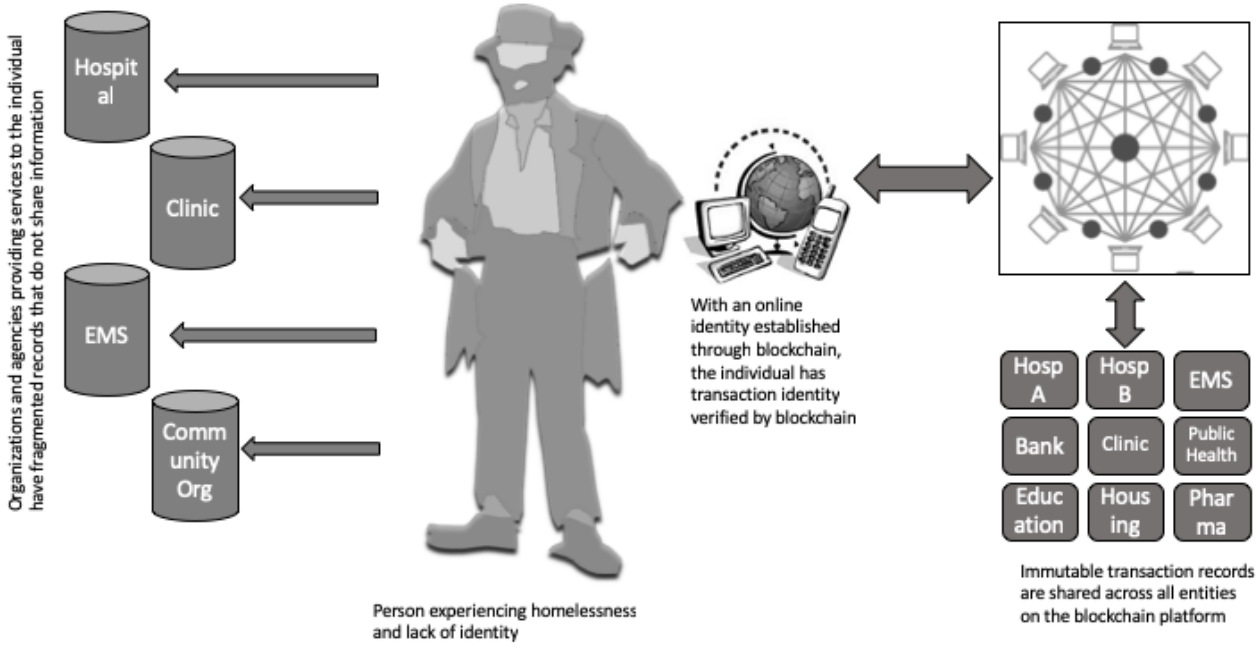
in the past as soon as the person gives them access to share the ledger (Figure 2).

The solution solves multiple existing problems about the lack of coordination and data sharing, difficulty in implementing "no-wrong-door" policies, duplication, rising programmatic costs, absence of person-centered care focus, and challenges with the portability of records in a highly mobile population. The flexibility and universality of the blockchain platform allow individuals to use any blockchain technology to claim their identity and transactions in the future.

Textbox 4. Steps for the blockchain program.

1. Persons experiencing homelessness, with no identity or incomplete health and financial records, are connected to a blockchain app through their phone.
2. Health and social service providers connect to the blockchain app to create their identities and become part of the blockchain network.
3. Persons experiencing homelessness, with their identity on the platform, are connected to the service providers on blockchain and can access those data through a mobile phone or computer.
4. Transactions at hospitals and clinics and with emergency medical services and other city agencies are recorded on the blockchain and then available to the person through the blockchain app.

Figure 2. Austin blockchain project for homelessness. EMS: emergency medical services; Pharma: pharmacy; Hosp: hospital.



Conclusion

This paper describes a few examples of how blockchain's DLT is being applied to create transaction identity for farmers, refugees, and microenterprise owners. The technology allows these people to become part of a distributed information and economic system and establish their identities through a secure, immutable, portable, and mobile system. In addition, it integrates all transaction data for an individual in this system to be available when needed. The replication of this technology platform for connecting social and health service providers of people experiencing homelessness is a novel and disruptive technology application. The Dell Medical School and the city of Austin are partnering to test this blockchain technology to connect service providers, including hospitals and clinics, and emergency medical services of the city. The proposal is for individuals experiencing homelessness to create an identity on a blockchain platform and to be able to record all their transactions with health providers and emergency medical services through the same ledger. The health providers and any social service agency serving the people experiencing homelessness will also need to become part of the transaction network.

Using blockchain technology solves many unsolvable problems in health and homeless care; it is a low-cost solution and does not require millions of dollars spent on this problem. In addition, it does not need building of expensive infrastructure to maintain databases defined by organizations and public departments in silos. Instead, it allows individuals to maintain all information related to their financial, health, or social history on the blockchain; it also connects providers without the expenditure of huge amounts of money to secure records. The Austin experiment of using blockchain technology for establishing transaction identity of persons experiencing homelessness has

the potential to open avenues for solving this issue across the country and even globally.

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Conflicts of Interest

AK has no conflicts of interest to declare. AG is the CEO of BanQu and has a financial interest in the company.

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Abbreviations

DLT: distributed ledger technology
EMS: emergency medical services
HMIS: homeless management information systems

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Protocol

Adherence Connection for Counseling, Education, and Support: Research Protocol for a Proof-of-Concept Study

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Abstract

Background: The highest rates of new HIV infections are observed in African Americans and Hispanics/Latinos (ethnic minority) adolescents and young adults (youth). HIV-infected ethnic minority youth are less likely to initiate and maintain adherence to antiretroviral treatment (ART) and medical care, as compared with their adult counterparts.

Objective: The objective of this research protocol was to describe our proposed methods for testing a peer-led mobile health cognitive behavioral intervention, delivered via remote videoconferencing and smartphones with HIV-infected ethnic minority youth, Adherence Connection for Counseling, Education, and Support (ACCESS). Our secondary aim was to obtain initial estimates of the biobehavioral impact of ACCESS on HIV virologic outcomes and self-reported ART adherence, beliefs and knowledge about ART treatment, adherence self-efficacy, and health care utilization (retention in care).

Methods: An exploratory, sequential mixed-methods study design will be used with conceptual determinants of adherence behavior informed by the information-motivation-behavioral skills model. HIV-infected ethnic minority youth aged 16 to 29 years with a detectable HIV serum viral load of more than 200 copies/ml (N=25) will be recruited. Qualitative pretesting will be conducted, including semistructured, in-depth, individual interviews with a convenience sample meeting the study inclusion criteria. Preliminary analysis of qualitative data will be used to inform and tailor the ACCESS intervention. Testing and implementation will include a one-group pre-posttest pilot, delivered by a trained *successful* peer health coach who lives with HIV and is well-engaged in HIV care and taking ART. A total of 5 peer-led remote videoconferencing sessions will be delivered using study-funded smartphones and targeting adherence information (HIV knowledge), motivation (beliefs and perceptions), and behavioral skills (self-efficacy). Participant satisfaction will be assessed with poststudy focus groups and quantitative survey methodology. Bivariate analyses will be computed to compare pre- and postintervention changes in HIV biomarkers, self-reported ART adherence, beliefs and knowledge about ART, adherence self-efficacy, and retention in care.

Results: As of December 2018, we are in the data analysis phase of this pilot and anticipate completion with dissemination of final study findings by spring/summer 2019. The major outcomes will include intervention feasibility, acceptability, and preliminary evidence of impact on serum HIV RNA quantitative viral load (primary adherence outcome variable). Self-reported ART adherence and retention in care will be assessed as secondary outcomes. Findings from the qualitative pretesting will contribute to an improved understanding of adherence behavior.

Conclusions: Should the ACCESS intervention prove feasible and acceptable, this research protocol will contribute to a shift in existent HIV research paradigms by offering a blueprint for technology-enabled peer-led interventions and models.

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KEYWORDS

HIV; smartphone; cell phone; technology; treatment adherence and compliance; methods

Introduction

The estimated prevalence of HIV-infection in the United States was 1.1 million among persons aged 13 years and older at year-end in 2015 [1]. More recently, in 2016, new HIV diagnoses in the Unites States totaled 39,782 with 41% represented by adolescents and young adults (youth) aged 15 to 29 years [2]. African Americans and Hispanics/Latinos (ethnic minority) youth are disproportionately affected by HIV infection with epidemiologic data highlighting sexual contact as the most common transmission category [3]. Initiation of antiretroviral treatment (ART) is recommended for all HIV-infected individuals [4]. Maintenance of optimal adherence to ART, defined as more than 95% for unboosted protease inhibitor–containing regimens and 80% adherence for boosted protease inhibitor regimens [5,6] is the single most important criterion to prevent ART and virologic failure [7,8], HIV-related morbidity and mortality [4,9], and behavioral transmission to seronegative individuals [4,10]. Among HIV-infected ethnic minority youth, suboptimal adherence is highly prevalent [11-17] with resulting HIV RNA viral suppression estimates of 30.5% (577/1891) [18] to less than 6.0% (4449/78,949) [19], thereby significantly increasing risk of sexual transmission [10,20-22]. HIV-infected youth are also less likely to initiate ART and be retained in care [19] with estimates of 56% (17,874/32,149) maintained in continuous HIV care during 2015 [23].

Both psychosocial and structural factors have been implicated as barriers to ART adherence with structural factors including travel to health care settings [24,25] and stigma [24,26]. Among psychosocial barriers to adherence are beliefs of ART futility [27] and concerns about use [27,28], ART knowledge and understanding [29], trauma [30-32], substance use and psychological distress [5], and decreased self-efficacy [33,34]. Facilitators of ART adherence include information and communication technologies [35], HIV/ART education [4,29,36], beliefs of medical necessity [25,28] and positive outcome expectancy of ART [37], and higher levels of self-efficacy [34]. Moreover, self-efficacy has been shown to mediate the relationship between ART adherence and stigma among HIV-infected adults [38].

To date, evidence from systematic and integrative reviews demonstrate a paucity of effective targeted adherence interventions for HIV-infected ethnic minority youth [15,39-45]. Cognitive behavioral interventions (CBIs) have shown promise to improve adherence in HIV-infected adults [46-48] and youth [49], and are designed to reduce cognitive biases (negative thoughts and beliefs) and build effective adherence self-management skills [50]. CBIs may be delivered using motivational interviewing (MI) techniques including expressing empathy and forming collaborative partnerships with participants [46]. Mobile media platforms represent a viable option to deliver behavioral interventions targeting ART adherence [36,51-53] and offer the potential to mitigate structural barriers, including travel to health care settings [54]. When used for delivery of behavioral interventions, these platforms allow for improved confidentiality, thereby decreasing fears related to anticipated HIV-related stigma [26] or inadvertent disclosure of HIV seropositive status during an HIV clinical encounter visit.

Improved health outcomes for HIV-infected ethnic minority youth are dependent on the design and implementation of interventions that entail community mobilization [55], such as peer support and counseling [24,56,57]. In addition to sharing experiential information, there is evidence to demonstrate that peers provide emotional support by conveying understanding and acceptance, thereby allowing for discussion of negative emotions [58]. Research findings show that peers competently deliver HIV behavioral interventions targeting ART adherence [57] and retention in care [59] and contribute to improved adherence [57] and retention outcomes [60].

In our pilot research including a cross-sectional descriptive survey design, beliefs of positive outcome expectancy were associated with optimal self-reported adherence to ART [37], and in a related substudy, ownership of cellular phones with internet access was commonly reported among HIV-infected ethnic minority youth [37,61]. In fact, the cell phone was the preferred route to communicate with a health care provider [37,61], a finding that is congruent with the observed increased patterns of smartphone ownership among ethnic minority youth in the United States [62,63]. Evidence from one small pilot demonstrated that remote videoconferencing is feasible and acceptable for adherence counseling, when delivered to HIV-infected ethnic minority youth on site, within the clinical setting. However, it has not yet been tested for preliminary efficacy in the community setting [64]. Given the high rates of suboptimal adherence to ART and poor retention in care among HIV-infected ethnic minority youth, there is a pressing need to develop and test novel interventions**.** Therefore, in this research protocol, we present the methods for an innovative proof-of-concept study, Adherence Connection for Counseling, Education, and Support (ACCESS). We expect that implementing this peer-led mobile health (mHealth) CBI delivered via remote videoconferencing using smartphones will be feasible and acceptable with the potential to influence ART adherence in HIV-infected ethnic minority youth.

Methods

Objectives

The primary aim of the ACCESS proof-of-concept study is to characterize the feasibility and acceptability of a peer-led

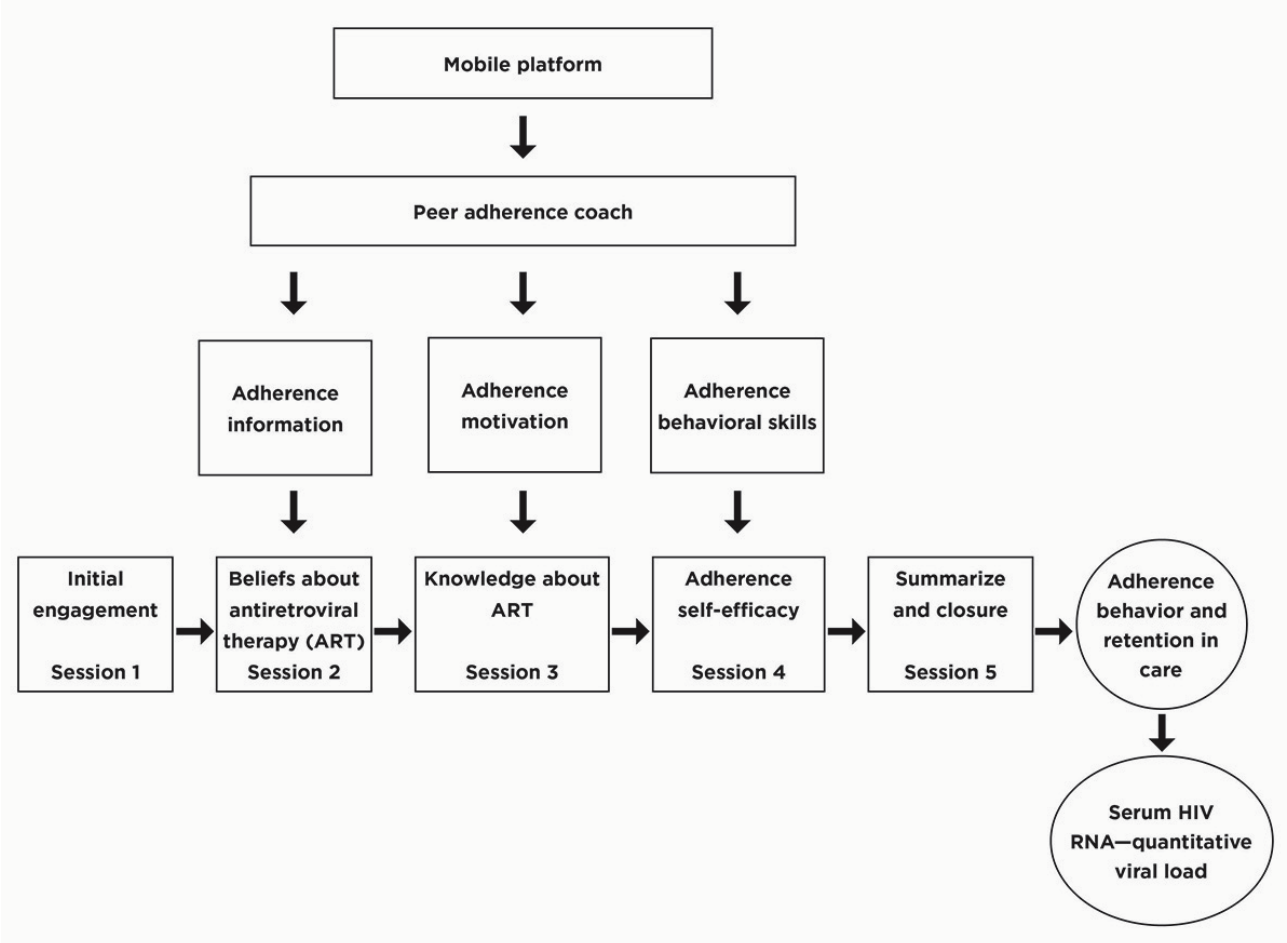
mHealth CBI delivered via remote videoconferencing using smartphones. Our secondary aim is to obtain initial estimates of the biobehavioral impact of ACCESS on HIV virologic outcomes and self-reported ART adherence, beliefs and knowledge about ART treatment, adherence self-efficacy, and health care utilization (retention in care). The major outcomes of this pilot study will include intervention feasibility, acceptability, and preliminary evidence of impact with respect to biobehavioral outcomes, namely, serum HIV RNA quantitative viral load (primary adherence outcome variable). Self-reported ART adherence and retention in care will be assessed as secondary outcomes.

Theoretical Foundation

The information-motivation-behavioral (IMB) skills model of antiretroviral adherence [65] will be used to identify the conceptual determinants of adherence behavior, namely, adherence information, motivation, and behavioral skills. These determinants are operationalized as knowledge and beliefs about ART and adherence self-efficacy. The primary adherence outcome variable is serum HIV RNA quantitative viral load. Recently, conceptualization of treatment adherence has been broadened to include linkage and retention in care [4] and, therefore, the IMB model was modified to include retention in care as an outcome variable (Figure 1).

During remote videoconferencing sessions, peer-health coaches will use cognitive behavioral strategies delivered using MI techniques to enhance problem solving and target beliefs and knowledge about ART and adherence self-efficacy for improved adherence behavior (Figure 1). The IMB model is supported for use with technology-enabled adherence interventions [66,67] and CBIs [68,69] delivered using MI techniques [70]. An assumption of this model is that motivation to adhere has a social component which is influenced by perceived social support received from important others including health care workers [65]. This supports the inclusion of peers [57,71]. Given the high prevalence of past traumatic [32] and stigmatizing [72] experiences among HIV-infected individuals, these constructs will be included in the approach as potential mediators or moderators of study outcomes.

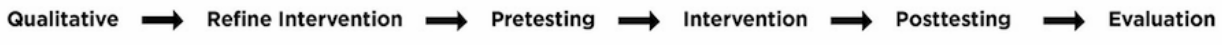
Figure 1. The potential impact of the Adherence Connection for Counseling, Education, and Support intervention on adherence behavior.



Study Design

An exploratory, sequential mixed-methods study design will be used (Figure 2) in a sample of HIV-infected ethnic minority youth (aged 16 to 29 years). Qualitative pretesting will be conducted with a convenience sample of HIV-infected ethnic minority youth meeting the study inclusion criteria. A preliminary analysis of qualitative data will be used to inform and tailor the ACCESS intervention. Testing and implementation of the ACCESS intervention will include a one group pre-posttest pilot with delivery by an HIV-infected trained peer-health coach. The sample size for the pilot will be 25 HIV-infected ethnic minority youth.

Figure 2. Schematic design of the Adherence Connection for Counseling, Education, and Support proof-of-concept study.



Participants and Recruitment

After receiving approval from designated institutional review boards, recruitment of HIV-infected ethnic minority youth will be initiated from 3 urban HIV centers in New York City, 2 public hospital centers, and 1 HIV nonprofit community health plan providing health care coverage to chronically ill Medicaid recipients. Recruitment efforts, effective with our previous work [37], will include posting of flyers and regularly scheduled visits to the outpatient clinical settings during times of high patient volume.

Inclusion criteria will include the following: HIV seropositive status (behaviorally and perinatally infected youth), aged 16 to 29 years, English speaking, current ART with a prescribed regimen, detectable quantitative HIV serum viral load more than 200 copies/ml, and no neurocognitive deficits which would impede participation in videoconferencing sessions or completion of study measures. Screening with the Folstein Mini-Mental State Exam (MMSE) will be performed to assess for the presence of neurocognitive deficits [73]. Participants with a score of 24 or greater will be eligible for study participation and this cutoff score is on the basis of our prior experience [37] and findings from other published evidence with HIV-infected ethnic minority youth [74].

Qualitative Pretesting

A convenience sample will be recruited. We will obtain informed consent and assent for 16- and 17-year-old participants before beginning qualitative data collection. Participants will meet study inclusion criteria serving as informants to the ACCESS intervention. Yet, these participants will also be eligible to participate in the ACCESS intervention. The estimated sample size is 12 to 15 participants; however, new participants will be interviewed until data saturation is reached [75]. The IMB skills model will be applied for the development of the interview guide. In-depth, individual, semistructured interviews including open-ended questions with probes will be conducted to gather qualitative data on the perceptions and beliefs of HIV-infected ethnic minority youth regarding the proposed study design, barriers and facilitators of ART adherence, and potential impact of the ACCESS intervention on ART adherence and retention in care. Interviews will be conducted in a private setting at each of the clinical agencies. Reflective notes on the events and processes observed during the interviews will be maintained, in addition to recording emerging codes, themes, and or any concerns [76]. All interviews with study participants will be digitally recorded, transcribed verbatim, and analyzed using ATLAS.ti (v8.2 Microsoft Windows), a software program for organizing, coding, and analyzing qualitative data. Directed content analysis will be conducted [77] to generate categories and broad themes, informing the ACCESS intervention. Methodological rigor will be ensured by performing member checks, establishing an audit trail, collecting thick descriptive data, and triangulating data sources [78].

Study Procedures

Upon obtainment of informed consent, and assent for 16- and 17-year-old participants, data collection will begin with administration of the Folstein MMSE [73] by the principal investigator (PI) or research assistant (RA) to screen for presence of neurocognitive deficits. Baseline virologic adherence estimates will be collected preintervention and postintervention including weeks 8, 16, and 24. The rationale for selection of these time points is because viral suppression (indicated by HIV RNA less than 48 copies/ml) could be expected to occur in 8 to 24 weeks among participants adhering to ART and without evidence of phenotypic or genotypic resistance to ART [4]. Self-reported adherence, beliefs and knowledge about ART, adherence self-efficacy, and retention in care will be measured at pre- (baseline) and postintervention. Survey instruments (described in the Measures section) will be completed by the participant on-site in the presence of the PI or trained RA (Table 1).

Table 1. Plan for data collection of primary study variables.

Data source	Baseline, preintervention	Post ACCESS[a] intervention	8 weeks postintervention	16 weeks postintervention	24 weeks postintervention
Self-reported adherence	X[b]	X	—[c]	—	—
Serum HIV RNA viral load	X	X	X	X	X
Beliefs	X	X	—	—	—
Knowledge	X	X	—	—	—
Self-efficacy	X	X	—	—	—
Health care utilization (retention in care)	X	—	—	—	X

[a]ACCESS: Adherence Connection for Counseling, Education, and Support.

[b]X: represents a data collection time point.

[c]—: represents a time point at which data was not collected.

Allocation of Smartphones

Participants will be provided with a study-funded smartphone to allow for uniform and uninterrupted access to the intervention. To minimize the total number of smartphones needed, the smartphones will be returned after completion of the intervention phase, reset to factory settings by university information technology (IT) staff, and reassigned to new enrollees. Return and reset of research-funded smartphones provided for HIV-infected minority youth has been demonstrated within the study procedures for a technology-supported behavioral intervention [79].

Mobile Platform

In conjunction with the university IT administrative staff, WebEx Communications Inc will be used to provide a secure and Health Insurance Portability and Accountability Act–compliant media platform for implementation of the remote videoconferencing sessions. WebEx mobile apps will be downloaded by IT staff to study-funded smartphones allocated to participants before initiation of videoconferencing sessions. Each study participant will be trained on the use of WebEx mobile apps by the PI upon receipt of their study phone. This education will also detail the necessity for receiving remote videoconferencing sessions in a private location using their password-protected study-funded smartphone. To deliver the intervention, the trained peer health coach will access WebEx remote videoconferencing sessions from a university-designated computer located in a private office within the academic setting. Members of the study team will be present and available to support the adherence coach during these scheduled sessions.

Training of Peer Health Coaches

A total of 2 *successful* peer health coaches who live with HIV and are well-engaged in HIV care and taking ART will be hired to deliver the ACCESS intervention, after completing a comprehensive training program. The training program will include a minimum of 40 hours of instructions [80] delivered during a 4-month period by content experts in their respective fields (ie, HIV, MI, and IT). The approach for education of peer health coaches will be guided by criteria and select resources from an existing national peer training program for HIV-infected individuals, *Train the Trainer* [81], and the HIV peer development toolkit [82].

The training format will be divided into 3 phases including instructive lectures and discussions, written practice for reinforcement of didactic material, and live role-playing of the intervention protocol using WebEx videoconferencing. Instructive lectures will be directed to impart knowledge on HIV disease, treatment adherence, HIV stigma, trauma, and ethical/human subjects' considerations, role of the peer and professional boundaries, MI techniques [83], and stages of change [84]. To reinforce MI techniques and other training content, written practice worksheets will be developed and included as homework assignments. Members of the research team will role-play using deidentified data from completed qualitative interviews, allowing peer health coaches to gain familiarity with adherence struggles frequently encountered by the enrolled study population. Ongoing feedback and support from the PI and study team will be offered to peer health coaches at all phases of training.

Adherence Connection for Counseling, Education, and Support Adherence Intervention

A cognitive behavioral approach delivered using MI techniques will target beliefs and knowledge related to ART, and adherence self-efficacy during the peer-led mobile videoconferencing sessions (ACCESS sessions 1 to 5). Problem-focused coping strategies will be used [46] to help participants manage common adherence challenges. Peer health coaches will also assist participants to define struggles related to medication adherence and brainstorm for possible solutions [46]. Consistent with the spirit of MI, peer health coaches will strive for a partnership with participants; motivation-to-change adherence behavior will be elicited by the participant and not because of direct persuasion [85]. Peer health coaches will recognize that readiness to change is a fluctuating process and that ambivalence is common [85]. Acceptance, affirmation, reflective listening, and freedom of choice will be among the MI tenets used for communication between the peer health coach and participant [85]. During each of the ACCESS sessions, peer health coaches will be attentive to change talk [85,86], and ask permission before delivering any unsolicited HIV health information [86] and or sharing experiences. The open questions, affirmation, reflective listening, and summary reflections skills-based model will be practiced by peer health coaches [83]. A formal, comprehensive written intervention protocol will be used.

At a mutually agreed time, a member of the study team will schedule the participant for each of the 5 weekly 60-min peer-led ACCESS sessions. After initial assignment to 1 of 2 peer health coaches, the participant will *meet* with this peer health coach for all 5 sessions. The rationale for the selection of 5 sessions is on the basis of the best available evidence from technology-delivered interventions using videos [87,88] and videoconferencing with ethnic minority HIV-infected adults [89,90] and psychoeducational interventions using applied technology in youth with type 1 diabetes [91,92]. In the event of a participant canceling or missing a scheduled session, appointments will be rescheduled within the week by the PI or RA. Active supervision of peer health coaches will include regular meetings with the PI and study team and review of audio-video intervention sessions to assess intervention fidelity.

Overview of Adherence Connection for Counseling, Education, and Support Sessions 1 to 5

ACCESS Session 1 will serve to engage the participant in the study, establish credibility of the study team, and foster peer-participant partnership [85]. Open-ended questions, affirmation, reflection, and restatement [83] will be used by the peer health coach to gain understanding of the participant's HIV history and experiences with ART, while sharing their own experiences living with HIV. This session will also allow for initial discussion of the participant's beliefs and perceptions influencing adherence motivation and allow the participant to establish their agenda and goals for study participation [86].

ACCESS Session 2 will provide continued support for participant engagement. Peer health coaches will continue to

explore adherence motivation by eliciting self-perceived barriers and facilitators of adherence [93] and discussion of beliefs surrounding ART [4,25,37]. Participant beliefs conducive to optimal ART adherence (ie, association between nonadherence and illness) will be encouraged and negative beliefs related to ART explored. Support systems will be examined, recognizing that HIV stigma, either perceived or real, leads to social isolation, thereby influencing health behavior [26,94].

ACCESS Sessions 3 will emphasize adherence information and knowledge about ART, as relevant ART adherence information is a prerequisite of consistent use of ART medications [65]. HIV education to support treatment adherence will be offered by viewing a video titled *Understanding HIV: Basics* [95]. Peer health coaches will provide a neutral context for information exchange [86] related to eliciting participant's understanding of video content presented including HIV health information, treatment adherence, ART side effects, and HIV biomarkers [4,96].

ACCESS Session 4 will offer a forum for dialogue of adherence behavioral skills or objective and perceived abilities (ie, self-efficacy) related to ART adherence . Recognizing that increased self-efficacy is associated with ART adherence [34], peer health coaches will facilitate the participant's identification of strategies to promote and reinforce adherence self-efficacy. During this session, peer health coaches will elicit from the participant behaviors leading to periods of optimal treatment adherence, while sharing their experiences in successfully maintaining adherence. Additionally, stressors, situations, and or events leading to ART missed doses among participants will be explored. Peer health coaches will facilitate active problem solving for the development of more effective adherence self-management skills tailored to the lifestyle needs of the individual participant [4]. The session will conclude with participant goal setting to support HIV health and ART adherence, cognizant of adherence barriers and facilitators discussed in prior sessions.

ACCESS Session 5 will allow for discussion of strategies to facilitate retention in care and provide time for intervention closure including review, reflection, and summary [83] of completed content from past sessions. The participant's history in adhering to HIV medical appointments (retention in care) will be explored by peer health coaches. Peer health coaches will elicit barriers, while sharing approaches for successfully maintaining HIV medical appointments, in response to challenges identified by participants. Goal setting initiated during ACCESS Session 4 will also be revisited with affirmation of progress reported. If the participant was unable to maintain their designated goal, the peer health coach will acknowledge the struggle and elicit contributing factors. This session will close with the peer health coach thanking the participant for their time, expressing respect for their autonomy and choices related to adherence behavior. An opportunity to provide additional feedback and or ask questions will be provided.

Participants will be compensated with gift cards for their time as follows: US $15 for each completed ACCESS videoconferencing session (US $75 for 5 sessions), and US $25 for each pre- and postintervention data collection visit (US $50 total). Participants completing qualitative interviews will be compensated for their time and travel with an additional US $25 gift card. Therefore, the total compensation for completing all 5 intervention sessions and pre- and postintervention follow-up will be US $125. If participating in the qualitative component, total compensation will be US $150.

Measures

Collection of baseline demographic and clinical data will be conducted using a PI-created instrument that includes the following: age, gender, level of education, mode of transmission, staging of HIV disease–AIDS diagnosis, length of time of current ART regimen, diagnosis of depression, and substance use. Depression and substance use are systematically assessed by health care professionals at recruitment sites and documented in the medical record. Medical record data extraction to assess depression and substance use among HIV-infected ethnic minority youth is feasible on the basis of our prior work [37].

Beliefs about ART will be measured with the Beliefs About Medication Scale. This 59-item health beliefs questionnaire uses a 7-point Likert scale to perceived threat, positive and negative outcome expectancy, and intent regarding oral medication adherence. Reliability (Cronbach alpha=.79-.87; test-retest reliability, r=.71-.77) and validity have been demonstrated in youth with chronic illness (n=133) [97].

Knowledge about ART will be measured with the HIV Treatment Knowledge Scale. This 21-item instrument uses true and false questions to assess knowledge of adherence, side effects, and antiretroviral resistance. Test-retest reliability (r=.83) and internal consistency (CFI>0.90) are satisfactory when tested with HIV-infected adults [98].

Adherence self-efficacy or the sense of being able to adhere to prescribed HIV medications [99] will be measured with the Adherence Self-Efficacy Scale. This 12-item survey measure uses a 10-point scale (0=cannot do it all; 10=completely certain can do it) to assess confidence in ability to carry out important treatment-related behaviors [100]. Psychometric evaluation demonstrates robust internal consistency (r=.90) and test-retest reliability when used with HIV-infected adults (r>.70).

Adherence Outcomes

Self-Report and HIV Biomarkers

A 3-day self-report of ART adherence will be measured to describe subjective adherence behavior. To minimize the potential for bias while collecting adherence estimates, questions will be worded in a nonjudgmental style assuming missed doses. For example, the PI or RA would ask, "before beginning the questionnaires, could you please tell me how many doses of medicine you missed yesterday?" Using this information, we will compute an average missed dose calculation: number of doses missed per medication multiplied by dosing schedule during the past 3 days divided by total number of prescribed doses over the past 3 days. This percentage will be subtracted from 100% to obtain the 3-day self-reported adherence estimate [101]. This method has demonstrated feasibility, acceptability, and validity in our pilot work with HIV-infected ethnic minority youth [37] and in other studies [102].

Serum HIV RNA quantitative viral load is the primary adherence outcome variable and will be measured to eliminate the potential for social desirability bias associated with subjective adherence reports. HIV viral load is a robust predictor of ART adherence in both HIV-infected ethnic minority youth [101,103,104] and adults [102,105]. Medical record data extraction will be performed to access HIV viral load results.

Health Care Utilization (Retention in Care)

A gold standard for measuring retention in care has not been established, and therefore, selection of a retention measure may be tailored to context [106]. For the purposes of this proof-of-concept study, retention in care will be calculated as a proportion of kept to scheduled visits (range 0%-100%); the denominator will exclude canceled visits [106,107]. Retention data for HIV health care visits will be extracted from the medical record and 6-month pre- and postintervention retention estimates compared.

Feasibility and Acceptability

Participant Satisfaction

The Client Satisfaction Questionnaire [108] will be administered at the conclusion of the intervention. This 8-item survey measure has been widely applied and is valid, reliable, and feasible for use with HIV-infected ethnic minority youth participating in technology-supported behavioral interventions [109]. Additionally, during ACCESS Session 5, the trained peer health coach will ask participants to briefly describe what was helpful and/or not helpful about any of the videoconferencing sessions. A trained RA will review and transcribe these videoconferencing segments.

Participant Acceptability With the Intervention

At the conclusion of the intervention phase, study participants will be asked to participate in a one-time session 60-min focus group to share feedback on acceptability of the intervention, quality of the video interactions, what was learned, strengths and weakness, and recommendations for improvement. Focus group sessions will be led by the PI and digitally recorded. A series of open-ended questions with probes will be developed to distinguish essential aspects of the information.

Intervention Fidelity

All audiotapes of the videoconferencing sessions will be reviewed. Fidelity to the study protocol by the peer health coaches will be assessed by a trained RA.

Sample Size and Statistical Power

The purpose of this proof-of-concept study is to test the concept of implementing a peer-led mHealth CBI delivered via remote videoconferencing and smartphones. It will not be a definitive test of intervention efficacy, and therefore, a power calculation will not be computed.

Data Analysis Plan

Data will be imported into SPSS Statistics, version 25 (IBM). Initially, we will compute descriptive statistics (mean and SD, median and range, and frequency and percentage) to summarize the following: psychosocial and demographic characteristics of the study population, adherence estimates, scores on survey instruments (beliefs, knowledge, and self-efficacy), and retention in care. Data will be assessed for normality, and nonparametric statistics will be used for data that are not normally distributed.

To test aim 1 (feasibility and acceptability of ACCESS), descriptive statistics will be computed summarizing participant response rates to remote videoconferencing sessions including the number of missed and rescheduled appointments, recruitment, and overall study retention and attrition rates. To evaluate participant satisfaction with the intervention, scores on the client satisfaction questionnaire [108] will be measured postintervention and summarized. Additionally, a descriptive analysis and summary of transcribed content from ACCESS Session 5 will be performed, including a participant description of what was helpful and not helpful about any of the videoconferencing sessions. All sessions will be appraised for fidelity to the intervention protocol. A subset will be randomly selected and MI skills of the peer health coaches appraised. Qualitative data obtained from postintervention focus groups will be reduced to categories and broad themes. ATLAS.ti (v8.2 Windows) will be used for data analysis.

To test AIM 2 (potential impact of ACCESS), the primary outcome variable of adherence as measured with serum HIV RNA will be dichotomized as a binary variable (less than 200 copies/ml; more than 200 copies/ml), with more than 200 copies/ml indicating virologic failure [4]. All participants will be unsuppressed at baseline. An interval estimate of the proportion with viral suppression at follow-up will indicate the potential impact of ACCESS. Changes in $\log_{10}$ viral load, scores of self-efficacy, beliefs about medications, knowledge about ART, self-reported adherence, and retention in care will be compared before and after the ACCESS intervention using McNemar chi-square or exact test for discrete variables, and paired *t* tests for continuous variables. Changes from baseline to postintervention will be explored. Bivariate associations with follow-up viral suppression will be estimated for other variables such as depression, substance use, and viral load at baseline. Multivariate analysis will not be performed, given the modest sample size for the pilot study.

Results

As of December 2018, we are in the data analysis phase of this pilot and anticipate completion with dissemination of final study findings by spring/summer 2019. Findings will determine the feasibility and acceptability of ACCESS, a peer-led mHealth CBI delivered via remote videoconferencing, using smartphones for HIV-infected ethnic minority youth. We also expect that the study findings will provide preliminary evidence of the potential impact of ACCESS on serum HIV RNA quantitative viral load and self-reported ART adherence and retention in care as secondary outcomes. Results of the qualitative pretesting will contribute to a better understanding of the information, motivation, and behavioral skills associated with ART adherence behavior in this high-risk cohort. Criteria from the Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth will be used to report final study results [110].

Discussion

Overview

We describe the design and methods for a novel peer-led mHealth CBI delivered via remote videoconferencing, using smartphones in HIV-infected ethnic minority youth. The objectives of ACCESS project are consistent with the goals and strategies of the national HIV/AIDS plan calling for increased access to HIV care, improved ART adherence support, and reduced health disparities among high-risk HIV-infected populations including ethnic minority youth [111]. Our approach has multiple strengths including the integration of peer health coaches, technology (videoconferencing and smartphones), and the mixed-methods study design. Therefore, we expect for the findings from this study to make several important contributions. These include establishing intervention feasibility and acceptability and offering preliminary estimates of impact on ART adherence and HIV biomarkers. Additionally, retention in care is a secondary study outcome, and these data will add to a body of evidence in need of development [44,112]. The ACCESS proof-of-concept study is also systematically designed to integrate qualitative data from important stakeholders (HIV-infected ethnic minority youth) [113,114]. Mixed-methods design is recommended when qualitative data will be used to inform the development of an intervention, and also for gaining a more complete understanding of a complex problem [115].

The ACCESS adherence intervention will be delivered by an HIV-infected ethnic minority trained health coach, representing a distinct approach to mitigate perceived stigma and bridge the gaps between the health care system and HIV-infected youth [81,116,117]. Published results of a recent meta-analysis provide evidence for building peer support into health care models for HIV-infected individuals [94]. More specifically, study findings show associations between experiencing HIV-related stigma and lowered levels of social support, ART adherence, and access to health care [94].

The ACCESS intervention is technology-enabled (videoconferencing and smartphones), allowing for a developmentally acceptable mode of communication between study participants and peer health coaches. As clinic-based interventions are limited in scope and scalability, technology is an ideal fit to support behavioral interventions with HIV-infected youth [53,118,119]. Moreover, delivery of technology-enabled interventions for HIV-infected individuals is associated with improvements in ART adherence [120], HIV biomarkers [121], engagement [122], and retention in care [121], while serving to extend reach and improve efficacy of HIV interventions [123].

Limitations

Although our approach has many strengths, the methodological limitations include a small sample size and potential for social desirability bias with self-reported adherence estimates. However, these estimates will be validated with HIV biomarkers.

Conclusions

In conclusion, most new cases of HIV-infection are sexually transmitted among ethnic minority youth [3] for whom adherence to ART is a major challenge. Staggering disparities exist in the HIV cascade of care, including the lack of sustained HIV viral suppression and poor linkage to care [19,124]. Presently, there is an urgent need for effective strategies to improve ART adherence among HIV-infected ethnic minority youth [125]. Should the ACCESS adherence intervention demonstrate feasibility and acceptability, this research protocol will offer a blueprint for the development of technology-enabled peer-led interventions and models.

Conflicts of Interest

None declared.

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Abbreviations

ACCESS: Adherence Connection for Counseling, Education, and Support
ART: antiretroviral treatment
CBI: cognitive behavioral intervention
IMB: information-motivation-behavioral
IT: information technology
MI: motivational interviewing

mHealth: mobile health
MMSE: Mini-Mental State Exam
PI: principal investigator
RA: research assistant

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Protocol

A Nurse-Led Self-Management Support Intervention (ZENN) for Kidney Transplant Recipients Using Intervention Mapping: Protocol for a Mixed-Methods Feasibility Study

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Abstract

Background: Optimal self-management in kidney transplant recipients is essential for patient and graft survival, reducing comorbidity and health care costs while improving the quality of life. However, there are few effective interventions aimed at providing self-management support after kidney transplantation.

Objective: This study aims to systematically develop a nurse-led, self-management (support) intervention for kidney transplant recipients.

Methods: The Intervention Mapping protocol was used to develop an intervention that incorporates kidney transplant recipients' and nurses' needs, and theories as well as evidence-based methods. The needs of recipients and nurses were assessed by reviewing the literature, conducting focus groups, individual interviews, and observations (step 1). Based on the needs assessment, Self-Regulation Theory, and the "5A's" model, change objectives were formulated (step 2). Evidence-based methods to achieve these objectives were selected and subsequently translated into practical implementation strategies (step 3). Then, program materials and protocols were developed accordingly (step 4). The implementation to test the feasibility and acceptability was scheduled for 2015-2017 (step 5). The last step of Intervention Mapping, evaluation of the intervention, falls outside the scope of this paper (step 6).

Results: The intervention was developed to optimize self-management (support) after kidney transplantation and targeted both kidney transplant recipients and nurse practitioners who delivered the intervention. The intervention was clustered into four 15-minute sessions that were combined with regular appointments at the outpatient clinic. Nurses received a training syllabus and were trained in communication techniques based on the principles of Solution-Focused Brief Therapy and Motivational Interviewing; this entailed guiding the patients to generate their own goals and solutions and focus on strengths and successes. Kidney transplant recipients were encouraged to assess self-management challenges using the Self-Management Web and subsequently develop specific goals, action plans, and pursuit skills to solve these challenges.

Conclusions: The Intervention Mapping protocol provided a rigorous framework to systematically develop a self-management intervention in which nurses and kidney transplant recipients' needs, evidence-based methods, and theories were integrated.

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KEYWORDS

chronic kidney disease; evidence-based nursing; self-management; transplantation

Introduction

Kidney transplantation is the best option for end-stage renal decease. However, kidney transplant recipients need to adhere to a lifelong medication regimen, and optimal self-management is essential for patient and graft survival, reducing comorbidity and health care costs while improving the quality of life [1-6]; this has led to an increasing interest in optimizing patients' self-management skills [7].

Self-management can be defined as the ability of an individual, in conjunction with family, community, and health care professionals, to manage symptoms, treatments, lifestyle changes, psychosocial, cultural, and spiritual consequences of health conditions to maintain a satisfactory quality of life [8]. Despite the importance of optimal self-management after transplantation, nonadherence to immunosuppressive medication, diet, and exercise have been reported to be relatively high (20%-35%) [9-11]. In addition, recipients report self-management tasks to be challenging, such as adhering to immunosuppressive medication, monitoring symptoms and managing side effects, lifestyle changes, and coping with psychological consequences [12], and report the need for improved self-management support from health care professionals [13-16]. Studies have revealed that self-management support can lead to higher patient well-being and quality of life, improved health, and a decrease in care consumption [3,17,18].

Interventions aimed at optimizing kidney transplant recipients' self-management are, however, scarce. Furthermore, the existing interventions have a number of limitations [19,20], such as a focus on medication adherence without sufficiently integrating psychosocial and behavioral challenges; insufficient tailoring to individual needs; and lack of theoretical framework and use of evidence-based behavioral change techniques. There is, therefore, a need for the development and testing of better-quality interventions, which improve upon these shortcomings.

An important consideration when developing an intervention is the choice of the health care professional providing self-management support. Traditionally, professionals had a paternalistic approach typified by a directive style rather than shared decision making and a focus on medical issues to the detriment of psychosocial issues [21]; this approach may be less effective in establishing a relationship of trust and promoting behavioral changes [21,22]. Nurse practitioners (NPs) are often key actors in psychosocial support and are in an excellent position to create an environment in which patients feel confident in talking about their concerns [23,24]. A self-management support intervention delivered by NPs may therefore help increase effectiveness. However, little is known about current self-management support practices, attitudes toward self-management support among nurses, and their needs to help improve the support offered.

This study aims to develop a nurse-led self-management support intervention in which the needs of kidney transplant recipients and NPs as well as theory and evidence-based methods, are taken into account; to ensure that these components were incorporated, the Intervention Mapping (IM) protocol was used [25]. The final intervention was called ZENN, an acronym derived from the Dutch translation of self-management after kidney transplantation (ZElfmanagement Na Niertransplantatie).

Methods

Intervention Mapping

The IM protocol [26] distinguishes 6 steps with corresponding tasks. Here we present the first 5 steps of the IM protocol (Figure 1). In total, the development and implementation of the intervention took 2 years (2015-2017).

Step 1: Needs Assessment

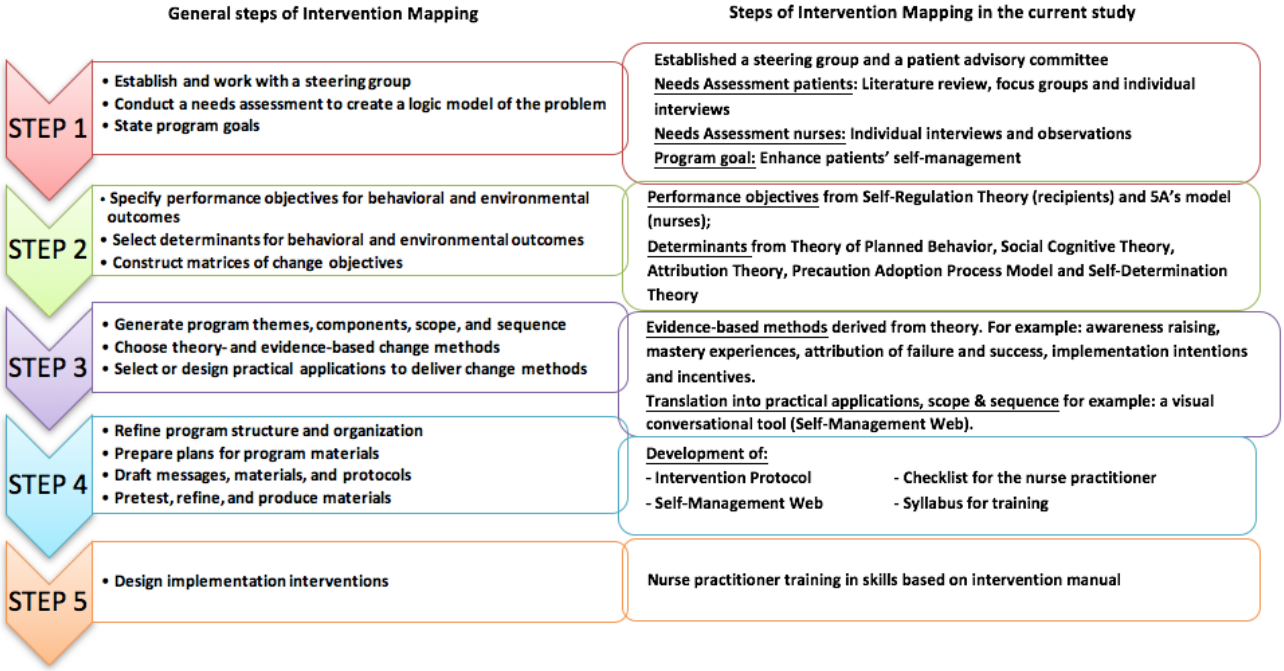
The first step is the needs assessment—a comprehensive exploration of the health problem and the needs of the targeted population. To ensure that important issues for both kidney transplant recipients and NPs were addressed throughout the process, we established a steering group consisting of NPs, nephrologists, nurse scientists (experts in self-management) and psychologists, alongside a patient advisory committee.

The needs of kidney transplant recipients and NPs regarding self-management (support) were explored in several studies, including a literature review of qualitative studies, interviews, and observations.

Assessment of Patients' Needs

First, we reviewed the qualitative literature on patients' needs and preferences for self-management support [27]; this review revealed that for patients with chronic conditions, it is important that self-management support is tailored to their individual needs. Furthermore, they need not only information but also instrumental, psychosocial, and relational support. Patients often reported that these needs were unmet because professionals focus on informational and instrumental support alone [27].

Figure 1. First 5 steps of Intervention Mapping in the ZENN study.



Developing a collaborative partnership with shared decision making is key to improving self-management support [27]. This encouraged us to further assess the specific needs, preferences, and challenges with regard to self-management support of kidney transplant recipients through focus groups and individual interviews (n=32) [28]. Participants were recipients from a single transplant center in a university medical hospital in the Netherlands. Results indicated a need for a holistic approach after kidney transplantation. Although recipients were satisfied with the medical care received, psychosocial support focusing on the emotional challenges of living with a transplant was often lacking. Recipients wanted to participate in shared decision making and be collaborators in the process; to achieve this, a relationship of trust was considered essential. This type of support was particularly important in the first year after transplantation. However, one size does not fit all, and self-management support should be adapted to individual needs and circumstances; this was confirmed in a Q-methodological study in the same transplant center, which found differing attitudes toward self-management support [29]. Q-methodology is a qualitative-quantitative method that provides a foundation for the systematic study of peoples' attitudes toward a certain topic using statements, which are ranked by participants in a quasi-normal grid ranging from completely agree to completely disagree.

Assessment of Nurses' Needs

To explore nurses' perceptions, attitudes, and potential needs, interviews were held and observations were performed. All participants worked at the same university medical hospital in various outpatient departments. Individual semistructured interviews with nurses and NPs were held (n=27) to investigate nurses' views on the concept of self-management in general and how these views relate to the self-management interventions they use in clinical practice [30]. Results showed 3 distinct views on self-management support as follows: adhering to a medical regimen; monitoring symptoms; and integrating illness into daily life; only the last viewpoint reflected a holistic approach with the nurse focusing on coaching. Medical management was the focus of self-management for many nurses. The lack of attention for psychosocial aspects may be attributed to a lack of confidence, skills needed to address psychosocial issues, or available tools or interventions that limit them in offering psychosocial support. Providing training or practical interventions protocols or tools for holistic self-management support could partially resolve this problem by giving nurses resources to encourage self-management effectively.

To more objectively assess NPs' roles and skills in outpatient consultations and how this compares with their perception of their responsibilities for patients with chronic conditions, NPs (n=5) were observed during daily practice [31]. Although NPs reported that they considered building a relationship with their patients of utmost importance, their consultations were mostly based on a conventional medical model of medical history taking. Little attention was paid to the social, psychological, and behavioral dimensions of illness. Finally, a realist review of the literature was conducted to understand how nurse-led interventions that support self-management of patients with chronic conditions work and in what context they work successfully. Interventions focusing on intrinsic processes were found to be the most effective, as opposed to focusing solely on education [32]. Textbox 1 outlines the main findings from the needs assessment.

Textbox 1. Summary of findings from the needs assessment [27- 32].

- Patients' needs assessment
  - Medical and psychosocial issues should both be addressed; attention to psychosocial needs often lacking
  - Tailoring of support to specific needs and preferences is important to patients
  - Self-management support most needed first-year posttransplant
  - Shared decision making is preferred
- Nurses' needs assessment
  - Nurses place emphasis on medical management to the detriment of psychosocial management
  - Nurses focus on education rather than on patient empowerment and coaching
  - Nursing interventions focusing on intrinsic processes are more successful in promoting self-management

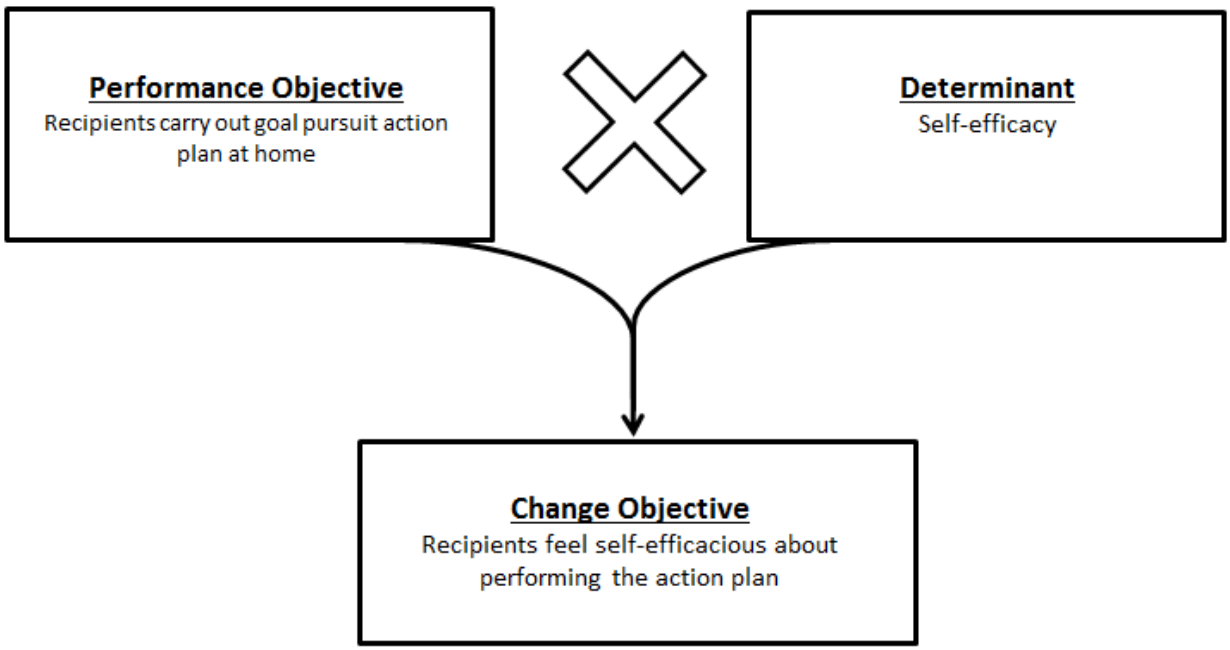
Program Goals

Based on the needs assessment described above, we developed a nurse-led self-management support intervention that included the following key elements: a general, open structure that leaves room for individual preferences and tailoring of support; a holistic approach encompassing medical, emotional, and social self-management challenges; promoting shared decision making between nurses and patients; and patient empowerment by supporting self-efficacy and intrinsic motivation. The overall goal of the intervention is for kidney transplant recipients to enhance their self-management skills to integrate their treatment and life goals and subsequently optimize their quality of life and health-related outcomes. In addition, we aimed to improve NPs' skills to optimize self-management support.

Step 2: Matrices of Change Objectives—Kidney Transplant Recipients

The second step of IM links the overall goals of the intervention to concrete actions by stating change objectives (COs); COs specify who and what will change because of the intervention. To generate COs, we combined performance objectives (POs) and the relevant determinants into a matrix. Figure 2 shows an example of combining a PO with a determinant to obtain a CO. DB and JWG formulated the COs and discussed these with EM for fine-tuning. After this process of revision, 74 COs were formulated and integrated into the intervention.

Figure 2. Creation of Change Objectives.



Performance Objectives

The overall program goal was translated into performance objectives (POs) that specify the behavioral actions the target groups need to perform to change behavior successfully. The target groups were kidney transplant recipients and NPs. Optimizing self-management after kidney transplantation requires intrinsic processes (eg, motivation and self-efficacy [33]) and long-term skills to establish and maintain behavior change and also abilities to adapt behavior when circumstances change. Well-developed self-regulation skills are supportive in performing these tasks. Therefore, the specific behavioral actions that contribute to the overall goal of the intervention were specified in POs based on the principles of self-regulation theories [34]. Studies on other chronic illnesses showed that interventions based on self-regulation theories could improve behavioral outcomes [35-37]. Overall, 8 POs were defined, including goal setting, planning, self-monitoring, feedback, and relapse prevention (Textbox 2).

Determinants

After the definition of POs, we explored which determinants were associated with the performance of the desired behavior, as stated in POs. The determinants were selected from the following health behavioral change theories: Self-Regulation Theory [34]; Theory of Planned Behavior [38]; Social Cognitive Theory [39]; Attribution Theory [40]; Relapse Prevention Theory [41]; Precaution Adoption Process Model [42]; and Self-Determination Theory [43]. Table 1 shows examples of the COs afor NPs for recipients derived from combining POs and determinants.

Step 2: Matrices of Change Objectives—Nurse Practitioners

Performance Objectives

POs for NPs were also guided by the Self-Regulation Theory. In addition, the intervention focused on 3 components of the Five A's model of behavior counseling [44] were incorporated, namely assessing behavior, beliefs, and motivation, agreeing with patients on realistic goals, and assisting to anticipate barriers and develop a specific action plan. The other two components of the 5A's model (advising and arranging) were not an integral part of the intervention because they are less in line with the focus on patient empowerment. To achieve the overall program goal and considering the needs assessment, 2 POs for NPs were formulated (Textbox 2).

Determinants

The determinants deemed most pertinent in predicting these POs for NPs were knowledge, skills, social and professional role and identity, self-efficacy, attitude, and outcome expectations. Table 2 shows examples of COs derived from combining POs and determinants. The full COs matrices are available on request.

Textbox 2. Performance objectives for kidney transplant recipients and nurse practitioners.

- Kidney transplant recipients
  - Recipients decide to improve their self-management on medical or emotional tasks they perceive as challenging
  - Recipients set, at least, one SMART goal
  - Recipients make an action plan to actively pursue and attain their chosen goal, taking into account possible facilitators, barriers, and resources
  - Recipients carry out their goal-pursuit action plan at home
  - Recipients monitor their goal-pursuit behavior in daily life
  - Recipients evaluate their progress with NPs
  - If successful, recipients maintain their new behavior or set a new goal
  - If unsuccessful, recipients adjust their goal, action plan, or outcome expectations
  - Recipients can cope with relapse and reinitiate goal pursuit
  - Recipients can generalize learned self-management skills to new goals
- Nurse Practitioners
  - The nurse practitioners (NPs) carry out the intervention during their consultations with recipients included in the study
  - The NPs assess whether recipients perceive medical, social, or emotional tasks as challenging
  - When recipients indicate that there is a problem in a specific life area, NPs stimulate and guide recipients to set a SMART goal to solve the problem and agrees with the recipient on the goal
  - NPs stimulate and assist recipients to make and implement action plans for attaining their goals
  - NPs encourage recipients to monitor and evaluate their progress toward goal attainment
  - NPs stimulate recipients to maintain goal pursuit or adapt goals or action plans
  - NPs help recipients to anticipate relapse and discuss relapse prevention
  - NPs help recipients to generalize learned techniques to new problems and goals
  - NPs focus on the positive desired outcomes rather than on the negative aspects of living with a kidney transplant

Table 1. Examples of change objectives for kidney transplant recipients derived from combining the performance objectives and determinants.

Performance objectives	Behavioral determinants						
	Awareness	Attitude	Self-efficacy	Autonomous motivation	Social support	Commitment	Skills
Recipients decide to improve an aspect of their life	Become aware of and acknowledge improvement is possible in one or more areas in their life; Are aware of the discrepancy between the desired and current situation	Have stronger positive feelings toward improving self-management than negative	Feel able to improve this aspect of their life	Are intrinsically motivated to improve aspect of life	N/A[a]	N/A	N/A
Recipients set, at least, one SMART goal	Are aware of the desired outcome	Have positive feelings toward the goal	Formulate a goal that they feel self-efficacious about	N/A	N/A	N/A	Are capable of setting a SMART goal
Recipients make an action plan to attain and actively pursue their chosen goal	Are aware of possible habits, facilitators, barriers, and resources	Have positive feelings toward the action plan	Draw up an action plan they feel able to carry out	N/A	Consider possible social support when making an action plan	N/A	Are capable of making an action plan in which facilitators, barriers, habits, and resources are considered
Recipients carry out their goal-pursuit action plan at home	N/A	Have stronger positive feelings toward carrying out the plan than negative	Feel able and self-efficacious about performing the action plan	Are intrinsically motivated to carry out an action plan	Use their social resources according to plan	Show commitment to pursuing the behavior in daily life	N/A

[a]N/A: not applicable.

Step 3: Theory-Based Methods and Practical Strategies

Step 3 aims to identify and select theory-based methods and translate these into practical strategies to influence each determinant to achieve the CO; for example, modeling (method) can be used to influence self-efficacy (determinant) by showing videotaped demonstrations of other patients performing self-management tasks (practical application). Methods and practical applications were reviewed and discussed with the steering group and patient advisory committee. From the methods identified, we selected applications for inclusion in the intervention based on the feasibility and the needs identified in Step 1.

Techniques from Motivational Interviewing [45] were used to promote motivation. The principles of Solution-Focused Brief Therapy (SFBT) [46] were used for the goal and action-oriented COs. SFBT is goal-directed, future-focused, and addresses solutions rather than problems. These key concepts make SFBT particularly useful to actively involve patients during nursing consultations. Furthermore, the social cognitive theories from which determinants of POs were selected were the source of behavioral change methods. The methods were translated into practical applications that were integrated into the intervention protocol. Table 3 shows examples of the theoretical methods and practical applications incorporated into the intervention.

Step 4: Program Production

In Step 4, the actual program was developed; this step contains the determination of program components, the creation of the program scope and sequence, and the development of program materials. Representatives of the steering group and patient advisory committee were presented the concept program and their feedback guided final adjustments.

Intervention Scope

The main theme of the program is optimizing self-management based on the principles of self-regulation theories—evaluating areas of life, establishing and setting goals, planning and preparing strategies for achieving the personal goals and actively pursuing goals, monitoring and evaluating goal progress, and preparing strategies for relapse prevention. Throughout the intervention, these steps are combined with the principles of SFBT to stimulate kidney transplant recipients to generate solutions rather than focusing on their problems.

Table 2. Examples of change objectives for nurse practitioners derived from combining the performance objectives and determinants.

Performance objectives	Behavioral determinants					
	Awareness	Knowledge	Skills	Self-efficacy	Attitude	Professional role and identity
NPs[a] carry out the intervention during their consultations with recipients who have been included in the study	Are aware of benefits using the intervention protocol	Know how to use intervention protocol and when to use which techniques	Have skills (ie, conversational and motivational techniques) to carry out the intervention	Feel self-efficacious to carry out the intervention	Have a stronger positive feeling toward carrying out the intervention than negative	Deem self-management support and carrying out the intervention as part of their professional role
NPs assess if recipients experience challenges or problems in several areas of life	Become aware of problems in recipients' life on other than medical domains and the benefits of assessing psychosocial areas	N/A[b]	Have skills to assess and discuss psychosocial and medical aspects	Feel self-efficacious about assessing and discussing psychosocial and medical aspects	Have stronger positive feelings about assessing psychosocial and medical aspects than solely assessing medical aspects	N/A
When recipients indicate that there is a problem in a specific life area, NPs stimulate recipients to set a SMART goal and agree with recipients on the goal	N/A	Know how to set a SMART goal together with the recipient	N/A	Feel self-efficacious about assisting recipients in setting a SMART goal	N/A	N/A
NPs assist and stimulate recipients to make and implement action plans for attaining their goals	N/A	Know how to assist the recipient to make an action plan which is achievable	N/A	Feel self-efficacious about assisting recipients in making an action plan	N/A	N/A

[a]NP: nurse practitioner.

[b]N/A: not applicable.

Table 3. Examples of the theoretical methods and practical applications incorporated into the intervention.

Change objectives	Determinants	Theoretical methods	Practical application and strategies
Recipient becomes aware of and acknowledges problems in various areas of life	Awareness (Precaution Adoption Process Model or Theory of Planned Behavior)	Awareness raising providing feedback using visualization	Recipients evaluate their life areas based on the Self-Management Web.
NPs[a] become aware of problems in recipients' life on other than medical domains and the benefits of assessing psychosocial areas	Awareness (Precaution Adoption Process Model or Theory of Planned Behavior)	Awareness raising providing feedback using visualization	Self-Management Web: NPs help assess recipients' life based on the Self-Management Web
Recipients belief in their capabilities to optimize self-management behavior	Self-efficacy (Social Cognitive Theory)	Mastery experiences; Attribution of failure and success	Recipients are asked to evaluate and appoint successes to stable, internal factors, and failure to external, unstable factors. When a recipient experiences success, an NP will emphasize the role of the recipient in the success.
NPs feel self-efficacious about carrying out intervention	Self-efficacy (Social Cognitive Theory)	Modeling	NPs receive training in which they practiced delivery using role-plays
Recipients implement new actions to reach goals and break through habits	Habits (Theory of Automatic Behavior)	Implementation intentions	Recipients need to specify if-then, when, where, how, what and where they are going to perform goal-related actions

[a]NP: nurse practitioner.

Intervention Sequence

The final program consists of four 15-minute sessions with an NP combined with regular appointments in the outpatient clinic. The frequency of intervention sessions is determined by the frequency of consultations within standard care. Therefore, the period between the sessions can range from 2 weeks to several months. If the period between sessions 1 and 2 is over 1 month, a telephone consultation with the NP is scheduled. During the first session, the emphasis is on assessment—raising awareness, evaluating areas of life, goal setting, and preliminary preparation of an action plan. In addition, motivation and self-efficacy are discussed using visual analogue scales ranging from 0 to 10. The second and third sessions are used to monitor and evaluate the progression on goal attainment during the past weeks and discuss outcome expectations. Throughout the second and third session, the action plan is further customized; self-efficacy is positively encouraged, and outcome expectations are discussed. During the fourth session, goal progress, relapse prevention, and generalization of learned skills to other challenges are discussed (Figure 3).

Figure 3. Content of sessions 1-4.

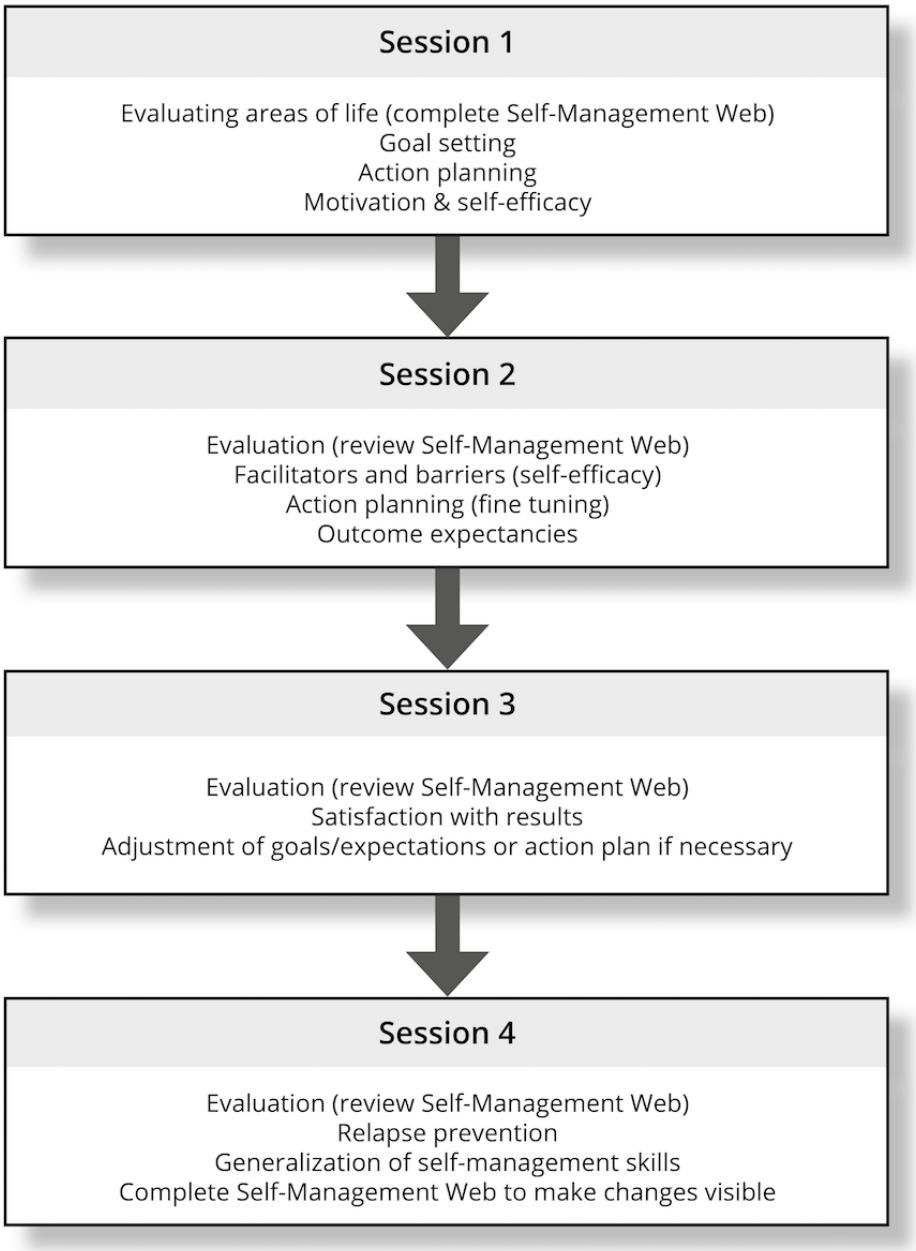
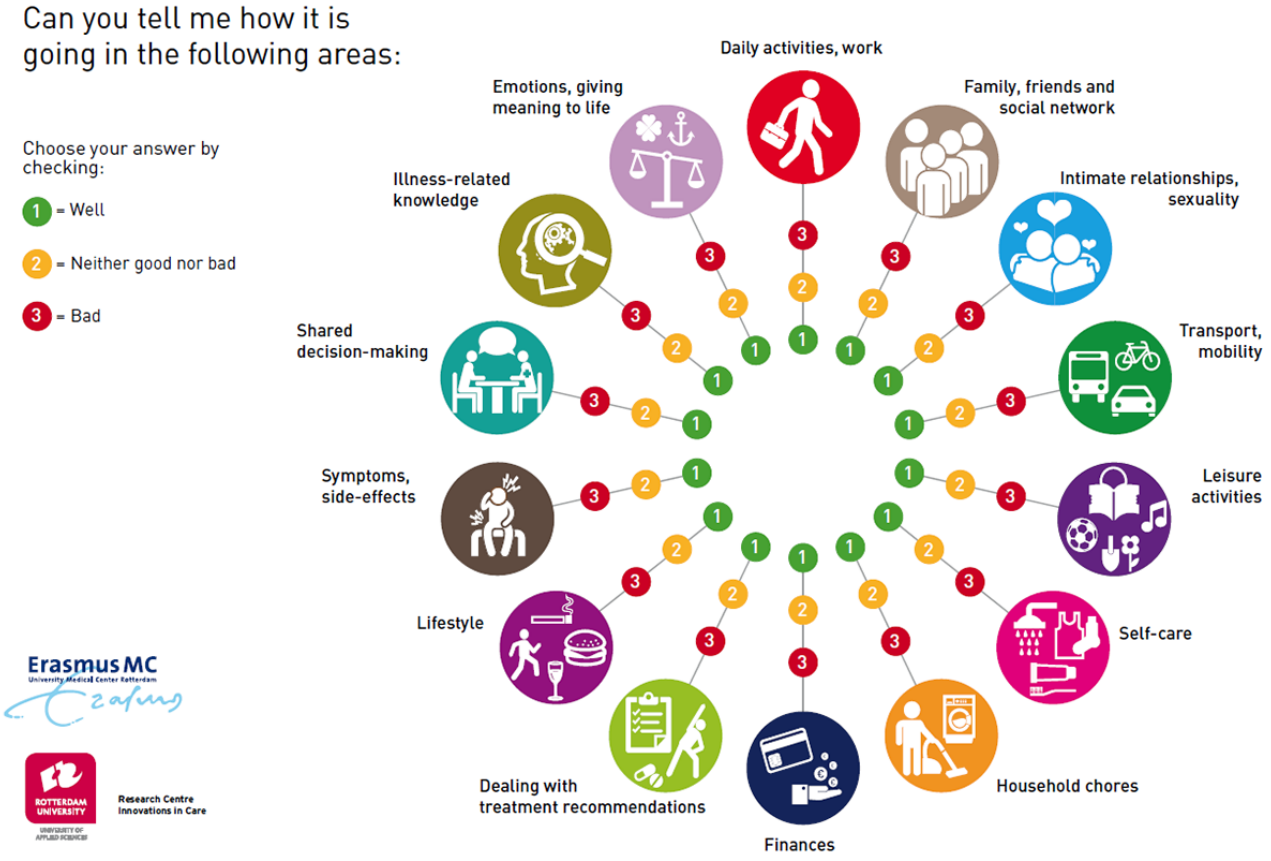


Figure 4. Self-Management Web.



Self-Management Web

A visual communication aid called the Self-Management Web (Figure 4) was developed to facilitate the achievement of the first CO (the recipient becomes aware of and acknowledges problems in various areas of life). The Self-Management Web is used to standardize the assessment of 14 life areas and offer a visual overview to guide the conversation between the professional and patient. The Self-Management Web was developed on the basis of the needs of patients with a chronic condition in general and can be used with a variety of patient populations; this tool ensures a holistic view, because multiple areas of life are represented in the Web, and enhances intrinsic motivation because patients determine the area they prefer to focus on. The discussion about goals results in shared decision making between nurses and recipients.

During the first session, NPs encourage kidney transplant recipients to evaluate their life domains and assess if they are doing well (1, green), neither good nor bad (2, orange), or bad (3, red) on each domain. Kidney transplant recipients mark the answer on the Web to visualize domains with difficulties, which contributes to awareness. When kidney transplant recipients report a 2 or 3, an NP asks open questions to clarify the problem. When multiple areas are rated as "bad," the NP invites the kidney transplant recipient to prioritize and select the area of life he or she wants to work on after which other steps of the intervention are carried out.

Intervention Materials

Prior to beginning the intervention, nurses were trained in delivery. A training syllabus was developed, which NPs received before the training. An intervention protocol was written for NPs, containing specific guidelines per session on how to approach kidney transplant recipients and which topics to discuss with suggestions on how to phrase specific questions. To support the implementation and adherence to the protocol, a checklist was developed for NPs to report on the steps executed per session per recipient.

Step 5: Adoption and Implementation

The effectiveness of an intervention is partially attributable to the quality of the implementation. To promote implementation and ensure fidelity to the intervention, NPs received 2 training sessions before the implementation of the intervention. During the implementation phase, NPs received booster sessions. The training was provided by an experienced psychotherapist (AvtS) and a psychologist (DB).

The training had a dual-purpose; on the one hand, it comprised an explanation on how to carry out the intervention protocol and on the other hand, NPs were trained in using techniques from SFBT and Motivational Interviewing. The training was divided over two 3-hour sessions. After explaining the theories on which the intervention was based and techniques to be used during consultations, trainers performed a role-play to show the steps (modeling). Subsequently, NPs were invited to participate in role-plays with trainers (mastery experiences). Anticipated problems were thoroughly discussed. At the end of the training,

the topics discussed were summarized, and the training was evaluated.

Throughout the implementation period, NPs received booster sessions during which problems encountered could be discussed and techniques practiced. Furthermore, video recordings were made as part of the evaluation of the intervention. NPs received feedback based on the video recordings.

Step 6

In a mixed-methods design, feasibility and preliminary effects of this intervention are being assessed. The outcomes of this step fall outside the scope of this study.

Results

The enrollment for the feasibility study was completed in March 2018. Data analysis is currently underway and the first results are expected to be published in 2019.

Discussion

Principal Findings

The development of the current intervention responds to the need for practical and effective interventions to optimize self-management support after transplantation, in which tailoring, a holistic approach, shared decision making, and patient empowerment is incorporated. In addition, this intervention is in line with the vision of the World Health Organization, which stipulates that the health care system should be addressed when improving self-management support [47] and with recommendations regarding enhancing self-regulation skills among kidney transplant recipients for optimizing the psychological well-being [48].

Although evidence indicates the importance of anticipating the individual needs of each patient to enhance effectiveness, most current interventions fail to do so [19,20,49]. It has been suggested that variance in the effectiveness of self-management support could be attributed to the mismatch between the individuals' needs and the offered intervention [50]. To improve the fit, the Self-Management Web was used to assess in which areas of posttransplant life recipients were experiencing challenges. The Self-Management Web was developed as part of a consortium on self-management and based on the needs of patients with a chronic condition in general and is therefore applicable to a variety of patient populations. Patients participated in the development and pilot evaluation. The use of the Self-Management Web ensured the standardization of the assessment of multiple areas of life while allowing room for a personalized approach.

In addition, our intervention responded to the tendency for self-management support interventions to focus mainly on medical management to the detriment of psychological and social aspects; this emerged from the needs assessment wherein recipients reported the need for psychosocial support in addition to medical guidance, whereas nurses and NPs acknowledged the shortcomings of their current approach. Studies have shown that psychosocial (eg, depression, anxiety) and behavioral factors could negatively affect self-management and are therefore important targets for self-management support interventions [19,20,33,49].

Furthermore, it has been suggested that interventions should be developed on the basis of theory and evidence-based methods [19,20,25,47]. There is an increasing emphasis on reporting specific behavioral change techniques used in interventions to increase the quality and replicability [51]. The IM protocol helped to integrate theory and evidence-based methods as well as the needs of kidney recipients and nurses into the intervention. Behavioral science offers several useful theories and strategies that enhance the effectiveness of interventions used in health behaviors [47]. Our realist review demonstrated that self-management support interventions focusing on intrinsic processes were most successful in the behavioral change [52]; this emulates earlier authors who have emphasized that education alone is insufficient for health behavioral changes. Examples of these processes were self-efficacy and (intrinsic) motivation, which were in the backbone of the current intervention. The Self-Management Web provides the basis on which important personal goals can be set, which ensures intrinsic motivation. Self-Determination Theory [53] stipulates that intrinsic motivation is an important factor for effective behavioral changes [43]. The intervention protocol encourages motivation during the intervention and also emphasizes increasing self-efficacy. Studies among kidney transplant recipients have stipulated the importance of promoting self-efficacy when supporting self-management in kidney transplant recipients [3,18]. In summary, the strengths of the intervention include tailoring, a holistic approach, focus on intrinsic processes, and promotion of shared decision making.

Limitations

Although the intervention is based on health behavioral change theories and the methods incorporated are evidence-based, this does not necessarily guarantee the effectiveness in the context of kidney transplantation. Because recipients determine the goals according to their needs and preferences, improving adherence or lifestyle is not always chosen. Goals attained in the intervention maybe too far removed from the health domain to directly relate to positive health outcomes. In contrast, one could also argue that problems in life areas other than health often impact health-related issues and thus self-management owing to the stress they generate. The effectiveness of the intervention is currently under investigation and results will be presented and discussed elsewhere.

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Conflicts of Interest

None declared.

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Abbreviations

CO: change objective
IM: intervention mapping
NP: nurse practitioner
PO: performance objective
SFBT: Solution-Focused Brief Therapy

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Original Paper

Patient Engagement and Attitudes Toward Using the Electronic Medical Record for Medical Research: The 2015 Greater Plains Collaborative Health and Medical Research Family Survey

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Abstract

Background: Electronic health records (EHRs) are ubiquitous. Yet little is known about the use of EHRs for prospective research purposes, and even less is known about patient perspectives regarding the use of their EHR for research.

Objective: This paper reports results from the initial obesity project from the Greater Plains Collaborative that is part of the Patient-Centered Outcomes Research Institute's National Patient-Centered Clinical Research Network (PCORNet). The purpose of the project was to (1) assess the ability to recruit samples of adults of child-rearing age using the EHR; (2) prospectively assess the willingness of adults of child-rearing age to participate in research, and their willingness (if parents) to have their children participate in medical research; and (3) to assess their views regarding the use of their EHRs for research.

Methods: The EHRs of 10 Midwestern academic medical centers were used to select patients. Patients completed a survey that was designed to assess patient willingness to participate in research and their thoughts about the use of their EHR data for research. The survey included questions regarding interest in medical research, as well as basic demographic and health information. A variety of contact methods were used.

Results: A cohort of 54,269 patients was created, and 3139 (5.78%) patients responded. Completers were more likely to be female (53.84%) and white (85.84%). These and other factors differed significantly by site. Respondents were overwhelmingly positive (83.9%) about using EHRs for research.

Conclusions: EHRs are an important resource for engaging patients in research, and our respondents concurred. The primary limitation of this work was a very low response rate, which varied by the method of contact, geographic location, and respondent characteristics. The primary strength of this work was the ability to ascertain the clinically observed characteristics of nonrespondents and respondents to determine factors that may contribute to participation, and to allow for the derivation of reliable study estimates for weighting responses and oversampling of difficult-to-reach subpopulations. These data suggest that EHRs are a promising new and effective tool for patient-engaged health research.

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KEYWORDS

electronic health record research; survey; caregivers; engagement

Introduction

In 2013, The Greater Plains Collaborative (GPC) was established as a Clinical Data Research Network (CDRN), funded by the Patient-Centered Outcomes Research Institute to securely collect and organize patient health information obtained during routine care in its member health systems [1]. To date, 13 such CDRNs have been funded, creating a national "network of networks." These networks are organized by a coordinating center and overseen by the National Patient-Centered Clinical Research Network (PCORnet) [2]. The purpose of CDRNs and PCORnet is to support efficient clinical research by creating centralized access to the deidentified data of millions of patients across the country. Each CDRN is responsible for harmonizing patient data across its member systems, and for creating streamlined governance and procedures to facilitate researcher access. Importantly, CDRNs actively involve a variety of stakeholders, including patients, clinicians, health care system leaders, and other stakeholders, to build and oversee CDRN activities. To test each CDRN's ability to identify and recruit patients with a particular condition, and to test the ability to harmonize data elements within a network, each CDRN was required to create three cohorts: one of a common disease [3], one of a rare disease (amyotrophic lateral sclerosis [in progress]), and one concerning height and weight; the GPC height and weight cohort is the one described herein.

Greater Plains Collaborative Member Sites

In phase 1 of funding, the GPC consisted of 10 health systems, with the data of approximately 6 million people across seven states, north and south across the Great Plains region. Member institutions included Children's Mercy Hospital (Kansas City, MO), University of Kansas Medical Center, Marshfield Clinic, Medical College of Wisconsin, University of Iowa Healthcare, University of Minnesota, University of Nebraska Medical Center, University of Texas Health Science Center at San Antonio, University of Texas Southwestern Medical Center, and University of Wisconsin-Madison.

Covering more than 1300 miles, the broad reach of the GPC network encompasses large swaths of rural populations as well as multiple urban centers. Four systems in the GPC have established significant relationships with Native American populations. Two health systems located in Texas, the University of Texas Southwestern Medical Center and the University of Texas Health Science Center at San Antonio, serve large Hispanic populations. Of the 10 member health systems participating in the Height Weight Cohort's Health and Medical Research Family Survey (HMRFS), all provide comprehensive adult and pediatric care, with the exception of Children's Mercy Kansas City, which exclusively serves children. In phase 2 of the GPC, two additional members were added—University of Missouri and Indiana University—but the data reported here predate their participation.

Health and Medical Research Family Survey

The purpose of the HMRFS was to conduct a demonstration survey (Textbox 1) across all participating GPC sites focused on the topic of pediatric height and weight, and specifically, pediatric overweight and obesity. The expected outcome of the project was to understand the practical challenges and operational details of a large, semi-interconnected system such as the GPC for conducting collaborative prospective data collection-based research focused on pediatric obesity. Aims of the project were to (1) estimate the willingness of individuals to be contacted about research activities, and their response rate; (2) obtain information on the attitudes of parents and adults of child bearing age about research, including participation of their child/ren; (3) gain insight into participant attitudes about the use of gathered data for both local and national research; (4) explore the impact of various demographic factors on survey outcomes and survey response rate; (5) examine if there are differences between individuals across various weight classes; and (6) determine if there are regional variations in all of these. Although previous studies have been published on adult obesity using a CDRN funded by the Patient-Centered Outcomes Research Institute [4], these studies were retrospective in nature and reported on the number of patients in the network who met certain criteria. In contrast, the HMRFS of the GPC not only gathered retrospective data on individuals who met certain specific inclusion criteria but also conducted prospective data collection by containing a random group of individuals from the subsample at each site with a survey invitation. The goal for all participating sites was to contact at least 1000 individuals or a number deemed sufficient to garner at least 100 complete responses per site to the survey.

Textbox 1. The Health and Medical Research Family Survey.

1. Have you or anyone in your family ever been a participant in any type of medical research?

2. Can medical researchers contact you to tell you about opportunities for you or someone in your family to participate in a medical research project?

2B. Please select any of the answers that describe what might help you decide to be contacted. You may choose one or more than one answer if you like: it depends on what the research is about; it depends on how much time it would take; it depends on whether my doctor thinks that it would be a good idea; it depends on whether I would be paid; it depends on whether it would involve just me or whether it would involve my child or children; it depends on something else.

3. Do you have a child or children under the age of 21?

4. If you have a child or children, would you be willing to be contacted about opportunities for your child or children to take part in a medical research project? You may choose one or more than one answer if you like: it depends on what the research is about; I would be interested if the research is about; it depends on how much time it would take; it depends on whether my doctor thinks that it would be a good idea; it depends on whether I would be paid; it depends on whether it would involve just me or whether it would involve my child or children; it depends on something else.

5. Would you be willing to talk to family members or friends about taking part in a medical research study?

6. The information your doctor collects about you is very important. When researchers combine health information obtained from many people, it can help find ways to improve health. It can also tell researchers which treatments work best for different people. How do you feel about *your medical information* being used for research?

7. The information your doctor collects about you is stored on computers. People have to have permission to look at or share your electronic health information. It is possible to remove personal information (like your name, birth date, etc) before it is shared. This process is called "deidentification." *If your health care provider deidentified your health information,* how would you feel about your information being shared?

Will you please answer the following questions about yourself, and (if appropriate) about your child.

8. How tall are you? Please write that information in the blanks below.

9. What is your approximate weight?

10. Do YOU have any of the following conditions? High blood pressure (also called hypertension), high cholesterol, high triglycerides or hyperlipidemia, high blood sugar or diabetes, cancer (any type)?

11. Do any of the following blood relatives (your biological father, mother, brother, sister, uncle or aunt, son or daughter) have any of the following conditions? High blood pressure (also called hypertension), high cholesterol, high triglycerides or hyperlipidemia, high blood sugar or diabetes, cancer (any type)?

Methods

The Height Weight Cohort team, which consisted of representatives from all sites, began regular meetings in January 2014. Based on discussions and collective interest, the group quickly decided to develop its cohort and survey around a pediatric population. Weekly working group calls established an interest in characterizing the cohort around data elements that would be attainable for the nascent GPC network and creating a survey that could be used as a building block for future GPC and healthy weight cohort work (manuscripts in preparation). Thus, the HMRFS focused on respondents' willingness to take part in future clinical research as well as key demographic and health-related issues theorized to impact these responses.

Institutional Review Board Process

Through its efforts to streamline governance, the GPC Institutional Review Board (IRB) Consortium was established to facilitate IRB review and approval. The consortium, including all the GPC sites, signed a common IRB reliance agreement and adopted standard operating procedures which would govern the reliance process. The University of Texas Health Science Center at San Antonio served as the reviewing IRB site for the HMRFS across the GPC network. The HMRFS team of investigators and staff developed the necessary IRB documents, which were submitted to the IRB at the University of Texas Health Science Center at San Antonio. Once the documents were reviewed and approved by the reviewing IRB, the documents were shared with all other participating sites' IRBs, and these documents were approved under the existing overall IRB reliance agreement. The GPC went on to be an early adopter of the SMART IRB platform, which now has more than 175 other participating institutions and is designed to facilitate multisite research and implement the NIH Single IRB Review Policy.

Data Harmonization

Data were extracted from an open source data warehouse platform called Integrating Informatics from Bench to Bedside (i2b2). Each of the participating sites had an i2b2 instance deployed, where a deidentified version of all structured data from their respective electronic health record (EHR) systems was stored. As a result, no site had to transmit any identifying information to any other site. The other required component was Research Electronic Data Capture (REDCap). REDCap is noncommercial software developed at Vanderbilt University for the purposes of conveniently capturing research data, including surveys. All participating sites hosted the online survey on their respective local REDCap servers. At sites where paper and telephone responses were accepted, survey personnel manually filled in REDCap surveys on behalf of the respondents. The survey data and the EHR data extracted from i2b2 were merged using a nonidentifying index. Data were extracted from the EHR using DataBuilder collated into an analyzable tabular form using DataFinisher.

Table 1. Detailed list of site, adult/pediatric cohort, and contact method.

Site	Cohort makeup	Contact method[a]
Children's Mercy Hospital	Pediatric	Email
University of Kansas Medical Center	Pediatric	Email
Marshfield Clinic	Pediatric	Email
Medical College of Wisconsin	Adult	Email
University of Iowa Healthcare	Pediatric	USPS
University of Minnesota	Pediatric	USPS
University of Nebraska Medical Center	Adult	Email
University of Texas Health Science Center at San Antonio	Pediatric	USPS
University of Texas Southwestern Medical Center	Pediatric	Email
University of Wisconsin-Madison	Adult and pediatric	Portal

[a]Email: electronic mail on file; portal: patient portal feature of the electronic medical record system; USPS: United States Postal Service.

Cohort Identification

Cohort selection was completed using the i2b2 web client [5]. The inclusion criteria were manually translated at each site to the equivalent local codes. Each site then ran the resulting query, and their local i2b2 server generated a "patient set"—a list of deidentified patient numbers. Each site's informatics team had a crosswalk file matching the deidentified patient numbers to actual medical record numbers or database keys for their local patients. Neither were shared externally. The local informatics teams would use these identifiers to obtain names and contact information from the local EHR system, and these contact lists were securely transmitted to the respective local HMRFS site leads, who used them for recruitment. Also, information regarding race, ethnicity, and class of insurance provider (eg, private, Medicaid, employer, government, self-pay) was gathered directly from each site's EHR. Income was gathered through median household income for the census block group in which each patient's address was located, as obtained from the 2013 American Community Survey census block group data (tables B19013 and B19013A-I) [6].

Participants

Using the EHR at each site, a list was developed of all individuals who met the inclusion and exclusion criteria for the study. Most sites targeted pediatric patients, but there were two sites for whom there were not sufficient pediatric patients available, so adult patients were targeted, and one site chose to target both pediatric and adult patients (see Table 1). For the pediatric patients, inclusion criteria included individuals who had at least one outpatient visit to the institution within the previous 36 months, with an age between 2 and 20 years, with both height and weight obtained at the same visit on at least one occasion, male or female gender, an address or email available in the EHR, a body mass index (BMI) over the fifth percentile for age and gender, as well as an identifiable parent or guardian. For the adult patients, some criteria were modified, and the criteria for an identifiable parent or guardian was removed. Specifically, age was modified to be between 21 and 49 years, and a BMI of 18.5 kg/m^2 or higher. After the list of patients who met inclusion criteria was developed, deceased patients were removed (exclusion criteria) as well as cases with nonsensical heights, weights, and BMIs. Pregnant adult females were also removed, as were duplicates, resulting in a finalized patient list.

Potential participants were contacted through one of three means: the United States Postal Service (USPS), email, or through the patient portal feature of the electronic medical record systems. The method of contact was selected by each HMRFS site principal investigator based on logistics and local policy requirements. For a detailed list of sites and contact methods, see Table 1.

Analysis Plan

Descriptive statistics were obtained for the overall cohort population, as well as the survey respondents. Univariate logistic regression models were fit to these observations as an exploratory screen in preparation for further analysis. Categorical variables with more than two levels were split into individual indicator variables to determine which levels correlated with increased participation. Predictor variables included patient demographics (age, race/ethnicity, BMI, income, insurance), recruitment type (USPS, email, EHR patient portal), and site. Finally, counts and percentages are reported for respondent attitudes toward research participation.

Results

Response Rates and Cohort Characteristics of Different Contact Methods

The final cohort included 54,269 individuals who met the inclusion and exclusion criteria (Figure 1). Of these, 34,934 (64.37%) were contacted via email, 14,336 (26.42%) were contacted via USPS, and 4999 (9.21%) were contacted via the portal in their site's electronic medical record with an invitation to participate (Table 2). Of these, 3473 (6.39%) were identified to have incorrect contact information.

Figure 1. CONSORT diagram including all sites.

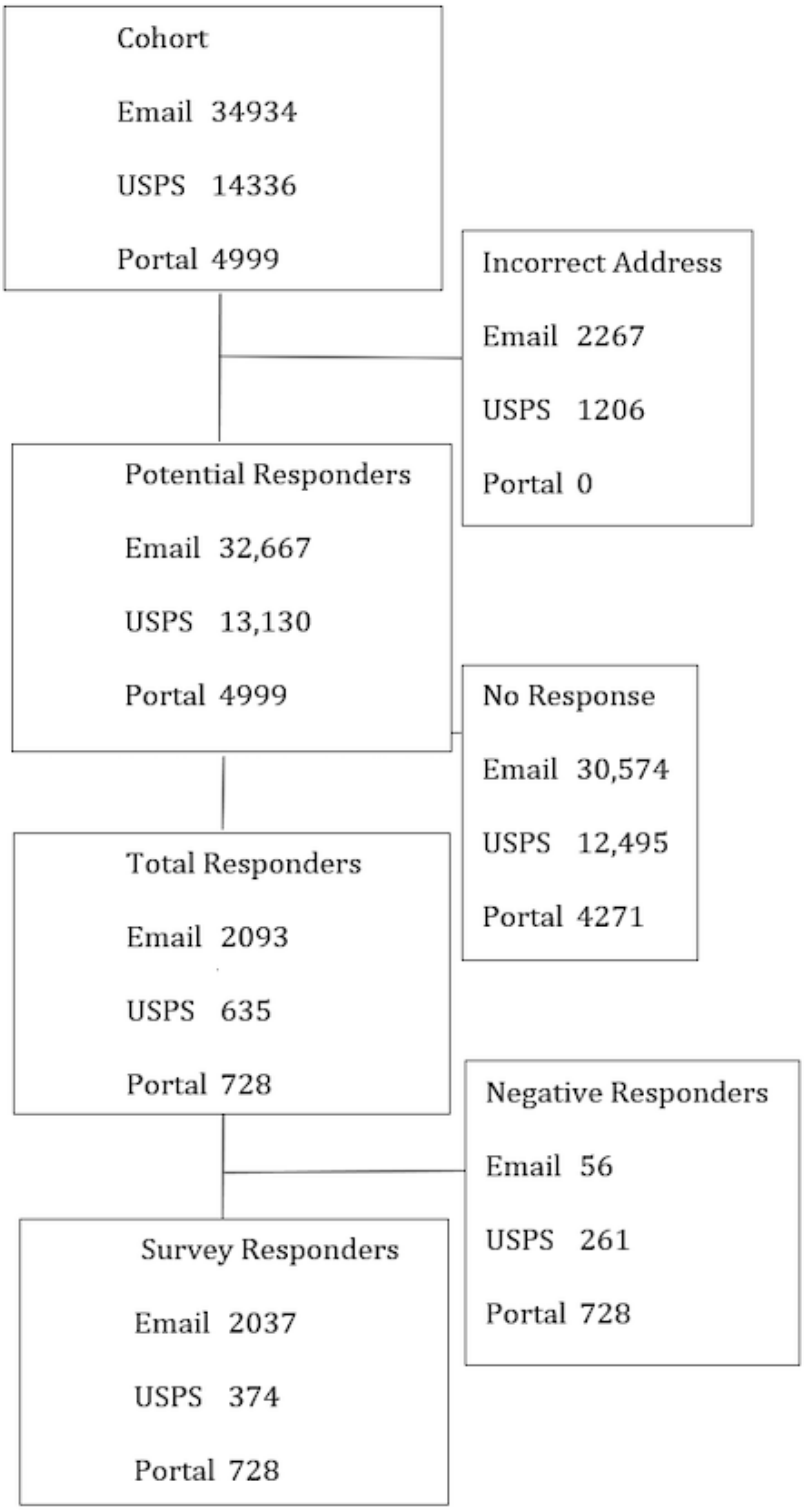

Table 2. Response rate by recruitment method across all sites.

Contact method	Cohort, n	Responders, n (%)
Email	34,934	2051 (5.55)
USPS	14,336	460 (3.11)
Portal	4999	728 (12.71)
Total	54,269	3239 (5.63)

No response was received from 47,340 of 54,269 (87.23%) individuals. This resulted in 3456 (6.37%) total responders, with 217 (6.26%) of these responding to indicate they wanted no future contact, and 100 (2.89%) responding only to the single question declining participation. A final sample of 3139 individuals were survey responders.

The index patient varied (adult or child) by site (Table 1), but cohort demographics are available individually for each site from the research team. Sample size by site varied from a minimum of 3411 (Children's Mercy Hospital) to a maximum of 9849 (University of Nebraska Medical Center). Among the entire cohort sampled, the proportion of males at each site varied significantly (35.8%, 3523/9849/to 55.3%, 2393/4328) as did the racial makeup of the site sample, although all sites were predominantly white and non-Hispanic. Insurance status also varied significantly by site; the most common were self-pay (53.25%, 3195/6000), Medicaid (38.93%,1685/4328), and private insurance (88.10%4398/4992). Estimated median household income ranged from US$42,770 to US$67,020. The mean age of the index patient (child) ranged from 9.47 to 14.83 years. As noted previously, three sites recruited adults because they did not have enough pediatric patients to meet accrual targets. The mean ages of their patients ranged from 35.37 to 47.82 years, so they were asked the same questions about children residing at home and participating in research as were asked of the other sites. Finally, BMI category for the index patient varied significantly by site, with values ranging from 15.8% to 45.7% for overweight and 15.1% to 43.9% for obese.

Results From Responders to the Health and Medical Research Family Survey

A total of 3139 responders completed the HMRFS across all sites (Table 3). Gender differed significantly by site, ranging from 25.3% (91/360) to 58.0% (47/81) male, as did race, ranging from 65.8% (75/115) to 95.5% (386/404) white. The percentage of Hispanic responders also varied significantly, with one site reporting a rate as high as 25.2% (29/115). Annual income ranged from US$45,000 to US$75,600. Age of index patient (child) ranged from mean 13.90 to mean 9.68 years, and age of the index patient (adult) ranged from mean 37.12 to 48.26 years. BMI category also varied significantly, for both overweight (11.6%, 11/95 to 51.9%, 42/81) and obese (12.9%, 51/396 to 44.5%, 289/728).

Responses indicate that across all sites, 29.44% (924/3139) of respondents (or their family members) had participated previously in medical research. Respondents were generally open to investigators contacting them about possible participation in studies (yes: 42.47%, 1333/3139; maybe: 38.71%, 1215/3139). Key factors in making the decision to participate in medical research included: topic of research (62.98%, 1977/3139), time (48.20%, 1513/3139), doctor recommendation (22.05%, 692/3139), reimbursement (17.23%, 541/3139), and child involvement (23.89%, 750/3139; Table 4). Most participants were in favor of their medical information being used for research (fantastic idea: 34.88%, 1095/3139; good idea: 48.01%, 1507/3139) with similar responses if the medical research was deidentified (fantastic idea: 31.98%, 1004/3139; good idea: 48.84%, 1533/3139).

The respondents who had children (2001/3139, 63.74%) also reported feeling generally positive about possibly allowing their child to take part in medical research (yes: 27.2%, 542/2001; maybe: 40.0%, 797/2001). Key factors in making the decision to allow their child to participate in medical research included topic of research (56.6%, 1132/2001), time (38.5%, 771/2001), doctor recommendation (26.4%, 529/2001), reimbursement (12.3%, 247/2001), and child involvement (13.7%, 275/2001; Table 5).

Table 3. Demographics of the sample and responders by recruitment method.

Demographics	Email	USPS	Portal	Total	*P* value
Sample					
Total, N	34,934	14,336	4999	54,269	
Responded, n (%)	2037 (5.8)	374 (2.6)	728 (14.6)	3139 (5.8)	
Gender (male)					<.05
Total, n	15,947	7397	1825	25,169	
Responded, n (%)	905 (5.7)	189 (2.6)	255 (14.0)	1349 (5.4)	
Race					<.05
White					
Total, n	25,708	10,208	4518	40,434	
Responded, n (%)	1766 (6.9)	307 (3.0)	680 (15.1)	2753 (6.8)	
African American					
Total, n	3344	985	108	4437	
Responded, n (%)	57 (1.7)	4 (0.4)	11 (10.2)	72 (1.6)	
Native American					
Total, n	160	69	21	250	
Responded, n (%)	6 (3.8)	1 (1.4)	4 (19.0)	11 (4.4)	
Asian					
Total, n	860	442	94	1396	
Responded, n (%)	38 (4.4)	7 (1.6)	17 (18.1)	62 (4.4)	
Other					
Total, n	2596	1951	5	4552	
Responded, n (%)	97 (3.7)	41 (2.1)	1 (20.0)	139 (3.1)	
Unknown					
Total, n	1014	623	93	1730	
Responded, n (%)	17 (1.7)	13 (2.1)	15 (16.1)	45 (2.6)	
Ethnicity (Hispanic)					<.05
Total, n	3057	2139	94	5290	
Responded, n (%)	68 (2.2)	34 (1.6)	16 (17.0)	118 (2.2)	
Insurance status					
Self-Pay					<.05
Total, n	5035	3190	2985	11,210	
Responded, n (%)	343 (6.8)	99 (3.1)	433 (14.5)	875 (7.8)	
Medicare					
Total, n	573	3	442	1018	
Responded, n (%)	16 (2.8)	0 (0.0)	71 (16.1)	87 (8.5)	
Medicaid					
Total, n	6672	2257	102	9031	
Responded, n (%)	232 (3.5)	35 (1.6)	17 (16.7)	284 (3.1)	
Private insurance					
Total, n	16,393	7847	966	25,206	
Responded, n (%)	1147 (7.0)	215 (2.7)	149 (15.4)	1511 (6.0)	
Other					

Demographics	Email	USPS	Portal	Total	*P* value
Total, n	1017	368	0	1385	
Responded, n (%)	30 (2.9)	8 (2.2)	0 (0.0)	38 (2.7)	
Unknown					
Total, n	4073	613	344	5030	
Responded, n (%)	215 (5.3)	16 (2.6)	58 (16.9)	289 (5.7)	
BMI category					
Overweight					<.05
Total, n	9159	4599	1349	15,107	
Responded, n (%)	510 (5.6)	115 (2.5)	207 (15.3)	832 (5.5)	
Obese					
Total, n	10,372	3713	1893	15,978	
Responded, n (%)	569 (5.5)	71 (1.9)	289 (15.3)	929 (5.8)	

Table 4. Adult respondents' (adults of child-rearing age or parents of index child patients) thoughts regarding their participation in research (N=3139).

Survey question	n (%)
1. Have you or anyone in your family ever been a participant in any type of medical research?	
Prefer not to answer	3 (0.01)
No	1838 (58.55)
Unsure	374 (11.91)
Yes	924 (29.44)
2. Can medical researchers contact you to tell you about opportunities for you or someone in your family to participate in a medical research project?	
Prefer not to answer	69 (2.19)
No	504 (16.06)
Maybe	1215 (38.71)
Yes	1333 (42.47)
2B. Please select any of the answers that describe what might help you decide to be contacted.	
What research is about	1977 (62.98)
Specific topics	240 (7.65)
How much time it would take	1513 (48.20)
My doctor's opinion	692 (22.05)
Being paid	541 (17.23)
Whether involves children	750 (23.89)
Other	70 (2.23)
3. Do you have a child or children under the age of 21?	
Prefer not to answer	13 (0.41)
No	1106 (35.23)
Yes	2001 (63.74)
5. Would you be willing to talk to family members or friends about taking part in a medical research study?	
Prefer not to answer	35 (1.12)
No	1102 (35.12)
Unsure	967 (30.81)
Yes	1000 (31.86)
6. How do you feel about *your medical information* being used for research?	
Unsure	331 (10.55)
Prefer no answer	23 (0.73)
Not good idea	30 (0.95)
Fantastic	1095 (34.88)
Good idea	1507 (48.01)
7. If your health care provider deidentified your health information, how would you feel about your information being shared?	
Unsure	379 (12.07)
Prefer not to answer	21 (0.67)
Fantastic	1004 (31.98)
Good idea	1533 (48.84)
Terrible	28 (0.89)
Not good Idea	72 (2.29)
Other	57 (1.82)

Survey question	n (%)
10. Do you have hypertension?	
Prefer not to answer	9 (0.29)
No	2479 (78.97)
Unsure	64 (2.04)
Yes	516 (16.44)
10. Do you have high cholesterol?	
Prefer not to answer	11 (0.35)
No	2281 (72.66)
Unsure	159 (5.07)
Yes	605 (19.27)
10. Do you have diabetes?	
Prefer no answer	9 (0.29)
No	2670 (87.93)
Unsure	95 (3.03)
Yes	276 (8.79)
10. Do you have cancer?	
Unsure	80 (2.55)
Prefer not to answer	13 (0.41)
No	2691 (85.76)
None	95 (2.89)
Yes	150 (4.78)
11. Do you have relatives with hypertension?	
Prefer not to answer	10 (0.32)
No	888 (28.29)
Unsure	200 (6.37)
Yes	1967 (62.66)
11. Do you have relatives with high cholesterol?	
Prefer no answer	11 (0.35)
No	973 (30.99)
Unsure	341 (10.86)
Yes	1718 (54.73)
11. Do you have relatives with diabetes?	
Prefer not to answer	10 (0.32)
No	1488 (47.40)
Unsure	188 (5.99)
Yes	1344 (42.82)
11. Do you have relatives with cancer?	
Unsure	140 (4.46)
Prefer not to answer	12 (0.38)
No	1388 (44.22)
None	95 (3.03)
Yes	1402 (44.66)

Table 5. Responses from caregivers with children regarding their child's participation in research (n=2001).

Question	n (%)
4. Would you be willing to be contacted about opportunities for your child or children to take part in a medical research project?	
Maybe	797 (39.83)
No	613 (31.48)
No children	4 (0.19)
Prefer not to answer	36 (1.79)
Yes	542 (27.09)
4B. What helps you decide about children research?	
What research is about	1132 (56.57)
Specific topics	133 (6.65)
How much time it would take	771 (38.53)
My doctor's opinion	529 (26.44)
Being paid	247 (12.34)
Whether involves children	275 (13.74)
Other	58 (2.89)

Looking at these responses by site (data available from study team), there was variability by site of more than 30% on some survey questions. For example, participation in previous medical research varied from 20.0% (35/174; University of Texas Health Science Center at San Antonio) to 68.4% (65/95; University of Texas Southwestern Medical Center). On the question of possibly being contacted for participation in future research, sites varied from a low of 39.5% (221/560; Medical College of Wisconsin) to a high of 68.8% (65/95; University of Texas Southwestern Medical Center). Regarding having a child in the home, responses varied from 99.1% (232/235; Children's Mercy Hospital, a pediatric hospital) to 30.9% (273/885; University of Wisconsin-Madison). The percentage of those with a child in the home who would allow that child to participate in medical research varied from 15.9% (57/360; University of Nebraska Medical Center) to 78.9% (75/95; University of Texas Southwestern Medical Center). Regarding the idea of their medical data being used in health research, favorable responses by site varied from a low of 78.0% (74/95; University of Texas Southwestern Medical Center) to a high of 92.6% (75/81; University of Minnesota). Finally, regarding the use of deidentified medical information being used in research, sites ranged from 79.3% (314/396; University of Kansas Medical Center) in favor to 90.1% in favor (73/81; University of Minnesota).

Electronic Health Record Predictors of Participation

Prior to analysis, the 54,269 cohort members were randomly assigned to a development (n=10,751), validation (n=10,748), and test (n=32,770) subsets to avoid overfitting and bias due to within-sample testing. All analysis decisions were made based on the developmental subset. The first goal was to identify candidate predictors for survey participation from among the variables available for all members of the cohort (ie, those listed in Table 3). Accordingly, for each candidate predictor, a separate logistic regression model was fit to the developmental subset with responder status as the outcome. Discrete variables with multiple levels were broken up into an equal number of indicator variables. Significant predictors of increased response included increasing age, being white, and having insurance self-pay. Adult patient recruitment sites were associated with increased participation. Several factors predicted decreased participation, including Hispanic ethnicity, having Medicaid, being African American, and (at the site level) recruitment via USPS and recruitment of pediatric patients.

Discussion

The purpose of the Height Weight Cohort's HMRFS was to conduct a prospective demonstration survey across 10 participating sites in the GPC to (1) assess the ability to recruit samples of adults of child-rearing age using the EHR; (2) prospectively assess the willingness of adults of child-rearing age to participate in research, and (if parents) their willingness to have their children participate in medical research; and (3) to assess their views regarding the use of the EHRs for research.

Recruitment of Parents and Adults of Child-Rearing Age Using the Electronic Health Record

These data suggest that the EHR can be used to recruit patients to medical research using the EHR portal, USPS, and email. The data indicate that the EHR portal obtained the most effective recruitment rate at 12.71%. Further analyses indicate that increasing age, being white, and having insurance self-pay predicted higher rates of participation, whereas Hispanic ethnicity, having Medicaid, and being African American predicted lower rates of participation. Regarding the recruitment method, recruitment via USPS predicted lower rates of participation, and the recruitment of pediatric patients also predicted lower rates of participation.

Interest in Research Participation for Adults/Caregivers and Their Children

Survey data indicate that most respondents had not participated in research previously, but were maybe (38.9%) or definitely (42.7%) willing to be contacted for research participation. Caregivers were also interested in being contacted for research appropriate for their children, with 27.2% indicating yes and 40.9% indicating maybe. As a team of researchers constantly seeking research participants for our work, we are encouraged by these affirmative responses. Other data surveying adults about their willingness to participate in research have not indicated such high enthusiasm [7]; only 7.1% of respondents were willing to participate in weight-related research, but 82.2% were willing to participate in healthy lifestyles research. These data indicate that the topic of the research is a key factor in decision making, but specific topics were not assessed in the current study.

Survey respondents were also asked their opinions on whether medical information should be used for research, and an overwhelming majority responded positively (83.9%). Responses were equally positive when asked about the use of deidentified data (81.9%). Responses to the final two survey questions about the use of medical information (deidentified or non-deidentified) were overwhelmingly positive.

This study did have several strengths. First, unlike many other surveys, we were able to collect demographic information on the entire cohort that was invited to participate (also known as the sampling frame). This type of information is very helpful in determining how the respondent sample may have been biased in some way. Second, because the methodologies for patient contact were low burden (email, portal, USPS) we were able to contact a very large number of patients with little to no budgetary implications. Also, we are one of the first studies to use the electronic medical record portal to contact participants for research. This study did have several weaknesses. First, our overall survey response was low (6.2%). Other studies conducted through the CDRN using survey methodology indicated response rates of 3% to 6% using the same methodologies used here [8]. Therefore, although these rates are low, they are consistent with previously published literature in this area. Even so, it is possible that the individuals who responded to our survey had a positive attitude toward research, which predisposed them to respond to the survey, and could have influenced our positive survey findings. Second, due to inconsistencies across sites, we were unable to use a single method of contacting participants (some sites did not have emails on file, others did not permit the use of their EHR for research). Third, for pediatric patients, when an email was listed in their medical record, it was unclear in some cases whether this was the child email or the parent email, which required further follow-up and clarification. We are hopeful that as sites move toward more electronic communication with their patients, there will be fields for both parent email and child email when appropriate.

Moving forward, questions remain about how best to use the EHR to identify and contact patients. As we have shown, each contact method has its limitations. Traditional mail can be labor intensive and expensive. Email is currently limited by the lack of data in the EHR system, but this should improve over time. Using the EHR directly through the electronic portal is limited by concerns about intrusion and privacy at some sites, which may not allow such contact in their health systems. Of note, the site in our study that used the EHR portal was only able to obtain permission for the use of the portal after the patient advisory board advocated for the project. The other concern [9] is that certain populations (such as the elderly) may be less likely to use electronic media such as email or the EHR portal, and thus may be excluded from studies using these methods. Most previous research studies have used the EHR to identify individuals followed by mailed invites and phone calls. There are reports of trials using the patient portal who found it was helpful, and in one case better than other methods, but not sufficient to use alone. It was also better at reaching younger patients. A recent survey of the Clinical and Translational Science Award consortium found that only 20% of institutions had EHR patient portals that could notify patients about research opportunities. However, another 70% were exploring or planning to use such tools [9]. Trials may consider using a combination of electronic methods for the majority with traditional mail for a subsample, but future research is needed on this topic.

In conclusion, this study demonstrates that the linkage of data from EHRs at multiple institutions can be a useful tool to gather large study samples for research. This study was novel in that we were able to gather data without sharing patient information outside of the home institution, which may provide a helpful example for future researchers required to do so. Also, this study focused on caregiver responses regarding their children, a population that has not been included in other research regarding the use of EHRs for research. Further research into how to maximize these new research opportunities is warranted.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Description of GPC funding.

[PDF File (Adobe PDF File), 847KB - resprot_v8i3e11148_app1.pdf]

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Abbreviations

BMI: body mass index
CDRN: Clinical Data Research Network
EHR: electronic health record
GPC: Greater Plains Collaborative
HMRFS: Health and Medical Research Family Survey
i2b2: Integrating Informatics from Bench to Bedside
IRB: Institutional Review Board

USPS: United States Postal Service

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Protocol

Identification of Motor Symptoms Related to Parkinson Disease Using Motion-Tracking Sensors at Home (KÄVELI): Protocol for an Observational Case-Control Study

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Abstract

Background: Clinical characterization of motion in patients with Parkinson disease (PD) is challenging: symptom progression, suitability of medication, and level of independence in the home environment can vary across time and patients. Appointments at the neurological outpatient clinic provide a limited understanding of the overall situation. In order to follow up these variations, longer-term measurements performed outside of the clinic setting could help optimize and personalize therapies. Several wearable sensors have been used to estimate the severity of symptoms in PD; however, longitudinal recordings, even for a short duration of a few days, are rare. Home recordings have the potential benefit of providing a more thorough and objective follow-up of the disease while providing more information about the possible need to change medications or consider invasive treatments.

Objective: The primary objective of this study is to collect a dataset for developing methods to detect PD-related symptoms that are visible in walking patterns at home. The movement data are collected continuously and remotely at home during the normal lives of patients with PD as well as controls. The secondary objective is to use the dataset to study whether the registered medication intakes can be identified from the collected movement data by looking for and analyzing short-term changes in walking patterns.

Methods: This paper described the protocol for an observational case-control study that measures activity using three different devices: (1) a smartphone with a built-in accelerometer, gyroscope, and phone orientation sensor, (2) a Movesense smart sensor to measure movement data from the wrist, and (3) a Forciot smart insole to measure the forces applied on the feet. The measurements are first collected during the appointment at the clinic conducted by a trained clinical physiotherapist. Subsequently, the subjects wear the smartphone at home for 3 consecutive days. Wrist and insole sensors are not used in the home recordings.

Results: Data collection began in March 2018. Subject recruitment and data collection will continue in spring 2019. The intended sample size was 150 subjects. In 2018, we collected a sample of 103 subjects, 66 of whom were diagnosed with PD.

Conclusions: This study aims to produce an extensive movement-sensor dataset recorded from patients with PD in various phases of the disease as well as from a group of control subjects for effective and impactful comparison studies. The study also aims to develop data analysis methods to monitor PD symptoms and the effects of medication intake during normal life and

outside of the clinic setting. Further applications of these methods may include using them as tools for health care professionals to monitor PD remotely and applying them to other movement disorders.

Trial Registration: ClinicalTrials.gov NCT03366558; https://clinicaltrials.gov/ct2/show/NCT03366558

International Registered Report Identifier (IRRID): DERR1-10.2196/12808

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KEYWORDS

Parkinson disease; movement analysis; gait; wearable sensors; smartphone; home monitoring; mobile phone

Introduction

Parkinson disease (PD) is a progressive and degenerative disorder of the central nervous system, affecting both the physical and psychological health of the patient [1]. James Parkinson described the physical symptoms of the disease in 1817 as "the shaking palsy" [2], naming rest tremor as one of the distinguishing features. Rest tremor, rigidity, and bradykinesia (ie, the slowness of movement) are considered the main motor indicators of PD [1]. In addition to these motor symptoms, PD may affect the cognitive ability by causing dementia and indirectly affecting the mental health by increasing the risk of depression [1]. In recent years, nonmotor manifestations of PD have been given more recognition, and updates in the diagnostic criteria have been made to systematize the diagnostic process [3].

Motor symptoms are caused by the accumulation of alpha-synuclein protein in the central nervous system and the loss of dopaminergic neurons, thus reducing limb movement and control of the body. The symptoms usually start asymmetrically as a rest tremor or rigidity in one of the upper or lower limbs. The symptoms degrade the physical condition and decrease movement, thus affecting the quality of life. [1] In clinical practice, the symptoms are evaluated on a visual basis, but several studies have used wearable sensors and smartphones to identify the symptoms such as tremor [4-6], freezing of gait [7-8], and dyskinesia [9-10]. Although the symptoms can be identified visually, wearable sensors provide the possibility to monitor the patient remotely and collect more quantifiable data of the progression of symptoms. To our knowledge, there are two medical devices for monitoring of PD: The Personal KinetiGraph system for measuring bradykinesia, dyskinesia, tremor, and sleep [11-12] and the Kinesia Technology [13] for measuring tremor, dyskinesia, and mobility.

The diagnosis of PD is based on an interview, a physical examination, and an evaluation of the medical history of the patient by a physician. The consulting neurologist confirms the neuropathological indicators of the disease and rules out other conditions with similar manifestations using imaging and laboratory tests. If clinically needed, the symptoms are suppressed by prescribing dopaminergic drugs after the PD diagnosis is confirmed. When the disease progresses, a variety of medications and different therapy techniques must be used to help with the symptoms. [14] Patients visit their neurologists to adjust their medications, while control visits are organized constantly throughout the progression of the disease.

There are three symptomatic states in PD that depend on the level of medication. (1) The "Off" state implies that the dopamine level is too low in the central nervous system, thus increasing the cardinal features of PD: tremor, slowness, and rigidity. (2) The "On" state is the optimal dopamine level in the central nervous system, which implies very little or no sign of the disease, depending on how much the disease has progressed. (3) The overmedicated state is a hyperkinetic state in which the dopamine level is too high. This causes dyskinetic movements, fast walking and movements, and dystonic changes in the posture or limbs. [15] The effect of the medication is fast, but it may also wear off fast, before taking the next dose.

There are several challenges associated with diagnosing and monitoring PD with the current clinical practice. Clinical heterogeneity complicates the diagnosis because the patient may have a variety of symptoms of varying intensity and timing [14]. The symptoms present during the clinic appointment may not reveal all of the issues that are present at home, and the ability to cope independently may vary substantially between the On and Off states. On the other hand, prescribing the right dose of medication and scheduling doses to prevent Off states is challenging. Sudden fluctuation of On/Off states may be recognizable with wearable sensors that have automated algorithms [16]. To handle this challenge of recognizing fluctuations, remote monitoring at home would help health care professionals prescribe medication, and with complicated PD, it would help decide the optimal timeframe for secondary, invasive PD treatments such as deep brain stimulators or intraduodenal levodopa infusions.

In addition to the previous studies on identifying motor symptoms and current medical devices, we aim to build an affordable remote monitoring system using patients' own devices, allowing long-term monitoring with minimal effort to the patient. The system is developed based on the findings from the data-collection process and future studies. This study is an observational case-control study that aims to collect a dataset from patients with PD and healthy controls by measuring their movements during daily life, using a smartphone and wearable sensors. The primary objective of the data analysis is to determine if PD-related motor symptoms can be detected and classified based on inertial signals recorded at home. Motor symptoms could also be used to determine whether the subject is in an early or progressed stage of the disease. The secondary objective is to distinguish changes in motor symptoms after a dose of the medication is taken. These changes should be visible with patients having distinct "On" and "Off" states in their motor symptoms. Home monitoring of patients with PD and automated data analysis could help health care professionals

validate the level of motor symptoms and monitor the effects of medication. The long-term goal is to develop an affordable and easy-to-use solution for remote home monitoring of PD.

Methods

Inclusion and Exclusion Criteria

The inclusion criterion for the study group is the diagnosis of PD according to the International Classification of Diseases-10 code G20 [17]. All subjects were recruited from the Satakunta region in Finland. The common inclusion criteria for both the study and control groups were minimum age of 30 years, ability to walk at least 20 steps unassisted (use of assistive devices such as a walking stick were allowed), and no deep brain stimulation therapy during the study. In addition, the subject must not have been diagnosed with diseases causing symptoms similar to PD, such as multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, Lewy body dementia, or parkinsonism induced by a dopamine antagonist drug (ie, an antipsychotic drug such as metoclopramide). In addition, all subjects were required to speak and write fluent Finnish.

The control subjects are not specifically age matched to the patients, since both groups are recruited and studied at the same time and we aim to maximize the number of participants in both groups. However, recruiting control subjects from the family members of patients, for example, partners, balances the age distribution. Medical background information is collected from both groups to record conditions that affect the walking skills.

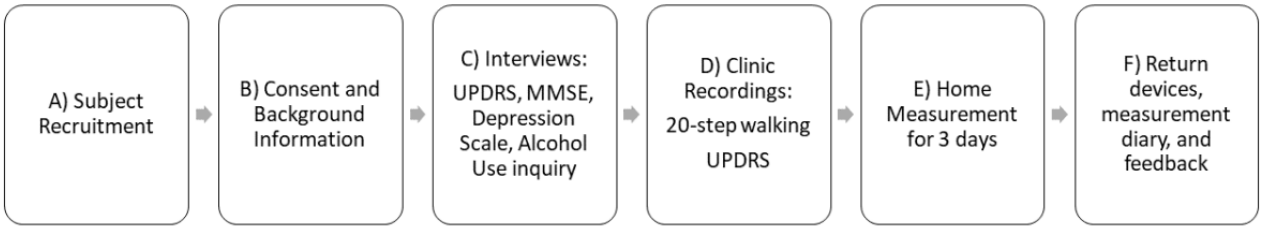
Study Design

A study sample of 150 subjects will be recruited, of which 100 will be patients with PD and 50 will be healthy controls. Approximately 50 of the patients with PD will be in an early stage of the disease and the other 50 will be in a progressed stage of the disease. This classification is based on the modified Hoehn and Yahr Staging of PD [18], where patients with a score of 0-2 are considered to be in the early or mild stage of the disease, and patients with scores of 2.5-5 are considered to be in the progressed or more severe stage of the disease. Both the study and control groups go through the same measurement protocol, including a clinic visit with questionnaires and tests and a home measurement for 3 consecutive days. The home measurement period aims to record data showing short-term changes in walking patterns related to the On/Off state changes or wearing-off effect of medication. In addition, the period can be used to evaluate the subjects' physical activity at home. Figure 1 presents the study protocol.

When a subject has been recruited, the study protocol begins with an appointment with a physiotherapist at Satakunta Central Hospital in Pori, Finland, or another appropriate location in the Satakunta region. First, the physiotherapist interviews the subject and collects his/her background information, diagnoses, medical histories, and current medications. Thereafter, the subject and physiotherapist fill in the structured questionnaires together. All the questionnaires were selected from official Finnish translations. The validated Finnish versions of the tests used in this study include the Alcohol Use Inquiry, C version [19]; the Depression Scale [20] to determine depressive symptoms; the Mini-Mental Status Examination [21] to determine the level of global cognition; and the Unified Parkinson's Disease Rating Scale (UPDRS) [22] to determine the severity of PD symptoms. The UPDRS examination includes both interviews and physical examinations performed by the physiotherapist. The subject also performs a 20-step walking test while wearing all the sensors in addition to the physical examination performed during the UPDRS test [23]. During this 20-step walking test, the subject walks straight at his/her own pace for 20 steps in a hallway. The physiotherapist counts the steps silently and asks the subject to stop walking after 20 steps. The subjects do not count their steps, since rhythmic aids may help patients with PD to walk more normally. The timing of the previous PD medication is recorded for reference.

After the appointment at the clinic, the subjects wear the sensors for 3 consecutive days during their daily lives. The sensors are not worn during sleep or while showering or swimming. During these 3 days, the subject registers the intake time of all PD medications in a smartphone app as well as in a paper diary format. This manual recording was added, since the patients were having problems using the medication registration button despite the simple user interface. The double registration process ensures that medication intake is recorded as accurately as possible. The subjects also record other events, such as falls and other adverse effects, and feedback in the diary.

Figure 1. The study protocol consists of six phases, all of which are completed by both patients and control subjects. MMSE: Mini-Mental Status Examination; UPDRS: Unified Parkinson's Disease Rating Scale.



Subject Recruitment

This study recruits subjects through two routes. In the first route, patients are recruited from Satakunta Central Hospital. These subjects are outpatients who visited the hospital due to PD in the past 5 years. The study physiotherapist sends an informational letter to the subjects and follows up by phone 1 week later. The physiotherapist introduces the study and asks if the patient is willing to participate. If the patient is willing to participate, the physiotherapist sets up an appointment at Satakunta Central Hospital.

In the second route, the physiotherapist and the responsible investigator (neurologist) visit local PD communities in the Satakunta region and give lectures on the study and its intentions. After the presentation, the patients and their family members (partners) have the opportunity to sign up for the study in either the study or control groups. If many volunteers sign up, the physiotherapist may organize appointments at clinics in these locations to minimize travel costs and effort from the patients.

If the study cohort is incomplete after these recruitment processes, an advertisement is published in the local newspaper, as well as the Satakunta Central Hospital newsfeed, to inform potential subjects about the study and ask for participation. Hospital staff and the research consortium were recruited as the control group, in addition to the family members of the study subjects.

Since the study is solely based on recruiting volunteers, there is a risk of some bias in the study cohort, both amongst patients and controls. It is difficult to recruit subjects with a lot of health problems or with very severe PD symptoms. For example, subjects with depression or severe cognitive issues may not want to participate, even if their physical condition is appropriate for the study. However, our aim is to include all the volunteers fulfilling the inclusion criteria into the study and consider the properties causing bias in the analysis phase.

Roles of the Research Staff in Data Collection

The physiotherapist involved in this study is a trained clinical physiotherapist who works with neurological patients in the hospital. The physiotherapist is responsible for contacting the subjects, scheduling appointments, conducting measurements, instructing the subjects to use the devices, and cleaning the measurement devices after each use. The subjects may contact the physiotherapist as well as the researchers to provide more information and ask for help when using the devices. All the devices are provided by the research group. Therefore, the subjects do not need their own smartphones or other devices in the study. The study smartphone is only used for data collection and not for any personal use.

A researcher at Tampere University in Tampere, Finland, assists in conducting the measurement protocol at the hospital and monitors the operation of the data-collection system. The data-collection system consists of sensors that measure the data and a smartphone that buffers and sends data through an internet connection to a server located at Tampere University, where the researcher inspects the data on a personal computer. The researcher assists the physiotherapist with the devices, if any problems occur.

Ethical Approval and Trial Registration

This study is conducted according to the Ethical Principles for Medical Research Involving Human Subjects, as stated in the 2013 revised version of the 1964 World Medical Association Declaration of Helsinki. All information collected by Tampere University is coded and does not contain identifying information. The identifying data are held appropriately in a locked storage facility at Satakunta Hospital District, and only the study physiotherapist and the responsible investigator are allowed to view them.

A favorable statement was obtained for the study protocol from the Ethics Committee of the Hospital District of Southwest Finland in Turku [24] on October 24, 2017 (ETMK 101/18012017). Minor changes to the study protocol were made based on tests of the measurement protocol with 10 pilot subjects. These changes were approved by the ethics committee in April 2018. For example, the UPDRS test was extended to the healthy control group. The changes to the measurement protocol are further discussed in the Results section of this paper.

In addition to the ethical committee statement, the National Supervisory Authority for Welfare and Health (Valvira) in Helsinki, Finland, approved the study in April 2018 (identification number 394-2018).

The KÄVELI study is registered at ClinicalTrials.gov (NCT03366558) [25].

Sensors Used in the Study

Data are collected using three types of sensors: built-in inertial sensors in a mobile phone (Nokia 6, HMD Global Ltd, Finland) provided by the study, a wrist-worn wearable device measuring a gyroscope signal (Suunto Movesense, Suunto Ltd, Finland [26]), and a smart insole measuring ground reaction forces in the feet (Forciot smart insole, Forciot Ltd, Finland [27]). The primary measurement device is the smartphone, since it is used both in the clinic and at home for all subjects. The other two devices are used mainly in the clinic, but the Forciot insole is also tested in home settings with a few subjects who were comfortable using the additional device.

The subjects also registered their PD medication intake in a smartphone app set to the home screen of the phone. However, to ensure that the medications are correctly registered, the subjects are asked to write their PD medication intake in a manual diary format as well. Figure 2 presents the sensors used in this study.

The smartphone contains built-in sensors for acceleration, angular velocity, and orientation, which are used to measure the movements of the phone while it is carried by the subject, thus providing information about their movement dynamics.

Figure 2. Sensors used in the study: Movesense smart sensor (upper left corner), Forciot smart insole (upper right corner), and Nokia 6 smartphone (lower left corner).

While the subject is wearing the device on the waist, the acceleration describes the changes in velocity and orientation of the subject in the linear direction, and cyclic movements such as walking are visible as cyclic changes in the acceleration. The gyroscope describes the rate of changes in orientation in relation to the center of the phone. The orientation signal describes the orientation of the phone in three dimensions, in which the phone orientation can be checked. This signal helps to check if the subject accidentally wears the phone in a different position than instructed.

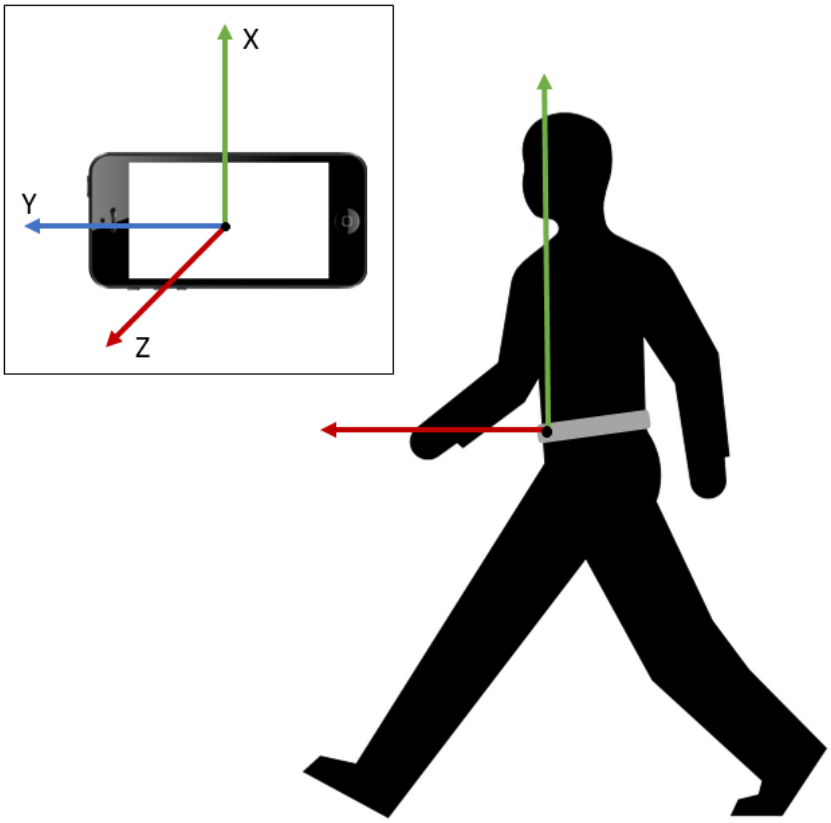
These sensors are available in most smartphones and are used, for example, in mobile games, compasses, and step counters. The smartphone is located in a waist-worn small bag in front of the stomach. Use of the bag ensures that the device can be worn regardless of the type of clothing; thus, no pockets are needed. The placement was set in front, so that it would not disturb the subject when sitting or lying down. The phone is oriented horizontally with the positive X-axis facing upward and the positive Z-axis facing forward. Figure 3 presents the phone's orientation and location.

The data recorded by the sensors are further used to classify the subject's walking patterns. We selected the Android 8–based Nokia 6 smartphone for data collection because of its ability to effectively disable all power-management settings. This is an important feature to successfully collect long-term data. The instantaneous sampling frequency of the sensors varies between 50 Hz and 100 Hz due to implementation of the data-collection framework. All the signals measured with the smartphone are resampled to 100 Hz during signal processing. The measurement ranges for the accelerometer and the gyroscope are ±16 g and ±34.9 radians/second, respectively, and their resolutions are 14 bit and 16 bit, respectively; in addition, their internal peak-to-peak noise level ranges were found to be roughly ±1 mg and ±0.005 radians/second, respectively.

Suunto Movesense, manufactured by Suunto Oy [26], is a heart rate– and movement-monitoring sensor worn on the wrist in this study during the physical examination of the UPDRS. The device communicates with the mobile phone using Bluetooth low energy, and the sampling frequency of Movesense is 52 Hz. The measurement range is ±34.9 radians/second. The data provided by this sensor can be used, for example, to measure the rest tremor and detect attenuated arm swing during walking, which is a typical symptom in PD.

The Forciot smart insole, manufactured by Forciot Oy [27], is a pressure-sensing insole prototype that includes 23 sensing elements distributed, so that they cover the whole area of the sole with a sampling frequency of 50 Hz. The smart insole also calculates the applied total force by integrating the data of the individual sensing elements. One insole is used during the UPDRS examination at the clinic appointments. Two subjects also used a pair of insoles during the home measurements. Thus, the insole provides information on the walking pattern and pressure distribution in the feet.

Figure 3. The orientation of the smartphone when worn on the waist. The X-axis measures vertical movement, the Y-axis measures horizontal movement in the lateral direction, and the Z-axis measures movement in the posterior-anterior direction. The phone is worn in a bag on the waist and inserted correctly on the stomach side with the screen out and the right side up.



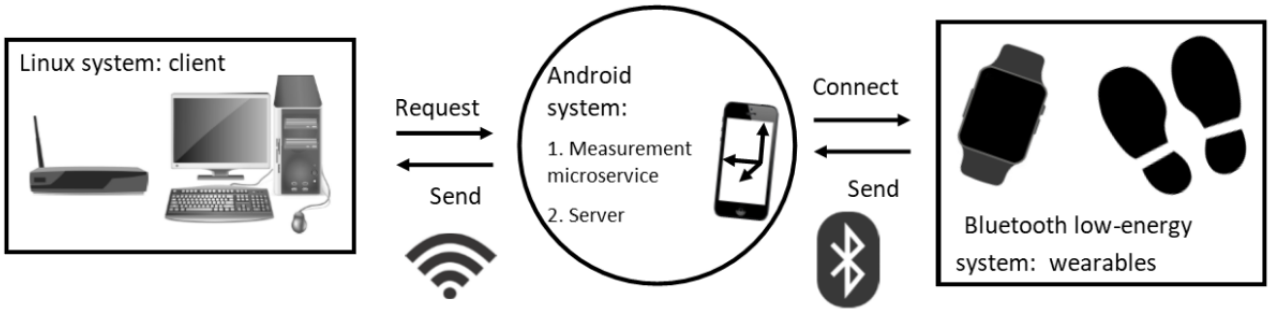
Data Collection and Management

This study introduces a novel perspective on the mobile microservice architecture in a data-transfer system [28]. In this system, all sensors and wearable devices act as independent services with their own architecture. However, with a common interface between the server and the services, data can be collected simultaneously and asynchronously. In fact, the entire front-end, back-end concept is flipped because the smartphone acts as a server behind the simple user interface, and the personal computer acts as a client who is requesting information according to the data-collection frequency set by the personal computer user. Figure 4 presents an overview of the data-collection system.

The smartphone worn by the subject collects information from all the sensors and stores it temporarily. The size of the buffer on the phone is adequate for storing data of up to 1 hour, but after that time, the system will start to overwrite the data. The wearable devices are paired with the smartphone in the beginning of a recording, but after a momentary loss of connection, they will reconnect automatically. The personal computer for data collection acts as a client and requests information from the smartphone via an internet connection by using the smartphone's internet protocol address. In this study, the frequency for requesting the signals is 5 minutes. The client receives the information via the internet connection and stores the data in text files. Several subjects can be measured simultaneously because each subject only requires one smartphone and the wearable devices. The personal computer for data collection can also save several data-collection streams simultaneously within the Linux operating system.

There are two approaches to securing information during data transfer: (1) encrypting the information before sending it through an unsecured connection and (2) building a secure connection between a smartphone and a router that cannot be accessed by any internet protocol addresses other than the ones used by the data-collection smartphones and the client's personal computer. The former approach was tested at the beginning of the study, and the data were collected successfully in an encrypted form. However, a secure connection improves efficiency during data management and signal processing, because the files are ready to use immediately after data collection. The second solution was also implemented and tested during the project in cooperation with a local telecommunications company. However, no identifying information is transmitted through the internet connection. The subject identification and smartphone are accurately linked manually before analyzing the data. This implementation will be more thoroughly discussed in future publications related to the data-collection system.

Figure 4. An overview of the structure of the data-collection system. The system consists of three independent systems: (1) a Linux system, (2) an android system acting as a temporary server, and (3) a Bluetooth low-energy system consisting of independent wearable devices.



This database will be granulized and compressed into a format that can be used in further analyses, including structuring the information, developing the metadata, and ensuring anonymity of the data. For example, rather than knowing the exact date of the measurement, only the time of the day and season will be recorded when analyzing walking habits.

Data Verification

Data verification requires confirming that the measured signals have the appropriate quality to accurately distinguish walking segments from other movements and to use the signals for further analysis. The possible issues faced during home or clinic measurements are also recorded and analyzed, including, for example, usability issues with the technology as reported by the participants or network issues leading to the loss of data. These analyses would confirm that there is an appropriate amount of high-quality data that is usable in machine learning applications. If any such problems are identified in the measurement setup, they will be fixed to ensure the quality of the data.

The collected signals are checked both visually and statistically to assess whether they contain the necessary information for the classification of different types of movements. A minimum sampling frequency of 50 Hz was required for the measurements conducted with the smartphone based on the previous studies presenting human walking under 10 Hz [29] and hand tremors in PD under 20 Hz [30]. The measurements will be discarded if they are below a 50-Hz sampling frequency. Suunto Movesense and Forciot use their own sampling frequencies of 52 Hz and 50 Hz, respectively.

Information is collected on how many files were successfully recorded during a 3-day measurement. Successful measurements are defined as those that are recorded and transferred correctly and have the appropriate sampling frequency. This information is used to monitor how well the measurement system functions when the subject is responsible for merely charging the smartphone and restarting it if the power runs out. The performance analysis includes battery life, possible network issues, and usability issues. These properties are studied and used in further development of the measurement system.

Data Analysis

Methods for data analysis are developed and structured based on a data-analysis pipeline. This pipeline includes data preprocessing, walking detection, calculation of features related to changes in walking, and feeding the features into a machine-learning system to classify the symptoms and subjects. The classification results and the performance of the classifier are then analyzed. The main features of data analysis include the identification of patients with PD from healthy subjects based on sensor data and prediction of UPDRS scores from the sensor data. The long-term target is to build an automated classification system that could support home monitoring by using machine learning methods. All the data analysis will be done in Python 3 (Python Software Foundation, Wilmington, DE) and MATLAB (The MathWorks, Inc, Natick, MA).

We will be using a data-driven approach to analyze and compare a large number of features calculated from the signals of the different sensors. However, we will consider possibilities to combine the information of different sensors to define such features or parameters that are likely relevant to PD, for example, the amount of arm swing during walking. The incompleteness of the data set (wrist and insole sensors not included in all the recordings), however, limits the use of parameters requiring combining sensor information. This will be discussed in future publications on the data analysis.

The preprocessing phase includes the signal-processing steps that are required before the signals can be used in further data analysis. The signals are resampled to obtain a constant sampling frequency; simultaneously measured signals are aligned to have the same starting and ending time; and, if necessary, the signals can be filtered with a basic low- or high-pass filters.

An accurate walking-detection algorithm and careful selection of machine-learning features are important when developing the data-analysis pipeline. Activity-detection algorithms have already been developed by other research groups, for example, based on the mean amplitude deviation [31-32], which is more thoroughly defined in another previous study [33]. An algorithm based on the existing literature will be developed and implemented during this study. The walking-detection algorithm may extract either walking segments or individual steps. When recognizing the walking patterns from home data, we may use the 20-step walking tests as a personal reference of the subject's walking style. Walking detection from the 20-step tests is rather easy, since the signals only contain walking or standing. Walking detection will be thoroughly analyzed and discussed in future publications considering the analysis of data from home measurements.

The selection of features is also important when building a machine-learning system for health care use. The features should describe real physiological changes in the walking patterns; for example, if the patient is in the On state with good balance in the medication, his/her walking is classified as better than the same patient without the medication (Off state). Although On and Off states are not specifically defined in this study, we aim to recognize the differences before and after taking the medication. Features can be selected with a statistical approach, for example, by applying the minimum Redundancy Maximum Relevance algorithm [34] or the theoretical understanding of PD to choose features related to the physiological changes in the patients. Features may include both statistical features of the signals such as mean, median, or SD, or they can be defined from the physiology and be based on traditional features used in gait analysis, such as step length or speed.

The subjective UPDRS classification performed by the physiotherapist is used to test the classification of the subjects from the 20-step walking tests. The UPDRS score can be used as the true label of the subject's current state, and the walking tests are classified into several groups identifying the severity of motor symptoms in walking. In home measurements, the UPDRS score defined at the clinic may be used to test whether the classification result before taking the PD medication differs from that soon after taking the medication. Alternatively, unsupervised learning methods such as clustering approaches may be used to study whether there are differences in the feature values before and after taking the medication.

The classification phase includes applying different machine learning classifiers to study the most feasible method for classifying the symptoms and changes in symptoms related to medication intakes. For example, a support vector machine [35] and random forest [36] will be used to classify walking patterns. Classification performance is evaluated by a confusion matrix and the metrics related to it including accuracy, sensitivity, specificity, and the receiver operating characteristic curve. Other measures may be added to evaluate the performance more thoroughly.

The data analysis aims to develop methods to answer the following hypotheses: (1) Can we distinguish patients with PD from healthy controls by using wearable sensors and machine learning classifiers? (2) Can we assess the severity of symptoms before and after medication intake? These key hypotheses may be further specified or expanded in further analyses. These methods, combined with the novel data-collection method, can be further developed into a home-monitoring system for health care professionals and neurological patients.

Results

Data collection began in March 2018 by testing the measurement protocol with 10 subjects. These subjects will be included in the final study sample. Minor improvements were made to the measurement protocol based on the first subject's recordings in the clinic and in-home measurements. The changes included (1) the double registration of medications, as discussed in the Methods section of this paper, and (2) the decision to conduct the UPDRS questionnaires and tests with the control subjects, even though they were not expected to have PD symptoms.

All three measurement devices were planned to be used in the home measurements, but due to the technical requirements of Suunto Movesense [26] and Forciot [27] insole, they were not implemented in the protocol for data collection at home. Forciot [27] insoles were tested with subjects for 1 day prior to the 3-day home measurement. Two subjects were tested during the study. This is because the insoles are operated by a battery, which only has a lifetime of 24 hours. In addition, Suunto Movesense [26] was connected using a Bluetooth connection, and the connection was not sufficiently stable to be used at home. Therefore, the device was only used in the clinic measurements.

After the pilot study, the capacity of simultaneous studies increased from 3 to 10. Most of the subjects were recruited from the PD community visits where there was a lot of interest to participate in the study. A secure internet connection was set up for data transfer by building a private mobile network for the research project in cooperation with a local telecommunications company. This network was tested and implemented in August 2018. After the update, encryption of the measurement data was not needed because the network was only accessible by devices in the study. By the end of December 2018, we collected data from a total of 103 subjects, 66 of whom are patients with PD and 37 are control subjects. Subject recruitment and data collection will be continued in the spring of 2019.

Discussion

This paper describes the research protocol for a PD-monitoring study involving the use of smartphones and wearable sensors, also known as the KÄVELI project. This study aims to gather a dataset of 150 subjects to develop methods for monitoring PD-related motor symptoms in daily life. The user-friendly measurement setup is enabled by a data-collection system that consists of several microservices that automatically collect movement information when a subject wears the measurement device and registers their PD medication intake manually and through a smartphone app. There has been an increasing trend in studies toward home monitoring of PD with, for example, smartphones [7,23,37-39] and other wearable sensors [4,8,37,40-42]. In addition, several research groups have developed algorithms for recognizing various types of movements such as walking, running, and climbing stairs [31,32,43-45]. Based on the literature, there is a potential for monitoring PD with wearable solutions and machine-learning principles. These principles are applied in order to recognize the descriptive features of walking segments as well as to determine what sensors are required to achieve accurate recognition of the symptoms and evaluate their severity. The selection of correct features is important for linking the results to real physiological changes that are evident in the subjects' walking.

Some mobile health platforms have been proposed to monitor PD patients during preset tests, such as PD Dr [6] and PD_manager [46], both of which have been tested on a relatively

small set of patients with PD. HopkinsHD [47] is collecting data from free-living people and has been tested on a set of 226 subjects, both control subjects and patients with PD. These platforms have resulted in indications that home monitoring of PD patients is feasible. Our aim is to provide a platform that is suitable for long-term monitoring and uses the patients' own smartphones or very affordable wearable sensors.

Most of the previous studies concentrating on the recognition of PD symptoms with wearable sensors have been conducted with relatively small datasets (10-50 subjects in total), which are feasible for proposing new methods in data collection or analysis, but not enough to validate the system with a larger variety of subjects. Some studies, however, have recruited more subjects [23,37,47]; these studies have collected larger datasets of several hundred subjects. Larger studies will be needed to validate systems before implementing them into a commercial product. The dataset collected in the KÄVELI project will be valuable in the investigation of PD motor symptoms in a quantitative manner, whereas the present clinical monitoring of PD is based on the subjective information provided by the patient and clinical observations by a neurologist or physiotherapist [25]. Despite the opportunities and new innovations presented by wearable sensors and machine learning, home monitoring has several practical challenges that must be evaluated and solved before they can become a common part of clinical routines. First, independent use of technological devices may create difficulties among the elderly, and acceptance of technology takes time and special effort in usability. Second, even if the technology itself is not new to the patients, severe motor symptoms and Off states combined with cognitive and memory disorders may complicate the registration of medication intakes or other tasks given to the patient [48]. Finally, even though home monitoring allows for measurements to take place in real-life situations that provide a more extensive view of symptoms, ensuring adherence to the measurement protocol is impossible outside of the clinical environment. For example, subjects can be reminded to register their medication intake, but they may forget to register it anyway, or the placement of the device might be changed unexpectedly.

The KÄVELI project's measurement protocol aims to minimize these challenges by developing a user-friendly interface for the smartphone that registers medication intake and by providing written and spoken instructions for the use of all devices included in the study. The level of instruction also aligns with the subject's confidence with technology. This is assessed by a question in the background interview: "How confident are you in using a smartphone?" which is also recorded in the study material. In addition, the physiotherapist can be reached by phone for further instruction if any challenges occur during the measurement period.

Despite the simple user interface of the smartphone (only one visible button for the medication recording), some subjects have had issues using the smartphone. Therefore, medications were also recorded in a paper format, which led to extra work for the subjects. This limitation, as well as any adverse effects or usability issues, will be recorded and considered in the development of the measurement system.

One potential limitation to the study is the recruitment of control subjects. It may be difficult to collect a dataset with a variety of mobility skills and still match the age group of patients with PD. We have recruited control subjects from among the patients' family members, but this might also be considered a limitation. These challenges must be addressed accordingly when carrying out the study.

In conclusion, this study will provide quantitative information on PD motor symptoms and their statistical properties. The collected dataset will be used to develop algorithms and create tools for remote monitoring of PD progression by physicians and to assist with adjusting the medication.

Acknowledgments

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Conflicts of Interest

None declared.

Authors' Contributions

MJ contributed substantially to the writing of the manuscript as well as data collection from the Android server and data analyses. JP was the principal medical investigator and medical supervisor of the study. JR was the principal technical investigator and project manager in the KÄVELI project. JP, JR, SM, AH, and HN designed the measurement protocol and the documentation for the ethical committee evaluation. They also contributed to the writing and commented on the manuscript. Furthermore, JP and JR implemented and tested the measurement protocol in the clinical setting. They also provided technical support during the measurements. AV contributed to the manuscript and provided academic supervision.

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Abbreviations

PD: Parkinson disease
UPDRS: Unified Parkinson's Disease Rating Scale

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Early Report

Concentric and Eccentric Pedaling-Type Interval Exercise on a Soft Robot for Stable Coronary Artery Disease Patients: Toward a Personalized Protocol

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Abstract

Background: Cardiovascular diseases are the leading causes of death worldwide, and coronary artery disease (CAD) is one of the most common causes of death in Europe. Leading cardiac societies recommend exercise as an integral part of cardiovascular rehabilitation because it reduces the morbidity and mortality of patients with CAD. Continuous low-intensity exercise using shortening muscle actions (concentric, CON) is a common training modality during cardiovascular rehabilitation. However, a growing clinical interest has been recently developed in high-intensity interval training (HIIT) for stable patients with CAD. Exercise performed with lengthening muscle actions (eccentric, ECC) could be tolerated better by patients with CAD as they can be performed with higher loads and lower metabolic cost than CON exercise.

Objective: We developed a clinical protocol on a soft robot to compare cardiovascular and muscle effects of repeated and work-matched CON versus ECC pedaling-type interval exercise between patients with CAD during cardiovascular rehabilitation. This study aims to ascertain whether the developed training protocols affect peak oxygen uptake (VO_{2peak}), peak aerobic power output (P_{peak}), and parameters of muscle oxygen saturation (SmO_2) during exercise, and anaerobic muscle power.

Methods: We will randomize 20-30 subjects to either the CON or ECC group. Both groups will perform a ramp test to exhaustion before and after the training period to measure cardiovascular parameters and SmO_2. Moreover, the aerobic skeletal muscle power (P_{peak}) is measured weekly during the 8-week training period using a simulated squat jump and a counter movement jump on the soft robot and used to adjust the training load. The pedaling-type interval exercise on the soft robot is performed involving either CON or ECC muscle actions. The soft robotic device being used is a closed kinetic chain, force-controlled interactive training, and testing device for the lower extremities, which consists of two independent pedals and free footplates that are operated by pneumatic artificial muscles.

Results: The first patients with CAD, who completed the training, showed protocol-specific improvements, reflecting, in part, the lower aerobic training status of the patient completing the CON protocol. Rehabilitation under the CON protocol, more than

under the ECC protocol, improved cardiovascular parameters, that is, VO_{2peak} (+26% vs −6%), and P_{peak} (+20% vs 0%), and exaggerated muscle deoxygenation during the ramp test (248% vs 49%). Conversely, markers of metabolic stress and recovery from the exhaustive ramp test improved more after the ECC than the CON protocol, that is, peak blood lactate (−9% vs +20%) and peak SmO_2 (+7% vs −7%). Anaerobic muscle power only improved after the CON protocol (+18% vs −15%).

Conclusions: This study indicates the potential of the implemented CON and ECC protocols of pedaling-type interval exercise to improve oxygen metabolism of exercised muscle groups while maintaining or even increasing the P_{peak}. The ECC training protocol seemingly provided a lower cardiovascular stimulus in patients with CAD while specifically enhancing the reoxygenation and blood lactate clearance in recruited muscle groups during recovery from exercise.

Trial Registration: ClinicalTrials.gov NCT02845063; https://clinicaltrials.gov/ct2/show/NCT02845063

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KEYWORDS

cardiovascular rehabilitation; concentric and eccentric exercise; high-intensity interval training; muscle oxygen saturation; near-infrared spectroscopy; peak oxygen uptake; ramp test; skeletal muscle power; soft robot

Introduction

Diseases of the cardiovascular system cause >4 million deaths annually in Europe, and coronary artery disease (CAD) is one of the most common causes responsible for approximately 1.8 million deaths [1]. According to the Swiss Federal Statistical Office, diseases of the cardiovascular system are the third most frequent cause of hospitalization and the most frequent cause of death in Switzerland [2,3]. The inflammatory process of atherosclerosis is the main cause of CAD [4]. Progression of the disease increases the risk of angina pectoris, myocardial infarction, and cardiac arrest.

According to the Swiss Heart Foundation, common risk factors for CAD are hypertension, hyperlipidemia, obesity, diabetes mellitus, smoking, and physical inactivity [5]. Various studies have shown that exercise reduces morbidity and mortality of patients with CAD [6-8]. Positive effects of exercise in patients with CAD include improved cardiovascular and muscular function, quality of life, and the reduction of depressive symptoms and psychological stress [9]. The molecular mechanisms on how exercise is beneficial for patients with CAD range from the normalization of endothelial dysfunction to vasculogenesis through endothelial progenitor cells [10]. Exercise is, therefore, recommended by leading cardiac societies as an integral part of cardiovascular rehabilitation [11].

The continuous low-to-moderate-intensity exercise was traditionally the training modality chosen for cardiovascular rehabilitation. Although this training method is considered to be safe and practicable and has almost no contraindications for stable patients with CAD, a growing clinical interest in high-intensity interval training (HIIT) has been recently developed for stable patients with CAD [12]; this type of training is characterized by high-intensity periods of exercise, which are alternated by rest or low-intensity periods [13]. In terms of improving the peak oxygen uptake (VO_{2peak}), HIIT has shown to produce superior outcomes compared with continuous low-to-moderate-intensity exercise in patients with CAD [14-16]. VO_{2peak} has shown to be an independent predictor of morbidity and mortality of cardiovascular diseases [17-19]. Therefore, it represents an important index when evaluating adaptations to exercise regimes during cardiovascular rehabilitation.

Often the training is performed on a cycle ergometer; thus, it mainly involves shortening (concentric, CON) muscle actions. However, lengthening (eccentric, ECC) muscle actions may be better tolerated by patients with CAD in clinical settings [20,21] because it can be performed with higher loads and lower metabolic cost than CON exercise [22-24], as shown by studies conducted on ECC ergometers [25-27]. Following such evidence, we have recently compared the cardiovascular and muscular adaptations to work-matched CON and ECC pedaling-type interval exercise of physically active and healthy subjects at an intensity being used during cardiovascular rehabilitation on a soft robot [28]; we found that indices of cardiovascular strain, such as VO_{2peak}, peak ventilation, peak cardiac output, and blood lactate (BL) values, were lower during ECC compared with CON exercise.

In this ongoing study, we developed a clinical protocol on a soft robot to compare work-matched CON with ECC pedaling-type interval exercise for patients with CAD during cardiovascular rehabilitation. This study aims to find out whether the developed training protocols affect VO_{2peak}, as well as aerobic muscle function (based on peak aerobic power output and muscle oxygen saturation), of patients with CAD during cardiovascular rehabilitation. We hypothesize that the CON and ECC protocol lead to distinct cardiovascular and muscular adaptations. This study presents preliminary data for cardiovascular and muscular adaptations to the CON and ECC exercise protocol in the first 2 patients with CAD.

Methods

Recruitment and Ethics

For the ongoing study [29], 10-15 patients for each experimental group are recruited by the Department of Cardiology of the University Hospital Zurich (Zurich, Switzerland). The study is approved by the Ethics Committee of the Canton of Zurich on March 23, 2015 (project number KEK-ZH-No. 2014-0319). All investigations were and will be conducted in accordance with the ethical standards of the Declaration of Helsinki of 1964.

Inclusion Criteria

Subjects who meet all the following inclusion criteria may be included in the study: aged between 20 and 70 years; stable coronary heart patients without ischemia; left ventricular ejection fraction >50%; drug therapy with angiotensin-converting enzyme inhibitors; VO_{2peak} of >86% of the medical target value; voluntary participation in the study; and written informed consent.

Exclusion Criteria

If one or more of the following exclusion criteria are met, subjects cannot be included in the study: relevant valvular heart disease; arterial hypertension (blood pressure at rest >140/90); arrhythmogenic cardiomyopathy; angiotensin-converting enzyme inhibitor intolerance; contraindication for ethical reasons; known or suspected noncompliance with the study plan; drug or alcohol disease; the inability of a patient to follow the study procedure (eg, owing to language problems, mental illnesses, and dementia); participation in another clinical study within the last 30 days prior inclusion and during the study; and other clinically significant comorbidities (cardiac arrhythmia, renal insufficiency, hepatic dysfunction, connective tissue disease—Marfan syndrome, Ehlers-Danlos syndrome).

Clinical Background of Patients

The first patient is a 63-year-old male patient with a known coronary 3-vessel disease. Twelve years ago, he underwent a coronary-aortic bypass surgery procedure with 3 grafts in the setting of an acute elevation of the ST-segment of the electrocardiogram, indicating a total occlusion of a coronary artery (ie, ST-elevation myocardial infarction) 1 month earlier. The left ventricular systolic function appeared normal. The last coronary angiography was 3 years ago where 2 drug-eluting stents were deployed. His cardiovascular risk profile comprises arterial hypertension, previous smoking (30 pack-years), hypercholesterinemia, diabetes, and positive family history for a premature cardiovascular disease. The arterial hypertension is currently well treated with combination therapy of perindopril, indapamide, and amlodipine. Diabetes did not necessitate treatment. Hemoglobin A1c, a long-term indicator of the quality of glucose control in diabetes, is currently 7.1%. Furthermore, he is on aspirin, bisoprolol, and rosuvastatin. Currently, he is free of symptoms; however, in light of secondary preventive aims, cardiovascular rehabilitation is warranted.

The second patient is a 62-year-old male who experienced an ST-elevation myocardial infarction 2 years earlier. The left anterior descending artery was successfully treated with 3 drug-eluting stents. On echocardiography, a normal left ventricular ejection fraction was noted; however, with regional wall motion abnormalities corresponding to the territory of the infarction (anterior and anteroseptal). His cardiovascular risk profile comprises a history of smoking (20 pack-years), treated hypercholesteremia, obesity (body mass index, 30 kg/m^2), and psychosocial stress. His present medication comprises aspirin, bisoprolol, lisinopril, and rosuvastatin.

Both patients are currently free of symptoms; however, in light of secondary preventive aims, cardiovascular rehabilitation in both patients is warranted.

Study Design

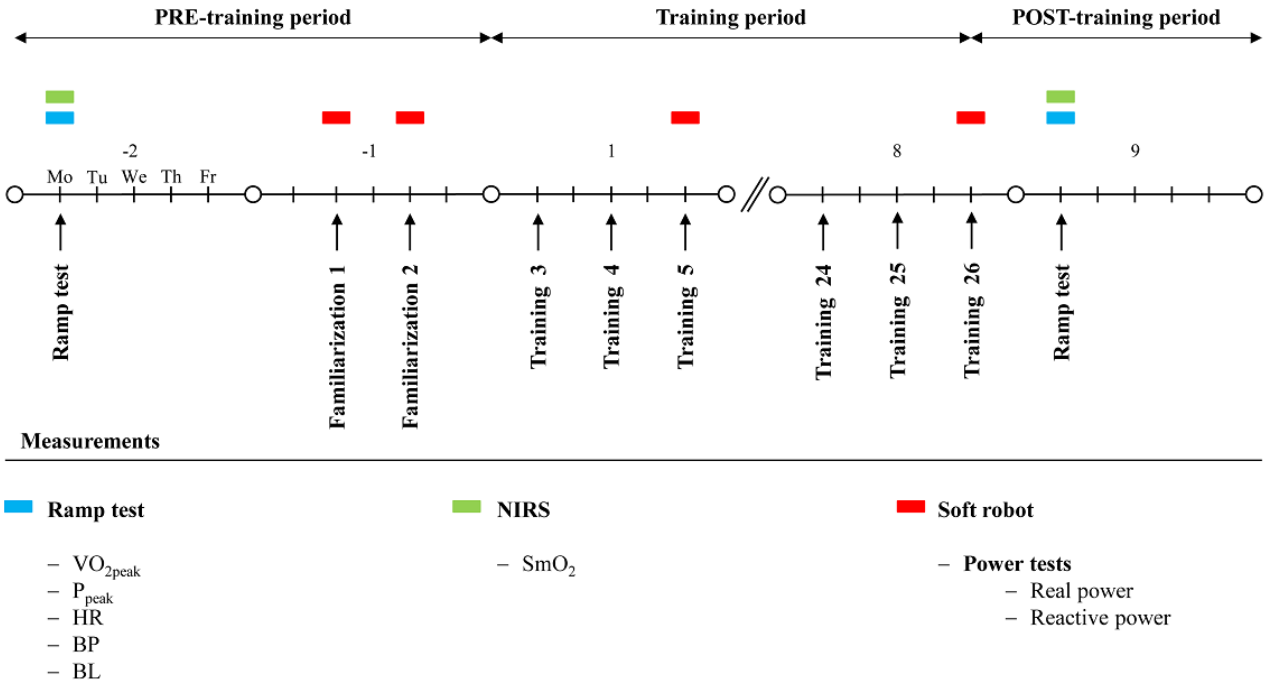
This study can be divided into 3 periods (Figure 1). The training on the soft robot is performed following either a CON or ECC protocol. Before the training period (PRE) during the first week, subjects complete a ramp test on a cycle ergometer to assess cardiovascular and aerobic muscular parameters. Subjects are then allocated into a CON or ECC group. In the second week, there are 2 training sessions to familiarize subjects with exercise on the soft robot. Before the 2 familiarizations and before every third training session, anaerobic muscle power is monitored using 2 power tests on the soft robot. Throughout the 8-week training period from the third to the tenth week, a pedaling-type interval exercise on the soft robot is completed, involving either CON or ECC muscle actions. The training is performed 3 times a week on nonconsecutive days. The training volume and intensity are progressively increased over the 8-week training period. In addition, the training load, training power, and positive or negative work are measured in all training sessions on the soft robot to monitor the training stimulus. After the training period (POST), subjects repeat the ramp test on the cycle ergometer to acquire POST values.

Ramp Test

The ramp test is completed in the exercise physiology lab of the Swiss Olympic Medical Center Balgrist Move>Med to determine cardiovascular parameters based on spiroergometry (VO_{2peak}, P_{peak}, heart rate [HR], and blood pressure) and SmO_2 based on near-infrared spectroscopy (NIRS). Before the ramp test, anthropometric data (height and body mass) of subjects are measured, and the body mass index is calculated. Subsequently, subjects fill out the Physical Activity Readiness Questionnaire. A resting electrocardiogram measurement is then performed and checked by a physician to ensure that subjects can conduct the ramp test. The exercise electrocardiogram during the ramp test is continuously monitored by the physician.

Subjects perform the test in an upright sitting position in an air-conditioned laboratory on an electrically braked cycle ergometer (ergoselect 200, ergoline). To determine VO_{2peak}, pulmonary gas exchange is measured with a spiroergometry measuring system (MetaLyzer 3B-R2, CORTEX Biophysics). The HR is measured continuously using an HR monitor (SUUNTO t6d, SUUNTO). Systolic and diastolic blood pressure (Sys BP and Dia BP, respectively) are measured on the upper right arm every 2 minutes using a BP monitor (Suntec Tango+, Suntec Medical Inc). In addition, BL is measured by collecting a sample of blood from the earlobe every 2 minutes using a lancing device (Akku-Check, Safe-T-Pro-Plus, Roche Diabetes Care) and a BL monitor (Biosen C-Line, EKF-diagnostic). Details on the NIRS measurement during the ramp test are provided in the following section.

Figure 1. The study design timeline. CON: concentric protocol; ECC: eccentric protocol; PRE: before training period; POST: after training period; VO_{2peak}: peak oxygen uptake; P_{peak}: peak aerobic power output; HR: heart rate; BP: blood pressure; BL: blood lactate; NIRS: near-infrared spectroscopy; SmO_2: muscle oxygen saturation.



The test protocol is modified as described elsewhere [30]. It starts with a 3-minute rest period, where subjects are asked to sit still on the cycle ergometer without pedaling, while maintaining a normal breathing pattern. Subsequently, subjects begin pedaling at an initial power of 25 W. The power is then increased in 5-W increments every 20 seconds (15 $W*min^{-1}$). Subjects are asked to keep a constant self-chosen pedal cadence throughout the test (optimally between 70 and 100 rpm). The test is stopped when subjects experience volitional exhaustion and are not able to maintain the target pedal cadence. After the stop, there is an 8-minute rest period.

Near-Infrared Spectroscopy

A muscle oxygen monitor (Moxy, Fortiori Design LLC), based on the NIRS technology, is used to measure SmO_2 during the ramp test noninvasively. The Moxy Monitor uses 4 different light sources covering wavelengths ranging from 630 to 850 nm and a modified Beer-Lambert law to perform measurements of SmO_2 [31]. SmO_2 refers to the percentage of hemoglobin and myoglobin that have bound oxygen of the investigated muscle [31].

The sensor is placed on the lower third of the *m. vastus lateralis* in the middle of the muscle belly on the left leg of subjects (Figure 2). The sensor is placed 10 cm above the upper lateral point of the patella along the axis of the leg. After the placement, the NIRS device is covered with an adhesive nonwoven fabric to protect it from ambient light. Prior to the placement, if necessary, the skin site is shaved using a disposable razor (Gallant, Dynarex) and cleaned with an alcohol swab (Webcol, Covidien). The sensor attachment is carried out using an attachment tape (Moxy Adhesive Attachments, Fortiori Design LLC). To protect the NIRS device from ambient light, it is covered with an adhesive nonwoven fabric (Hypafix, BSN Medical).

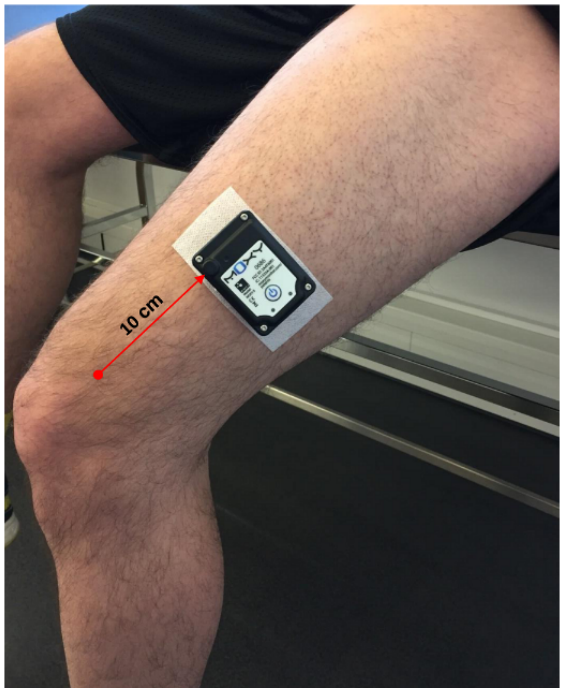
Soft Robot

Description of the Soft Robotic Device

A technical description of the soft robotic device (Allegro, Dynamic Devices, Zurich, Switzerland) to be used has been rendered before [28]. In brief, the Allegro soft robot is a closed kinetic chain, force-controlled interactive training, and testing device for the lower extremities. The Allegro device has a leg press layout and consists of two independent pedals and free footplates that are connected to pneumatic artificial muscles through shafts and levers. The seat has an adjustable height and a declinable backrest.

Force application to the pedals is controlled through the supply of pressurized air to the artificial muscles via a software-controlled actuation mechanism for each work cycle. The forces and speeds being produced by the artificial muscles, and those being applied by the user, are controlled during each cycle and displayed via a monitor. This visual feedback allows the user to tune its performance to the target workload through a work cycle. In addition to programmable exercise protocols, the Allegro is equipped with several fundamental test protocols allowing to asses motor accuracy, peak force, positive impulse, negative impulse, net impulse, and power for cyclic movements, reaction time, force control, and force steadiness.

Figure 2. Moxy monitor placement.



Pedaling-Type Interval Exercise

The supervised training is carried out at the Swiss Olympic Medical Center Balgrist Move>Med with the *Cardio Power Training* protocol on a soft robot (Allegro, Dynamic Devices). Subjects perform the training 3 times per week with a minimum rest period of 48 h between training sessions. The range of motion (ROM) and movement speed are audiovisually controlled through the integrated screen (Figure 3). Dotted yellow lines, the starting and end knee joint flexion angle and, thus, determine the ROM. During the work phase, the blue and red bar alternately move up and down and, thus, set the movement speed. Blue and red dots represent the current knee joint flexion angle of the left and right leg, respectively. Subjects aim to follow the 2 bars and adhere to the defined ROM. ROM is set to a knee joint flexion angle of 5°-90° and movement speed is 30 rpm. Each interval comprises 1-minute work and 1-minute passive rest period. Training volume and training load are progressively increased over the 8-week training period (Figure 3). For the CON group, the training intensity and volume are determined as follows. During the first 2 weeks, the external load is set to 65% of P_{peak} achieved on the cycle ergometer during the ramp test, and the training comprises 10 consecutive intervals. During the third and fourth week of training, the volume is increased to 15 intervals without changing the external load. During the fifth and sixth week of training, the external load is increased to 70% of P_{peak} while maintaining the volume. During the seventh and eighth week of training, the external load is further increased to 75% of P_{peak}. For the ECC group, the calculated training loads are multiplied by factor 1.4. To ensure that both groups perform the same external work, the ECC group completes only 7 and 11 intervals, respectively.

Power Tests

A *Real Power* and a *Reactive Power* test are performed on the soft robot to monitor anaerobic muscle power of the lower extremities. The power tests are performed before and after both familiarizations and every third training session.

The *Real Power* test is used to determine anaerobic muscle power during a simulated squat jump. The external load corresponds to 50% of the body mass per leg. Subjects are instructed to flex both legs until a knee joint flexion angle of 90°. With the command “Push,” subjects have to extend both legs as fast as possible. Figure 4 (left) illustrates the provided visual feedback.

The *Reactive Power* test is used to determine the skeletal muscle reactive power during a simulated countermovement jump. The external load corresponds to 50% of the body mass per leg. Subjects have to flex and extend both legs as fast as possible. The test is considered valid if both legs reach a knee joint flexion angle of 90°. Figure 4 (right) illustrates the provided visual feedback.

In Figure 4, the blue and red lines show the knee joint flexion angle of the left and right leg versus time. Green zone, the target knee joint flexion angle of 90°.

A previous characterization has indicated high reliability and comparability for values of force and power between soft robot-based measurements of simulated squat jumps and force-plate measurements during real squat jumps [28].

Figure 3. Top: Display of the audiovisual feedback to control training on the soft robot. Bottom: Timeline for the progressive increase of training volume and intensity for the CON and ECC protocol, respectively. ROM: range of motion; CON: concentric protocol; ECC: eccentric protocol; P_{peak}: peak power output (Source: Daniel Fitze, Dynamic Devices AG).

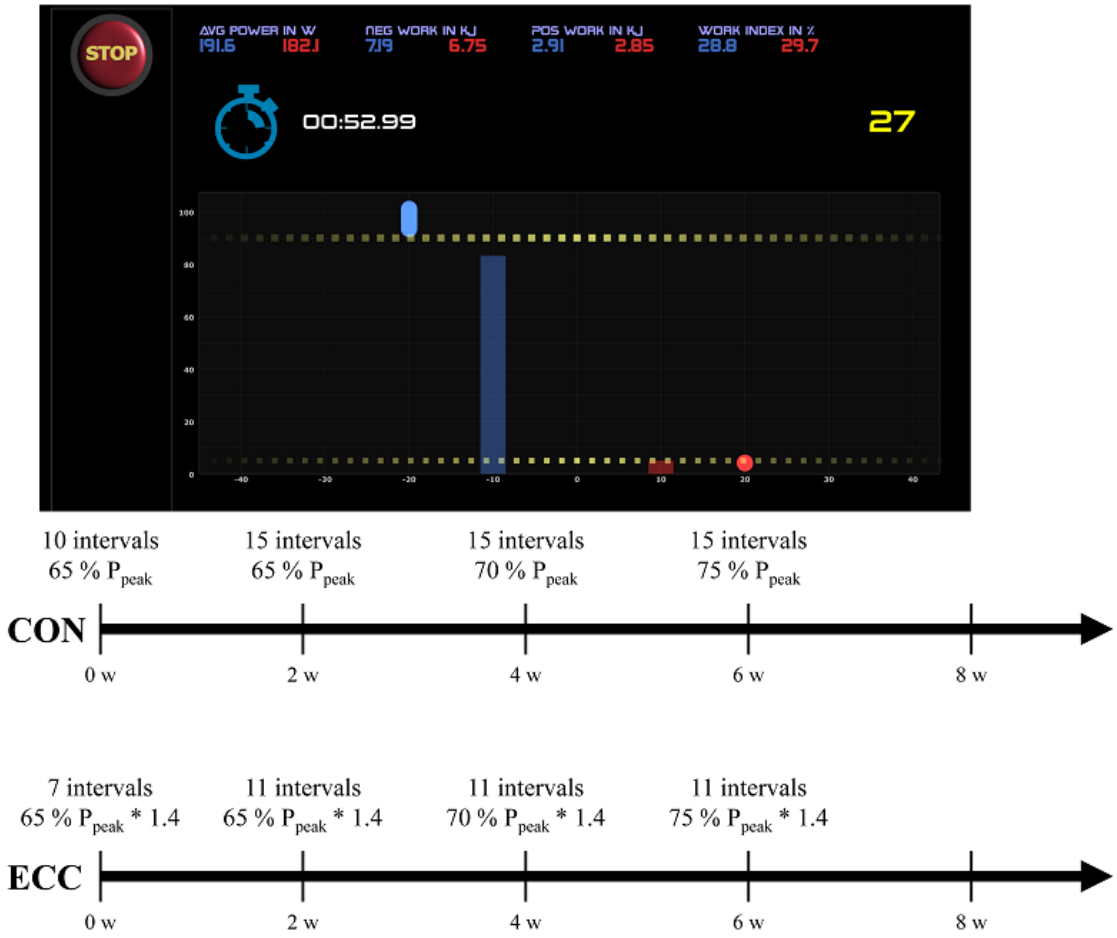


Figure 4. Left: Display of the visual feedback during the Real Power test on the soft robot. Blue and red lines, the knee joint flexion angle of the left and right leg versus time. Right: Display of the visual feedback during the Reactive Power test on the soft robot (source: Daniel Fitze, Dynamic Devices AG).

Data Analysis

Ramp Test

VO_{2peak} is defined as the highest VO_2 value averaged over a period of 30 s. P_{peak} corresponds to the peak aerobic power output on the cycle ergometer. Peak heart rate (HR_{peak}) represents the peak 5-s HR value. Peak systolic and diastolic blood pressure (Sys BP_{peak}, Dia BP_{peak}, respectively), and peak blood lactate (BL_{peak}) define the measured peak values achieved during the ramp test.

Near-Infrared Spectroscopy

Figure 5 shows a representative example of the SmO_2 course during the ramp test of a healthy subject including raw data, processed data, and different parameters. Data processing and

analysis are performed using a data processing program (MATLAB 2015a, The MathWorks). SmO_2 data are filtered using a second-order zero-phase shift Butterworth low-pass filter with a cut-off frequency of 0.03 Hz. Data extraction is performed based on the description of the NIRS signal interpretation provided elsewhere [32]. $SmO_{2baseline}$ represents the mean value of the 3-minute prerest period. The minimum SmO_2 value during the ramp test ($SmO_{2\ min}$) is extracted by taking the last local minimum of the filtered SmO_2 prior to reoxygenation. Furthermore, $\Delta_{deoxygenation}$ is the difference between $SmO_{2baseline}$ and SmO_{2min}; $t_{deoxygenation}$ is the time from the beginning of the ramp test until SmO_{2min} is reached; $slope_{deoxygenation}$ is calculated using $\Delta_{deoxygenation}$ over $t_{deoxygenation}$; SmO_{2max} is defined as the highest value achieved within the 8-minute postrest period; $SmO_{2\ 1/2reoxygenation}$ is defined as 50% of the difference between SmO_{2max} and SmO_{2min}; $\Delta_{1/2reoxygenation}$ is the difference between $SmO_{2\ 1/2reoxygenation}$ and SmO_{2min}; $t_{1/2reoxygenation}$ is defined as the time between SmO_{2min} and $SmO_{2\ 1/2reoxygenation}$; $slope_{1/2reoxygenation}$ is calculated using $\Delta_{1/2reoxygenation}$ over $t_{1/2reoxygenation}$; and $SmO_{2overshoot}$ represents the difference between SmO_{2max} and $SmO_{2baseline}$.

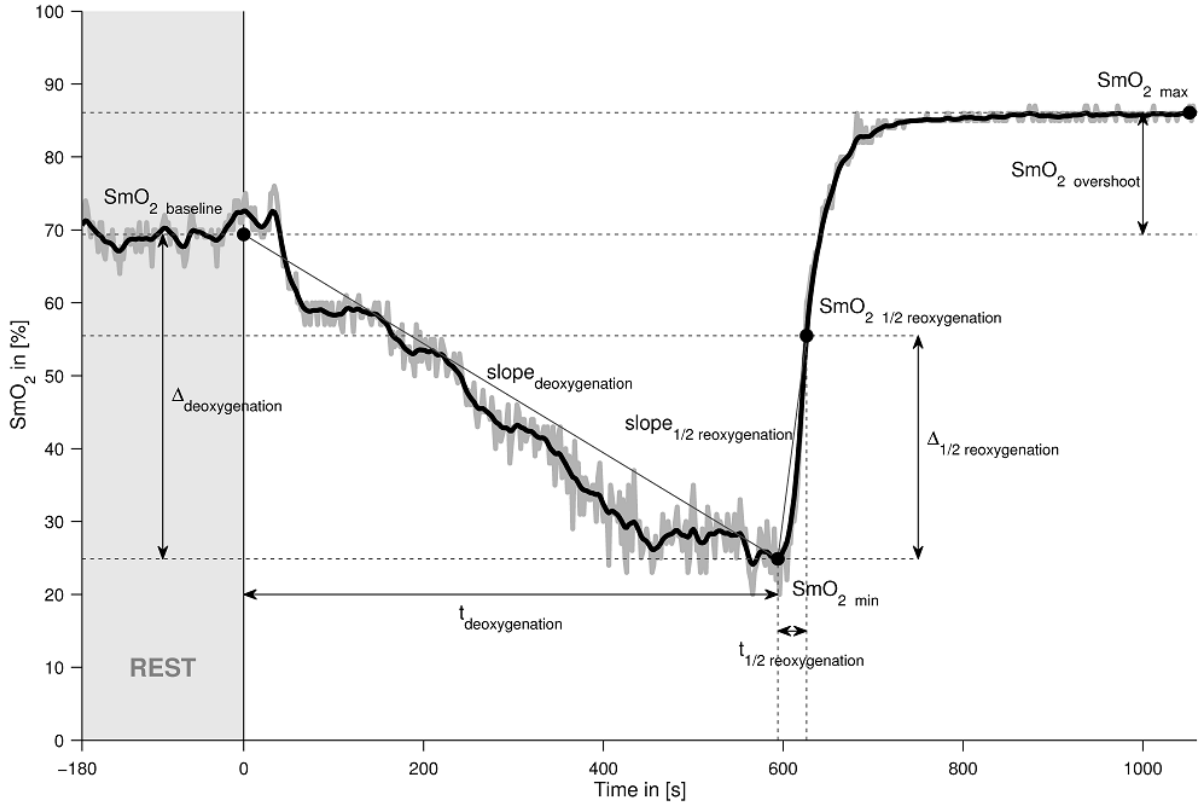
Soft Robot

For the *Real Power* and *Reactive Power* test on the soft robot, the average and the peak value of the 4 test attempts are extracted.

Statistical Analysis

Data will be analyzed for interaction effects of the exercise type on training-induced alterations using a mixed analysis of variance with repeated measures using statistical software (SPSS Statistics 22; IBM). Effects will be localized posthoc with the least significant difference of Fisher. Furthermore, effect sizes and power will be estimated subsequently with publicly available G*Power software (gpower.hhu.de/).

Figure 5. The representative example of the SmO_2 course during the ramp test of a healthy subject including raw data, processed data, and different parameters. SmO_2: muscle oxygen saturation; t: time; min: minimum; max: maximum.



Results

Description of Effect

The results of the first 2 patients who completed the CON and ECC protocol, respectively, are listed below as percentage changes. Multimedia Appendix 1, and 3 present absolute PRE and POST values.

Ramp Test

Figure 6 shows training-induced percentage changes in cardiovascular performance. Before training, the patient completing the ECC protocol had better values of cardiovascular performance than the patient completing the CON protocol, that is, absolute VO_{2peak} (3.16 vs 1.94 $mL \cdot O_2 \cdot min^{-1}$), relative VO_{2peak} (29.01 vs 20.9 $mL \cdot O_2 \cdot min^{-1} \cdot kg^{-1}$), and P_{peak} (250 vs 150 W). After training, the patient completing the CON protocol demonstrated an increased absolute VO_{2peak} (+26%), relative

VO_{2peak} (+26%), and P_{peak} (+20%), when the ECC patient showed reduced values for absolute VO_{2peak} (−7%) and relative VO_{2peak} (−6%), while maintaining P_{peak}. HR_{peak} and BL_{peak} concentration during exercise were increased by 28% and 24% after the CON protocol and 2% and 9% reduced after the ECC protocol, respectively.

Near-Infrared Spectroscopy

Figure 7 shows training-induced percentage changes of SmO_2 parameters. Details of the extracted SmO_2 parameters can be found in the section data analysis. Gray shaded area refers to the observed baseline differences of the measurements prior to training. The minima of SmO_2 during the ramp test were further reduced by training under either protocol, whereby changes being reflective of muscle deoxygenation were more increased after training for the CON respective to the ECC protocol, that is, SmO_{2min}, $\Delta_{deoxygenation}$, $t_{deoxygenation}$, and $slope_{deoxygenation}$. In contrast, SmO_{2max} and $SmO_{2overshoot}$ increased in the patient completing the ECC protocol, while the values for these parameters decreased in the patient completing the CON protocol (Multimedia Appendix 2).

Figure 6. Training-induced changes of cardiorespiratory parameters in the first 2 patients completing the CON or ECC protocols. Bar graph of the percentage changes after versus before the training period (ie, POST vs PRE). VO_{2peak}: peak oxygen uptake; P_{peak}: peak aerobic power output; HR_{peak}: peak heart rate; Sys BP_{peak}: peak systolic blood pressure; Dia BP_{peak}: peak diastolic blood pressure; BL_{peak}: peak blood lactate concentration.

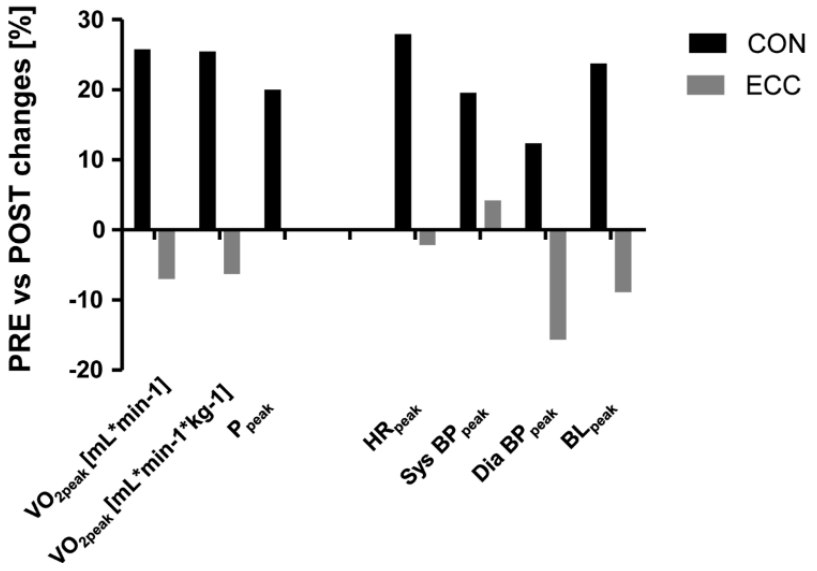
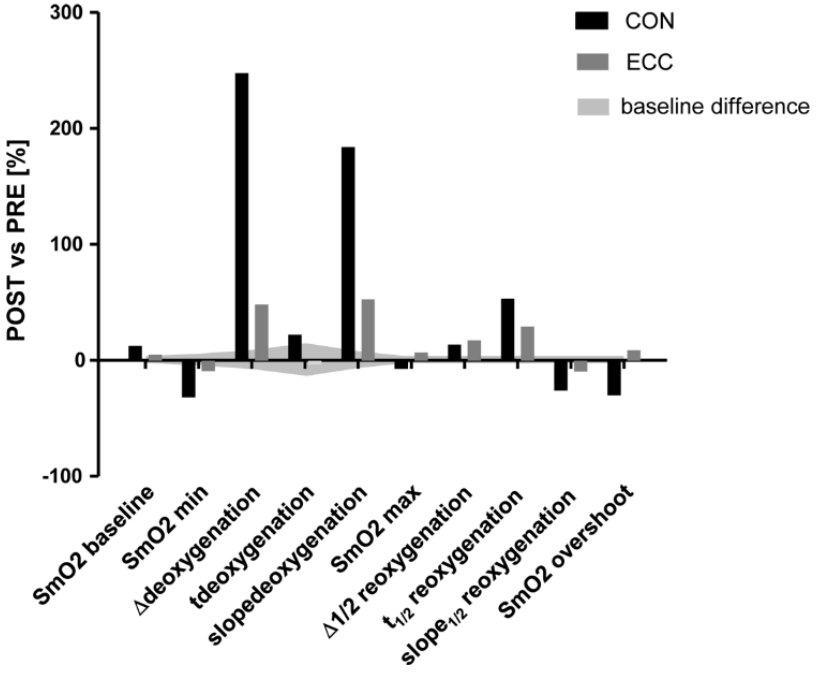


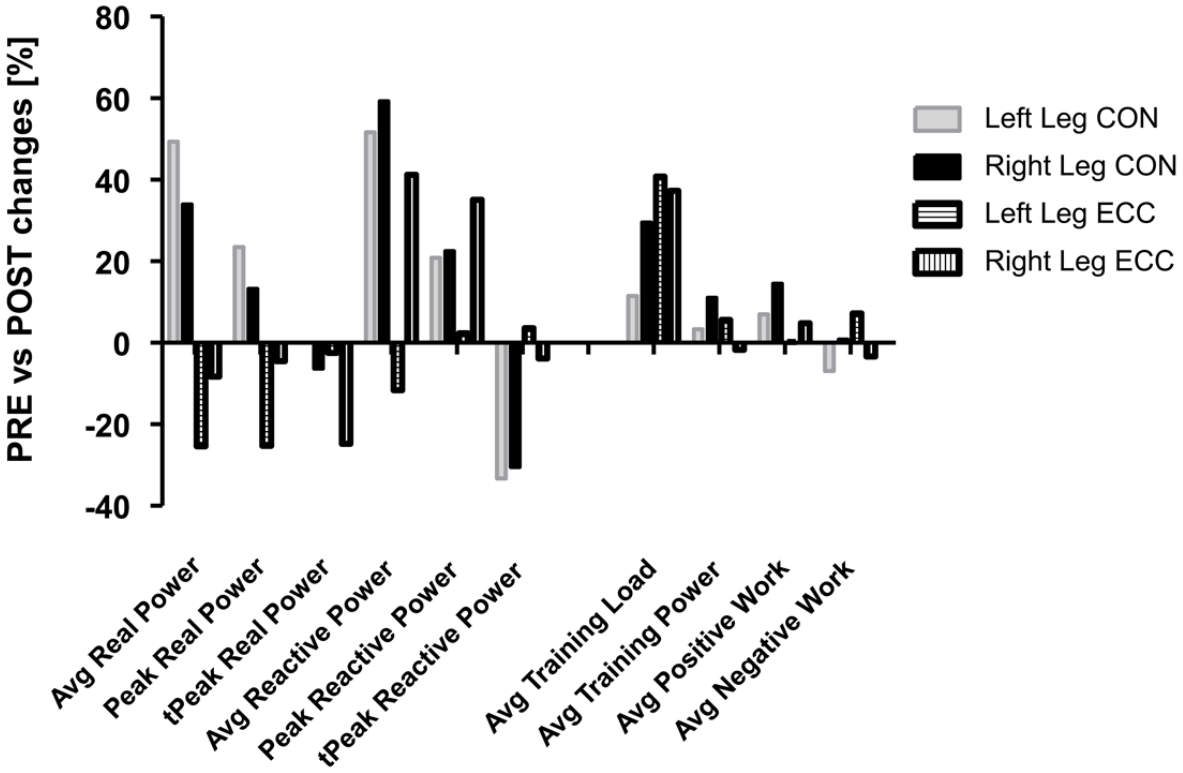
Figure 7. Training-induced changes of SmO_2 parameters in the first 2 patients completing the respective CON or ECC protocols. Bar graph of the percentage changes POST versus PRE. SmO_2: muscle oxygen saturation; t: time; min: minimum; max: maximum.



Before training, the patient entering the ECC protocol had 25% and 23% higher peak real power values of the left and right leg, respectively, than the patient entering the CON protocol (Multimedia Appendix 3). In contrast, the peak power of the left and right leg in the reactive power test was 28% and 19%, respectively, lower for the patient entering the ECC protocol than the patient entering the CON protocol.

Figure 8 shows training-induced percentage changes of anaerobic muscle function as assessed separately for both legs on the soft robot. The CON protocol exhibited an improvement in the average power (+49%, +34%) and peak power (+24%, +13%) for the left and right leg during the real power test, when these values were reduced after the ECC protocol (left: −25%, −25%; right: −8%, −5%), despite a larger average increase in the training load. Power during the reactive power test was improved with both protocols, whereby leg differences revealed for the ECC protocol.

Figure 8. Training-induced changes of the muscle performance on the soft robot for patients completing the respective CON or ECC protocols. Bar graph of the percentage changes POST (after the training period) versus PRE (before the training period). CON: concentric protocol; ECC: eccentric protocol; Avg: average; t_{peak}: time to peak.



Discussion

Principal Findings

We developed a novel exercise protocol on an interactive soft robot to investigate the effects of work-matched CON versus ECC pedaling-type interval exercise on cardiovascular and muscular parameters of stable patients with CAD during cardiovascular rehabilitation.

One of the strengths of the protocol is that the measured cardiovascular and muscular parameters have well-documented prognostic relevance in patients with CAD. Furthermore, the combination of HIIT and ECC muscle actions in stable patients with CAD during cardiovascular rehabilitation can be considered innovative. Implementing the combination of these training modalities has the potential to make the exercise protocol practicable and more time-efficient for CAD patients with CAD. A further strength is its personalized approach. The initial power on the training device is determined based on P_{peak} during the ramp test; this allows an individualized control of the training intensity but could also represent a limitation of the study, as the power on the cycle ergometer does not match exactly the power of the soft robot.

Ramp Test

The data demonstrate that the CON pedaling type of interval exercise protocol is capable of producing a substantial increase in VO_{2peak} in absolute and relative terms (ie, +26%) and P_{peak} (ie, +20%) in patients with CAD. In addition, increased values for HR_{peak}, Sys BP_{peak}, Dia BP_{peak}, and BL_{peak} were found during the ramp test after the training period under the CON protocol. As VO_{2peak} seems to reflect a continuum between health, cardiovascular disease, and death, it is important to design effective programs for exercise-induced gains of VO_{2peak} [14]. The increased VO_{2peak} can lead to a more active lifestyle, which can favor additional preventive benefits; this is assisted by the improved P_{peak}, which is related to improved mobility [33].

Previous studies have shown that HIIT is an effective method for improving VO_{2peak} in patients with cardiovascular diseases.

A study investigated the effects of HIIT compared with continuous moderate-intensity exercise in stable patients with CAD, showing an increase of the VO_{2peak} by 17.9% in the HIIT group [14]. The exercise protocol consisted of 4-minute intervals at 80%-90% of VO_{2peak} with 3-minute active recovery periods at 50%-60% of VO_{2peak}. The increase in VO_{2peak} was significantly higher in the HIIT group compared with the continuous moderate-intensity exercise group (17.9% vs 7.9%). Similar or even better VO_{2peak} improvements were shown in studies that used shorter but more intensive intervals in stable patients with CAD. A 16-week interval training, in which the intervals consisted of 2-minute work phases at 85%-95% of the HR and VO_2 reserve and 2-minute rest periods at 35%-45% of the HR and VO_2 reserve, led to a 15% VO_{2peak} improvement in highly functional CAD patients [34]. In addition, a 12-week interval training period, in which subjects completed ten 1-minute phases at 89% separated by 1-minute phases at 10% of peak power output, led to an improvement of the VO_{2peak} of 20% [35].

The aforementioned studies underlined the importance of the training intensity to effectively increase VO_{2peak}. HIIT allows patients with CAD to train for longer periods of time at a higher-intensity, as it would be possible with continuous training [36]. However, protocols that use very short intervals, such as Wingate-based HIIT, may not be safe and tolerable for patients with metabolic diseases [12]. The selection of the exercise intensity, the duration of the intervals, and the use of active or passive rest have a profound influence on the acute physiological responses and exercise tolerance in patients with CAD [36]. Therefore, we decided on a protocol consisting of 1-minute work phases and 1-minute phases of passive rest; the results show that a considerable increase in VO_{2peak} can be achieved with the selected training intensity and volume and their progressive increase during the 8-week CON pedaling-type interval exercise protocol on the soft robot. Furthermore, the increased values for HR_{peak}, Sys BP_{peak}, Dia BP_{peak}, and BL_{peak} during the POST ramp test show that the patient was able to exercise to a higher degree.

Near-Infrared Spectroscopy

A number of changes in SmO_2 parameters during the ramp test were identified after the training period. The most noteworthy are the changes in the parameters $\Delta_{deoxygenation}$ and $slope_{deoxygenation}$, both of which have been more than doubled after training. The increased deoxygenation could indicate a better O_2 extraction of the *m. vastus lateralis* during the ramp test. As the deoxygenation depends primarily on the O_2 uptake of the mitochondria [37], this result could reflect the typically observed increased mitochondrial volume density within the examined muscle after the training period.

Exercise-induced changes in the skeletal muscle deoxygenation have been shown in patient populations. In postmyocardial infarction patients, it has been shown that the skeletal muscle deoxygenation was impaired [38] and that a 12-week training period led to increased deoxygenation of the *m. vastus lateralis* during the ramp test [39]. The NIRS measurement performed in addition to the determination of VO_{2peak} can provide information about the peripheral adaptations in the skeletal muscle. As VO_{2peak} is dependent on a central (ie, cardiac output), as well as a peripheral (ie, arteriovenous O_2 difference), component, and peripheral metabolic adaptations, such as mitochondrial enzyme activity, in the skeletal muscle are critical for improving endurance performance [40], we decided to measure VO_{2peak} and skeletal muscle oxygenation. Assessing skeletal muscle deoxygenation responses can be helpful to clarify peripheral impairment and its relation to reduced VO_{2peak} in patients after myocardial infarction [38].

Power Tests

An increase in the average and peak power during both soft robot power tests was observed after the training period. Increasing the skeletal muscle power should be another target during cardiovascular rehabilitation because it has been shown to decline earlier and more rapidly than muscle force, and, therefore, it represents a more discriminant predictor of functional performance in older adults [41]. The observed increase can improve the ability of patients to cope with daily activities and, thus, remain active and independent. The former possibility is indicated for the CON protocol by the enhanced real power and reactive power.

Protocol

The pilot evidence from the first patients with CAD show differing adjustments in cardiovascular performance (and muscle reoxygenation) in response to the ECC and CON protocol. Specifically, we identify that P_{peak} (VO_{2peak}) was maintained in the patient after training with the ECC protocol, despite a moderately reduced cardiovascular performance. Hence, it is relevant to consider that the ECC patient demonstrated a better endurance training status than the CON patient before the training. Hence, a considerable part of improvements in the patient exercising on the CON protocol was related to an improvement in the cardiac function (Figure 6). In addition, it is known that at a similar mechanical power, ECC muscle work induces lower metabolic and cardiovascular responses than CON muscle work [42]. Possibly, the effects in the first 2 of our patients reflect interactions between the training state of the patients, and task-specific adaptations to the training that was matched by the mechanical output (ie, work). For the CAD patient training under the ECC protocol, the observations indicate that an increase in the endurance component, for instance, by increasing the number of work intervals, would have been beneficial to improve cardiovascular parameters.

Furthermore, we identified that peak real power was reduced with the ECC protocol and that reactive power was only improved for the right leg while both parameters were improved with the CON protocol. These observations are of interest with respect to the training status prior to entering the protocols and higher training-related increases in the average training load, and the lower metabolic stress and improved muscle reoxygenation with exhaustive exercise in the ramp test, for the ECC compared with the CON protocol. It indicates that the selected ECC exercise protocol affected the muscle strength primarily by affecting bioenergetic pathways and that this is

also affected by the initial training status. For the specific ECC patient, a future closer supervision and coaching of how the task was performed with either leg would have been an option to avoid leg differences in adaptation.

Interestingly, the results show a selective improvement in the maximal oxygenation of the knee extensor muscle after recovery from the exhaustive ramp test after training under the ECC protocol; this finding can be related to the reportedly larger gains in capillary perfusion (ie, based on the capillary-to-fiber ratio) after the eccentric type of cycle endurance training [43]. It indicates that the ECC protocol may specifically enhance the rate of muscle oxygenation during recovery from exercise (reviewed in [44]).

Conclusions

To summarize, this study indicates the potential of the CON pedaling-type interval exercise protocol to increase VO_{2peak}, peak aerobic power output, parameters of SmO_2, and anaerobic muscle power of a patient with CAD during cardiovascular rehabilitation. In addition, our first observations show that the ECC exercise protocol is well tolerated and maintains the peak aerobic peak aerobic power output in relation to lowered metabolic stress and improved oxygen delivery to the recruited muscle group during recovery from exhaustive exercise. The results of the ongoing study, specifically because they allow addressing the performance of each leg individually through the haptic feedback of the soft robot, may contribute to optimizing exercise protocols during cardiovascular rehabilitation.

Acknowledgments

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Authors' Contributions

MF conceived the study design. CMS and DN recruited patients. KC and DL performed ramp test measurements. DPF and MVF performed NIRS measurements and drafted the manuscript. SC supervised training sessions and conducted power tests. WLP conceived and performed NIRS data processing. DPF, MVF, MF, and SR edited and revised the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Cardiorespiratory parameters pre- and posttraining for the patient, which followed the CON and ECC protocol, respectively.

[PDF File (Adobe PDF File), 253KB - resprot_v8i3e10970_app1.pdf]

Multimedia Appendix 2

Parameters of muscle oxygen saturation (SmO_2) pre- and posttraining for the patient, which followed the CON and ECC protocol, respectively.

[PDF File (Adobe PDF File), 81KB - resprot_v8i3e10970_app2.pdf]

Multimedia Appendix 3

Parameters of muscle performance pre- and posttraining for the patient, which followed the CON and ECC protocol, respectively.

[PDF File (Adobe PDF File), 107KB - resprot_v8i3e10970_app3.pdf]

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Abbreviations

BL_{peak}: peak blood lactate
BL: blood lactate
CAD: coronary artery disease
CON: concentric
CAD: coronary artery disease
Dia BP_{peak}: peak diastolic blood pressure
ECC: eccentric
HIIT: high-intensity interval training

HR_{peak}: peak heart rate
NIRS: near-infrared spectroscopy
POST: after the training period
P_{peak}: peak aerobic power output
PRE: before the training period
ROM: range of motion
SmO_2: muscle oxygen saturation
VO_{2peak}: peak oxygen uptake

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Protocol

Time to Treatment and In-Hospital Major Adverse Cardiac Events Among Patients With ST-Segment Elevation Myocardial Infarction Who Underwent Primary Percutaneous Coronary Intervention (PCI) According to the 24/7 Primary PCI Service Registry in Iran: Protocol for a Cross-Sectional Study

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Abstract

Background: Patients with ST-segment elevation myocardial infarction (STEMI) experience major adverse cardiac events (MACEs) following primary percutaneous coronary intervention (PCI). Although the relationship between time to treatment (eg, door-to-balloon time, symptom onset-to-balloon time, and symptom onset-to-door time) and 1-month all-cause mortality was assessed previously, its relationship with in-hospital MACEs and the effect of some clinical characteristics on this relationship were not considered. Furthermore, previous studies that were conducted in developed countries with a different quality of care cannot be applied in Iran, as Iran is a developing country and the studies were not performed according to the 24/7 primary PCI service registry.

Objective: The objective of this study protocol is to determine the relationship between time to treatment and in-hospital MACEs.

Methods: This cross-sectional study will take place at the Tehran Heart Center (THC), which is affiliated with Tehran University of Medical Sciences (TUMS) in Tehran, Iran. Data related to patients with STEMI, who underwent primary PCI between March 2015 and March 2019, that have been prospectively recorded in the THC's 24/7 primary PCI service registry will be analyzed. The study outcome is the occurrence of in-hospital MACEs. Data analysis will be conducted using SPSS for Windows, version 16.0 (SPSS Inc). We will perform chi-square tests, independent-samples t tests, or the Mann-Whitney U test, as well as univariate and multivariate binary logistic regression with a significance level of less than .05 and 95% CI for odds ratios.

Results: From March 2015 to September 2017, 1586 patients were included in the THC service registry, consecutively. We will conduct a retrospective analysis of this registry on patient entries between March 2015 and March 2019 and data will be analyzed and published by the end of 2019.

Conclusions: To our knowledge, this is the first observational study based on the 24/7 primary PCI service registry in Iran. The findings of this study may reveal current problems regarding time to treatment in STEMI management in the THC. Results from this study may help determine appropriate preventive strategies that need to be applied in order to reduce time-to-treatment delays and improve patients' outcomes following primary PCI in the setting of STEMI at the THC and similar clinical centers.

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KEYWORDS

time to treatment; ST elevation myocardial infarction; percutaneous coronary intervention; cross-sectional studies; registries; Iran

Introduction

Cardiovascular diseases continue to be a main cause of premature mortality and long-term disability worldwide [1]. In addition, ischemic heart disease was the first leading cause of death globally among men and women in 2013 [2]. In 2015, acute myocardial infarction was estimated at 7.92 million cases globally [1]. In Iran, one of the largest Middle Eastern countries in South-Western Asia, there is a high and increasing prevalence of acute myocardial infarction [3], with a variation of 5% to 15% in different cities [4-6]. According to a review study in 2016, the in-hospital case-fatality rate of myocardial infarction was 12.1%; ST-segment elevation myocardial infarction (STEMI) and being over 84 years of age were contributing factors [7].

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for patients with STEMI [8] because of the lower rate of total stroke, hemorrhagic stroke, and reinfarction; the increase in patency of infarct-related artery; and the improvement in the in-hospital and long-term survival rate [9]. In addition, it can be a reliable substitute for patients with thrombolytic therapy contraindication [10]. Furthermore, it can be performed faster and result in a lower mortality rate if performed in high-volume hospitals [11]. However, patients with STEMI undergoing primary PCI may experience major adverse cardiac events (MACEs) [12].

Although the recent guidelines have emphasized performing reperfusion strategy for patients with STEMI in a timely manner [13], longer total times have been found [14]. Time to treatment includes symptom-to-door time (ie, time between symptom onset to hospital arrival), door-to-balloon time (ie, time between hospital arrival and balloon inflation), and symptom-to-balloon time (ie, time between symptom onset and balloon inflation) [15]. Longer time to treatment may have an impact on outcome following primary PCI [16]. Thus, time-to-treatment delays should be acknowledged as a key issue [8] and as the easiest audit index of care quality in STEMI management; it should be recorded and reviewed regularly in every health system providing care to patients with STEMI [17].

Door-to-balloon time of less than 90 minutes has been considered as the maximum target time for primary PCI [17]. Previous studies found that door-to-balloon time was associated with better in-hospital outcomes and long-term survival [18-23]. In the Korea Acute Myocardial Infarction Registry (KAMIR), the rate of achieving the target door-to-balloon time increased from 70.3% in 2008 to 90.2% in 2011 [15]. In Iran, according to the Iranian Project for Assessment of Coronary Events 2 (IPACE2) study, although Iranian patients with STEMI received in-hospital reperfusion in a timely fashion, there were long patient delays [24]. However, the effects of these delays on MACEs among patients with STEMI undergoing primary PCI in health care settings of a developing country such as Iran is still unknown.

In contrast, despite improvements in door-to-balloon time over the years, several studies demonstrated no improvement in clinical outcomes and survival rates of patients who underwent primary PCI [15,25-28]. These studies often focused on door-to-balloon time, while symptom-to-balloon time and total ischemic time, as better predictors of clinical outcomes, had not been considered [29].

Although previous studies indicated no relationship between door-to-balloon time and 1-year MACEs [21,26], there is a controversial relationship between symptom-to-balloon time and in-hospital and 1-year MACEs in the literature. Despite the strong relationship between symptom-to-balloon time and 1-year MACEs, no relationship was found between symptom-to-balloon time and in-hospital MACEs [29,30].

Because time to treatment can be important for predicting clinical outcomes, the relationship between time to treatment and 1-month all-cause mortality was assessed by Kim et al in 2017 for the first time [15]. However, its relationship with in-hospital MACEs and the effect of some clinical characteristics on this relationship were not considered. Furthermore, previous studies that were conducted in developed countries with a different quality of care cannot be applied in Iran, as Iran is a developing country and the studies were not performed according to the 24/7 primary PCI service registry.

There is no information on the relationship between time to treatment and in-hospital MACEs among patients with STEMI undergoing primary PCI in Iran. Such information is necessary for health care systems to identify sources of time delays, to help them plan better, and to allow them to apply preventive strategies for improving clinical outcomes following primary PCI in STEMI management. Therefore, this study has been designed to determine the relationship between time to treatment and in-hospital MACEs among patients with STEMI who have undergone primary PCI according to the Tehran Heart Center's (THC) 24/7 primary PCI service registry in Iran.

Methods

Study Design

This is a cross-sectional study that has been approved by the Institutional Review Board (#9511171022) and the Research Ethics Committee (REC) of Tehran University of Medical Sciences (TUMS), Tehran, Iran, on July 25, 2018 (approval ID: IR.TUMS.MEDICINE.REC.1397.290). This study protocol is based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [31].

Setting

The study will take place at the THC affiliated with TUMS. The THC is a "cardiac center of excellence" and provides medical services by full-time specialists and well-trained nursing staff; it is considered one of the best-equipped diagnostic and therapeutic cardiology centers in Iran and in the region. From 2001 to the end of 2017, about 1,300,000 outpatient visits, 280,000 hospitalizations, and 35,000 angioplasties have been recorded for the THC [32]. In addition, primary PCI has been performed at the THC since 2004, and 2380 patients underwent primary PCI as of September 2017 (Third Report of the Databank of the THC, 2017 [internal report]).

Participants

Patients of both genders, over 18 years of age, experienced STEMI and received primary PCI within the recommended time interval (ie, 120 minutes from STEMI diagnosis) [13] through the standard technique and without bolus administration of fibrinolysis in one of six catheterization laboratories in the THC; those with complete registered data in the THC's 24/7 primary PCI service registry from March 2015 to March 2019 will be included in the study. Thus, patients with incomplete time-to-treatment data, such as symptom onset, hospital arrival, and balloon time, will be excluded from the study.

Variables

Variables such as demographic and clinical characteristics and study outcome will be used for statistical analysis (see Table 1). Study outcome will be the occurrence of in-hospital MACEs, which will be measured during hospital admission following primary PCI. The occurrence of in-hospital MACEs is a composite index of different elements (eg, myocardial infarction, stroke, cardiac death, target vessel revascularization, and target lesion revascularization), which have been defined in Textbox 1.

Data Sources and Measurement

We will use the THC 24/7 primary PCI service registry as the main data source in our study. The THC joined this service registry in March 2015. At first, it was conducted at the THC as a pilot scheme for several months. Afterward, in September 2015, it was applied as a default treatment strategy for patients with acute STEMI (Third Report of the Databank of the THC, 2017 [internal report]).

The THC 24/7 primary PCI service registry was approved by the REC affiliated with TUMS and informed consent was obtained from all patients for data collection and follow-ups. Data related to patients with STEMI who underwent primary PCI in one of the six catheterization laboratories in the THC were collected prospectively through a STEMI management registry form. Data were collected by trained emergency department nursing staff at admission time, catheterization laboratory nursing staff, and interventional cardiology fellows; data will be entered into the service registry by research staff on a weekly basis. Patients who expired before beginning the procedure were not included in the registry.

The STEMI management registry form, which is completed prospectively, includes data related to patient demographics (eg, name, birth date, identification code, and gender); admission (eg, mode of patient's transfer, symptom onset time, first medical contact, first electrocardiogram [ECG] in ambulance, and door time); electrocardiographic assessment (eg, infarcted territories, first hospital ECG time, STEMI ECG time, and STEMI ECG verification time); initial reperfusion therapy (eg, transfer to catheterization laboratory, only fibrinolysis, or no reperfusion with reason); procedure in the catheterization laboratory (eg, arrival time, device time, type of intervention performed, infarct-related artery, initial and final Thrombolysis in Myocardial Infarction [TIMI] flow, and stent thrombosis); and additional treatments from symptom onset to coronary intervention (eg, transvenous or external pacemaker, ventilator support, inotropes, intra-aortic balloon pump, left ventricular assistive device, Impella, cardioversion and defibrillator, and cardiopulmonary resuscitation). In this registry, 30-day, 6-month, and 1-year follow-ups for outcome assessment will be conducted by dedicated research staff via phone calls and outpatients' clinical record review.

Bias

As the 24/7 primary PCI service registry has been conducted in the THC since March 2015, there may be a considerable number of patients with missing treatment times. Excluding these patients from the analysis may introduce selection bias. As an additional analysis, we will compare baseline characteristics between excluded and included groups in order to find any discrepancy and evidence of selection bias. Moreover, to minimize the bias, strict control of quality and professional supervision on the service registry will be applied.

Study Size

We will conduct a retrospective analysis on patient entries in this service registry between March 2015 and March 2019. From March 2015 to September 2017, data related to 1586 patients were recorded in the THC's 24/7 primary PCI service registry (Third Report of the Databank of the THC, 2017 [internal report]); we expect to reach 2500 patients by March 2019.

Table 1. Demographic and clinical variables and outcome included in the study.

Variables	Description	Presentation
Demographic characteristics		
Age	Age in years at time of admission	Mean (SD); <65 years or ≥65 years, n (%)
Sex	Male or female gender	Male or female, n (%)
Current smoker	Smoking status at time of admission	Yes or no, n (%)
Clinical characteristics		
Past medical history	Previous myocardial infarction, PCI[a], and coronary artery bypass graft surgery	Yes or no, n (%)
Comorbidities	Having diabetes mellitus, hypertension, and hyperlipidemia at time of admission based on patient or family self-report	Yes or no, n (%)
Family history of cardiovascular diseases	Having family history of cardiovascular diseases based on patient or family self-report	Yes or no, n (%)
Emergency medical service user	Transferred to the THC[b] by emergency medical service	Yes or no, n (%)
First medical contact	Emergency medical service arrival time at scene or patient arrival time at emergency department of the THC	Median (IQR[c]), minutes
First ECG[d] time	Time that first ECG was taken at the THC	Median (IQR), minutes
STEMI[e] ECG time	Time that STEMI was detected on ECG by emergency department staff	Median (IQR), minutes
STEMI verification time	Time STEMI was verified by the emergency department physician	Median (IQR), minutes
24/7 code time	Time that the 24/7 code was activated at the THC	Median (IQR), minutes
Number of diseased vessels	Number of single, double, and triple diseased vessels	Single, double, and triple diseased vessels, n (%)
Infarct-related artery	Infarct-related artery	Left coronary artery, left anterior descending artery, left circumflex artery, right coronary artery, or posterior descending artery, n (%)
Infarcted territory	Territory of myocardial infarction according to the ECG	Anterior, posterior, inferior, or lateral, n (%)
Killip class	Patients' risk classification for development of heart failure in order to predict mortality	I, II, III, or IV, n (%)
Preprimary PCI TIMI[f] flow	Level of coronary blood flow before primary PCI	0, 1, 2, or 3, n (%)
Postprimary PCI TIMI flow	Level of coronary blood flow following primary PCI	0, 1, 2, or 3, n (%)
Symptom-to-door time	Time from self-reported onset of symptoms to time of hospital arrival	Median (IQR), minutes; <90 minutes, n (%)
Door-to-balloon time	Time from hospital arrival to time of reperfusion (ie, wire crossing)	Median (IQR), minutes; <90 minutes, n (%)
Symptom-to-balloon time	Time from self-reported onset of symptoms to time of reperfusion (ie, wire crossing)	Median (IQR), minutes; <180 minutes, n (%)
Procedural supports	Devices and medications used before, during, and after primary PCI	Pacemaker, mechanical ventilation, intra-aortic balloon pump, inotropes, cardioversion, and defibrillator, n (%)
Stent type	Type of stent used during reperfusion	Bare metal stent, drug-eluting stent, or no stent, n (%)
Outcome		
In-hospital MACEs[g]	Composite of myocardial infarctions, stroke, and cardiac death following primary PCI before hospital discharge	Occurrence of MACEs: yes or no; total MACEs, n (%)

[a]PCI: percutaneous coronary intervention.

[b]THC: Tehran Heart Center.

[c]IQR: interquartile range.

[d]ECG: electrocardiogram.

[e]STEMI: ST-segment elevation myocardial infarction.

[f]TIMI: Thrombolysis in Myocardial Infarction.

[g]MACE: major adverse cardiovascular event.

Textbox 1. The composition of different elements included in the study.

- Myocardial infarction: clinical evidence of acute myocardial ischemia and detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile upper limit and at least one of the following:
  - Symptoms of myocardial ischemia
  - New ischemic electrocardiogram changes
  - Development of pathological Q waves [33]
- Stroke: a new focal neurological deficit taking longer than 24 hours and confirmed by imaging [29]
- Target vessel revascularization: either percutaneous coronary intervention or coronary artery bypass graft surgery of the target vessel as the main coronary vessel proximal and distal to the target lesion [34]
- Target lesion revascularization: either percutaneous coronary intervention or coronary artery bypass graft surgery of the target vessel due to restenosis and other complications related to target lesion, which includes the treated segment from 5 mm proximal to the stent to 5 mm distal to the stent [34]
- Cardiac death: any death related to myocardial infarction, cardiac arrhythmia, and heart failure [26]

Statistical Methods

We will conduct statistical analysis using the statistical package SPSS for Windows, version 16.0 (SPSS Inc). Categorical variables will be reported as numbers and percentages and will be compared by chi-square test. In order to compare continuous variables, independent-samples *t* tests or Mann-Whitney U tests will be used and they will be reported as mean (SD) or median (interquartile range [IQR]). Univariate binary logistic regression analysis will be used to determine the relationship between time to treatment and in-hospital MACEs. Multivariate analysis will be performed to identify predictors of in-hospital MACEs by the binary logistic regression model. Each correlation between the variables will be expressed as an odds ratio with a 95% CI. All statistical tests will be set as two-tailed tests, with a significance level of less than .05.

Results

Data from March 2015 to September 2017 related to 1586 patients with STEMI who underwent primary PCI in the THC have been recorded consecutively in the THC service registry. Data analysis of this service registry will be conducted retrospectively on patient entries between March 2015 to March 2019. Data will be analyzed and published by the end of 2019.

Discussion

As the first study on the 24/7 primary PCI service registry in Iran, it may reveal current problems regarding time to treatment in STEMI management at the THC. To our knowledge, this is the first observational study of the relationship between time to treatment and in-hospital MACEs according to the service registry in Iran. Therefore, the findings of this study may help us detect sources of delays—patient delays, system delays, or both. These findings may assist us in applying appropriate preventive strategies in order to reduce time-to-treatment delays and improve patients' outcomes following primary PCI in the STEMI setting in the THC and similar clinical centers.

There are some limitations in this study. First, this is a single-center observational study. Thus, no causal relationship between time to treatment and in-hospital MACEs can be proven conclusively. Second, the study population consists of patients with STEMI who were treated with primary PCI. Therefore, the findings cannot be generalized to patients with STEMI who received thrombolytic therapy.

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Conflicts of Interest

None declared.

Authors' Contributions

All authors made substantial contributions to the conception, design, and preparation of the primary study protocol draft or to its critical refinement for important intellectual content. In addition, all authors agreed to be accountable for all aspects of the work and approved the final version of this study protocol.

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Abbreviations

ECG: electrocardiogram
IPACE2: Iranian Project for Assessment of Coronary Events 2
IQR: interquartile range
KAMIR: Korea Acute Myocardial Infarction Registry
MACE: major adverse cardiac event

PCI: percutaneous coronary intervention
REC: Research Ethics Committee
STEMI: ST-segment elevation myocardial infarction
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
THC: Tehran Heart Center
TIMI: Thrombolysis In Myocardial Infarction
TUMS: Tehran University of Medical Sciences

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Protocol

Early Identification of Preterm Neonates at Birth With a Tablet App for the Simplified Gestational Age Score (T-SGAS) When Ultrasound Gestational Age Dating Is Unavailable: Protocol for a Validation Study

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Abstract

Background: Although rates of preterm birth continue to increase globally, identification of preterm from low birth weight infants remains a challenge. The burden of low birth weight vs preterm is greatest in resource-limited settings, where gestational age (GA) prior to delivery is frequently not known because ultrasound in early pregnancy is not available and estimates of the date of the mother's last menstrual period (LMP) may not be reliable. An alternative option is to assess GA at birth to optimize referral and care of preterm newborns. We previously developed and pilot-tested a system to measure the simplified gestational age score (SGAS) based on 4 easily observable neonatal characteristics.

Objective: The objective of this study is to adapt the scoring system as a tablet app (potentially scalable approach) to assess feasibility of use and to validate whether the scoring system accurately predicts prematurity by itself, over and above birth weight in a large sample of newborns.

Methods: The study is based in Nagpur, India, at the Research Unit of the National Institute of Child Health and Human Development's Global Network for Women's and Children's Health Research. The Android tablet app for the SGAS (T-SGAS) displays de-identified photographs of skin, breasts, and genitalia across a range of GAs and line drawings of infant posture. Each item is associated with a score. The user is trained to choose the photograph or line drawing that most closely matches the newborn being evaluated, and the app determines the neonate's GA category (preterm or term) from the cumulative score. The validation study will be conducted in 3 second level care facilities (most deliveries in India occur in hospitals, and women known to be at risk of preterm birth are referred to second level care facilities). Within 24 hours of delivery, women and their babies who are stable will be enrolled in the study. Two auxiliary nurse midwives (ANMs) blinded to prior GA assessments will use the T-SGAS to estimate the GA status of the newborn. An independent data collector will abstract the GA from the ultrasound recorded in the hospital chart and record the date of the mother's LMP. Eligibility for analysis is determined by the ultrasound and LMP data being collected within 1 week of each other to have a rigorous assessment of true GA.

Results: Publication of the results of the study is anticipated in 2019.

Conclusions: Until GA dating by ultrasound is universally available and easy to use in resource-limited settings, and where there are restrictions on ultrasound use due to their use for sex determination and abortion of female fetuses, this study will determine whether the T-SGAS app can accurately assess GA in risk categories at birth.

Trial Registration: ClinicalTrials.gov NCT02408783; https://clinicaltrials.gov/ct2/show/NCT02408783 (Archived by Webcite at http://www.webcitation.org/75S2kmr3T)

International Registered Report Identifier (IRRID): DERR1-10.2196/11913

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KEYWORDS

gestational age assessment; last menstrual period; mHealth; newborn; prematurity; ultrasound

Introduction

An estimated 15 million children per year (11% of live births) are born prematurely (less than 37 weeks of gestation), predominantly in Africa and Asia [1]. Prematurity rates are increasing globally and of concern because prematurity is a well-recognized risk factor for increased neonatal mortality and morbidity [2-4]. In settings where the incidence and adverse consequences of prematurity are the highest (ie, resource-limited settings), pregnant women may not know the date of their last menstrual period (LMP) and ultrasound is often not available—particularly first-trimester ultrasound, when estimates of gestational age (GA) are more accurate [5]. Since premature birth may not be anticipated by health care providers prior to labor and delivery [6,7], it is important that prematurity be identified at birth so that preterm neonates receive effective interventions as soon as possible after delivery [8].

When prenatal GA is unavailable, it can be estimated at birth by physical examination of the newborn using scoring systems such as the 12-item New Ballard Score (NBS) [9] and the 22-item Dubowitz score (DWS) [10]. A simplified 11-item scoring system adapted from the NBS was developed by Meharban Singh in 1975 and is in use in India [11]. However, even the use of simplified GA scoring systems in first (Primary Health Centers) and second (district and regional healthcare centers) level facilities in resource-limited settings, where the majority of the world's neonates are born, is difficult. Further, predicted GA from these scores has often been compared with women's reports of their LMP, and is not a reliable gold standard, such as first trimester ultrasound [12]. In addition, these scoring systems have not been adequately evaluated for regional, geographical, racial or ethnic robustness. A pragmatic postnatal GA assessment tool that can be used by community birth attendants or auxiliary nurse midwives (ANMs) who deliver the majority of newborns in rural health settings is urgently needed to optimize referral and care of preterm neonates when prenatal GA is unavailable.

We previously used the NBS, DWS and Meharban Singh scoring system to develop a 4-item simplified gestational age score (SGAS) for use in low birth weight newborns in India [13]. The 4-item scoring system is as follows: posture (0 to 4), skin (–1 to 5), breasts (–1 to 4), and genitals (–1 to 4). The total score was used to define 4 SGAS categories: <32 weeks, ≥32 to <35 weeks, ≥35 to <37 weeks, and ≥37 weeks. The SGAS then underwent initial testing in 171 newborns [13] and was found to have a high positive predictive value for very preterm (<32 weeks gestation) and moderate preterm (32-35 weeks gestation) neonates compared with the NBS. In our prior study, a score of <14 predicted that a newborn was preterm (GA of <37 weeks). Agreement between independent raters for the SGAS was higher than that for the NBS (Cohen's kappa 0.83 and 0.71, respectively) indicating that the SGAS was promising to assist with community-based triage and referral decisions for preterm neonates, but in need of further validation.

We elected to conduct a validation study after adapting the SGAS scoring system as a mobile health (mHealth) intervention for two reasons. First, the items used for the SGAS were derived from the NBS and the scoring is based on a description of the skin, breasts, and genitalia that require appropriate training when used by community health workers (such as ANMs) [14]. We proposed that it would be easier to train first level facility health care workers to estimate the score for each item if there was a photograph as well as a text description of the item. Second, since providing a standardized photograph for comparison would be easier using an mHealth app and, given the widespread availability and use of mobile phones, and even tablets, in resource-limited settings [15], this approach would be novel and potentially feasible. As recently reviewed by McBride et al [16], mHealth is increasingly being accepted by community health workers to improve knowledge about maternal and child health [17] and access to care [18], but there are few studies that have used mHealth apps to guide need for referral of neonates to second level care facilities. In this paper, we describe the development of a pictorial-based tablet app for the SGAS (T-SGAS) and its use as an assessment tool. The T-SGAS will be evaluated by ANMs, who are the frontline skilled birth attendants, particularly in first and second level care facilities in most of India, to assess GA compared with ultrasounds obtained as early as possible during pregnancy.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development's (NICHD's) Global Network for Women's and Children's Health Research is a partnership and collaboration between 7 multidisciplinary research units and a Data Coordinating Center dedicated to improving maternal and child health outcomes and building health research capacity in resource-limited settings. Goals include testing feasible, cost-effective, sustainable interventions to provide guidance for the practice of evidence-based medicine. The research unit in Nagpur, India and the Data Coordinating Center at RTI International developed and will help validate the T-SGAS.

The objective of this paper is to describe the development of the T-SGAS, its preliminary assessment of feasibility, and a protocol to evaluate whether it accurately predicts prematurity in a large sample of newborns. The programmatic feasibility of using the app will be evaluated by assessing the agreement of GA assessments performed by 2 ANMs. The accuracy of the app will be assessed by comparing the assessment of preterm

vs term-based newborns on LMP alone, ultrasound alone, and the combination of LMP and ultrasound.

Methods

Development of the Tablet App for the SGAS (T-SGAS)

The development of the T-SGAS was achieved through the following steps: (1) collection of a repository of photographs of the items in the SGAS for preterm and term newborns; (2) selection of photographs for the range of scores for skin, breasts, and genitalia and consensus of neonatology experts for the best photograph of each item score; and (3) development of the Android T-SGAS for visually matching the newborn to the photographs, which auto-calculates the total SGAS and assigns a GA after the user choses the appropriate photograph. A score of <14 is considered to represent preterm, as we had found in our prior study [13].

De-identified photographs of skin texture, breasts, and genitalia of 1800 newborns of varying GA within 24 hours of birth were obtained from five tertiary care hospitals in Nagpur, India, after obtaining written informed consent from the mother of the neonate. A panel of three senior neonatologists, trained in the use of the NBS, selected photographs that best matched the original text description of the development of the skin, breasts, and genitalia [9] based on agreement of at least two of the neonatologists. Since the goal was to select the most unambiguous pictures, whenever possible, we chose pictures selected by all three neonatologists to match each description. The neonatologists did not use the score to make their selection—the score was automatically assigned based on the text and picture description. The three neonatologists selected and matched the photographs together (not independently and not blinded to the interpretation of the other neonatologists). If more than one photograph matched an item and score, the photograph with the best clarity, lighting, and detail was selected. Posture was depicted by line diagrams instead of using photographs of newborns that could be identified. The 25 images selected by the neonatologists (7 photographs of the skin, 6 of the breasts, 6 of the male genitalia, and 6 of the female genitalia) and the line diagrams of posture with their descriptions were embedded in the T-SGAS (see Figure 1). Note that the scoring range from –1 to +5 was based on the original Ballard Scoring System [9] and retained in the NBS System. For example, skin ranged from –1 to +5, breast and male and female genitalia ranged from –1 to +4, and pictures of posture ranged from 0 to +4. This is why there are 5 empty slots in Figure 1. Each item has an associated score. The T-SGAS then auto-calculated the total score and classified the newborn's GA. The conversion of T-SGAS to GA categories is shown in Table 1.

The T-SGAS was designed to collect data in 5 different forms using the same tablet (forms SGAS01-SGAS05). Forms SGAS01 and SGAS02 were used by ANM-1 and ANM-2 to assess GA, blinded to each other's assessment. Form SGAS03 contained data on demographic details of the mother and the newborn, foot length of the newborn, GA based on LMP, and GA based on the earliest ultrasound in pregnancy to determine study eligibility. Form SGAS04 was a random sample verification form for quality assurance by the master trainers to assess the GA, as well as to verify the details from the source documents. Form SGAS05 recorded any protocol deviations or unexpected events in the course of the neonate's enrollment.

The T-SGAS was written in Java and was developed using the Eclipse platform to run on Android-based tablets, as a cost-effective and easy-to-use app that includes support for multiple-languages, enables field data collection in low- and middle-income countries, and has capabilities to integrate diverse data management methodologies. We would also consider developing a version of the T-SGAS for iOS should there be interest from potential users. The software was developed as a suite of software tools for form design, implementation, and reporting. Various data management models were developed to work in diverse conditions including: SIM based tablet or Wi-Fi transmission with Dropbox/Dropsync integration, File Transfer Protocol (FTP), migration of data over SD cards or USB cables and use of Wi-Fi capable external drives. Confidentiality of the data was ensured through encryption of the data on the tablet and during upload to Dropbox or the FTP site. Access to the data are limited to a few personnel who work on the server, which is behind a firewall. The T-SGAS was tested frequently during development for usability and reliability on SIM card–enabled Android tablets. The final T-SGAS was secured by user-specific passwords.

Built-in validations and range checks were implemented as needed on questions to prevent users from moving to the next question on the form if the validation failed. Examples of system-checks and automation include:

- Based on the eligibility questions on the first data collection form (SGAS01), the T-SGAS automatically generated the rest of the forms for potentially eligible subjects (although the potential accuracy of GA was not known at this stage).
- Based on gender (male or female) the app presented the 3 neonatal characteristics with the correct gender assignment as the fourth neonatal characteristic.
- Cross form checks were also programmed for questions (such as the current status of the baby, sex of the baby, etc).
- To reduce errors, key fields from the enrollment form SGAS01 (such as date and time of delivery, consent obtained, etc), were also programmed to be present on the introduction screens of forms SGAS02 to SGAS05, which recorded the results of the actual GA assessment.

Figure 1. Photographs of the neonatal characteristics for the tablet app for the simplified gestational age scoring system (T-SGAS).

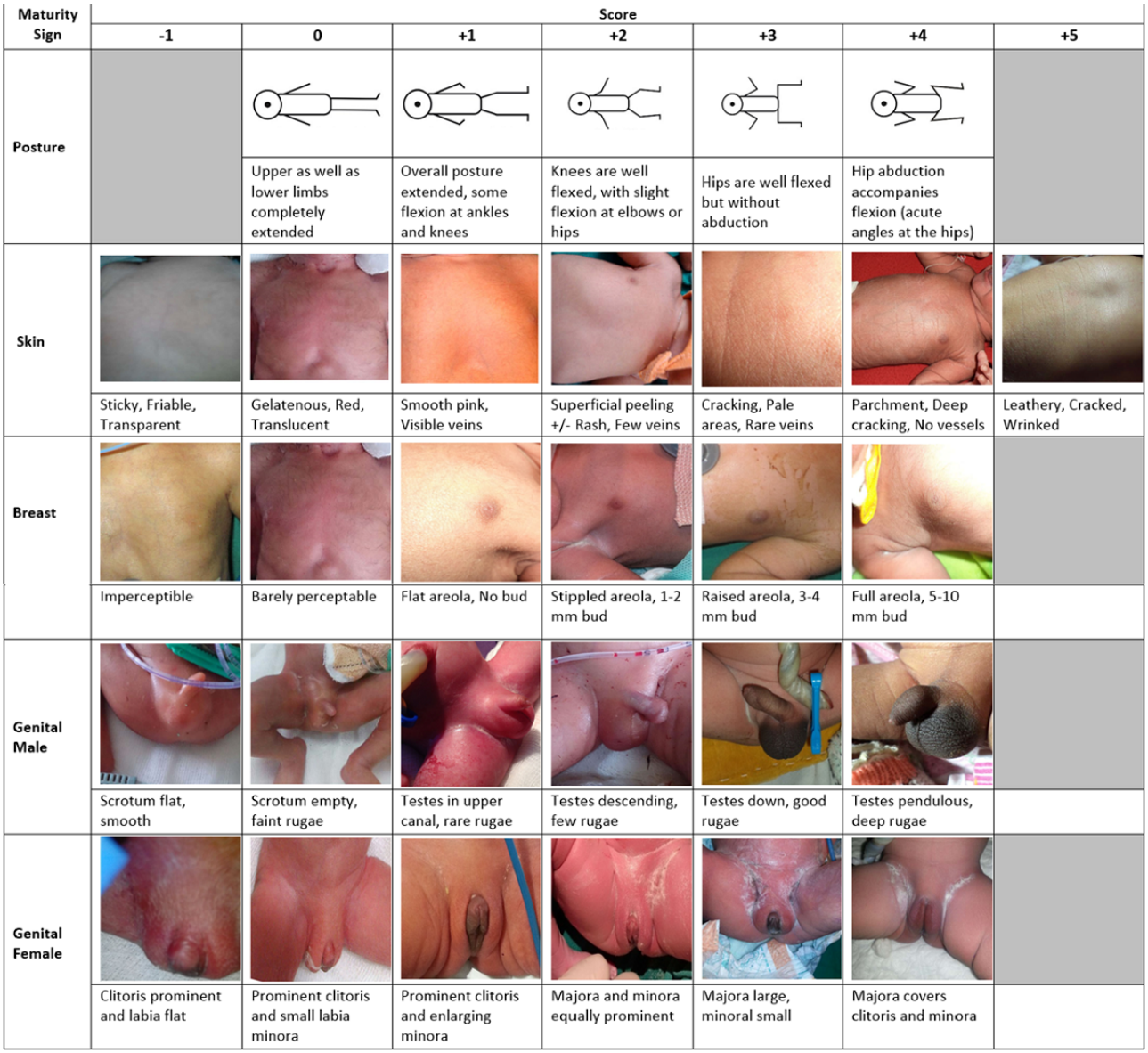


Table 1. Conversion of the tablet app for the simplified gestational age scoring system (T-SGAS) to gestational age categories [13].

T-SGAS total score	Gestational age (weeks)
<7	<32
7-9	≥32 to <35
10-13	≥35 to <37
>14	≥37

Study Design for the T-SGAS Validation Study

The study is a multicenter evaluation of the T-SGAS that will be conducted in three second level care birthing facilities in and around Nagpur, India (Daga Memorial Hospital, Nagpur; Government Hospital, Bhandara; and Government Hospital, Wardha), where most of the deliveries are conducted by ANMs. Each facility will have a team of ANMs and data collectors trained to use the T-SGAS. Over the study period, two ANMs will be available at all times to independently use the T-SGAS to calculate the newborn's GA within 24 hours of birth. Since the ANMs will be blinded to the neonates actual GA, the data collector will obtain the actual GA data by assessing the mother and her chart, to ascertain her neonate's eligibility for analysis. This will be done after the ANMs have assessed all neonates whose mother has consented to her newborn participating in the study.

Eligibility Criteria for the Newborns

During 12-hour study shifts, all mothers who meet the inclusion criteria and have no exclusion criteria (Textbox 1) will be informed about the study and invited to participate. Exclusion

criteria were determined on the basis of conditions that could interfere with the assessment of the neonate's posture. Mothers who are willing to participate will complete a consent process and sign the consent form.

Since it is frequently not possible to obtain and confirm the estimated GA by ultrasound, we decided *a priori* to have additional exclusion criteria for analysis eligibility, to improve the likely validity of the GA estimated by ultrasound, as follows:

- Women whose estimated GA from the date of the LMP is not within 1 week of the GA estimated from the ultrasound;
- Neonates with GA at birth <20 weeks or >44 weeks based on either the date of the LMP or ultrasound;
- Two independent assessments of the newborn were not available within the first 24 hours of life; and
- ANMs who had not assessed at least 100 newborns during the study were unavailable.

Ethics and Consenting

The protocol and the informed consent documents were submitted and approved by the Institutional Review Boards (IRBs) and ethics committees of the Lata Medical Research Foundation IRB (FWA00012971), the Partners Human Research Committee, Boston, MA, and the Boston University Medical Campus IRB. This study is supported by The Eunice Kennedy Shriver NICHD's Global Network for Women's and Children's Health Research. The study was registered on ClinicalTrials.gov (NCT02408783).

Study Variables

Study variables include the date and time of the neonate's delivery, delivery outcome, gender, birth weight, and maternal demographic data, including level of maternal education (none, primary, secondary, postsecondary), mode of delivery (vaginal, cesarean section, vaginal assisted), birth weight (grams), date of her LMP, and GA per the hospital-based ultrasound report.

Implementation of the Study Protocol

Three senior neonatologists with experience in GA assessment at birth and an obstetrician (master trainers) will train the ANMs on the use of the T-SGAS. The training will consist of 4 days of classroom teaching sessions, which include training on Good Clinical Practice guidelines, how to examine the newborn, the different aspects of the 4 physical characteristics of the newborn at different GA, and how to use the T-SGAS. The ANMs will be trained in 3 batches and a final one-day re-orientation training for all ANMs will be conducted prior to the start of the study. The ANMs will then participate in a two-week practical training in the study hospitals. The first week of practical training will be conducted in the delivery room, postnatal wards, and in the special care neonatal units. Training includes adherence to asepsis protocols of the nursery, as well as one-on-one training of how to use the T-SGAS for assessing singleton live births, conducted by the master trainers. The second week, the trainees will independently assess 30 newborns of varying GA before these babies are independently reassessed by the master trainer. ANMs whose scores for each item agree with the master trainer's score at least 80% of the time will be considered successfully trained.

The tablet-based forms are password protected and accessible only by using log-in credentials. After log-in, a Case Management Screen appears with the list of facilities and a preinstalled drop-down menu of identification numbers (IDs). The first ANM (ANM-1) sequentially allocates the IDs to the women who consented and delivered singleton live births. ANM-1 evaluates the newborn and uses her log-in credentials to open the electronic study form (SGAS01) that records date and time of delivery, gender of neonate, consent status, and then uses the touch screen to choose pictures that most accurately represent the neonate's skin, breasts, genitals, and posture (Figure 2). The GA score is then auto-calculated and the neonate is classified into a specific GA group. On completion of the form, a pop-up warning message appears on the screen to verify the assessment and form entries. When verified, the form is saved and cannot be reopened by ANM-1. Completion of the form enables automatic population of subsequent forms with the same ID for the same participant. Color coding is used to identify the pending forms, so that ANM-2 can assess the same newborn using her log-in credentials within 24 hours of birth (using form SGAS02).

Textbox 1. Inclusion and exclusion criteria to participate in the tablet app for the simplified gestational age scoring system (T-SGAS) study.

Inclusion criteria

- Mother had regular menstrual cycles prior to pregnancy
- Mother knew the date of her last menstrual period
- Mother has a report of at least one prenatal ultrasound assessment of gestational age during pregnancy (ideally in the first trimester)
- Mother and baby are clinically stable
- Mother delivered singleton neonate at the study hospital
- Neonate is within the first 24 hours of life

Exclusion criteria

- Neonates with birth asphyxia or who were resuscitated
- Neonates with major congenital anomalies or signs of neurological depression

Data collectors are senior nurses trained to abstract study data from the hospital records. After ANM-1 and ANM-2 have completed their assessments, the data collector logs in to add the GA from the ultrasound report and the date of the LMP on form SGAS03. This procedure ensures that GA assessment by the T-SGAS is done by the ANMs who do not know the baby's estimated GA at birth. Additional demographic details of the mother and the newborn, foot length of the newborn, and birth weight are included in this form. These data are used to determine final eligibility for analysis (Figure 3).

Periodic 2-day retraining will be provided to the ANMs and their assessments will have to meet the standard of 80% agreement of items with that of the master trainers. Focus group discussions for the master trainers and ANMs will be conducted to understand the limitations, challenges, and ease of use of the T-SGAS.

Figure 2. Tablet screens showing use of the tablet app for the simplified gestational age scoring system (T-SGAS).

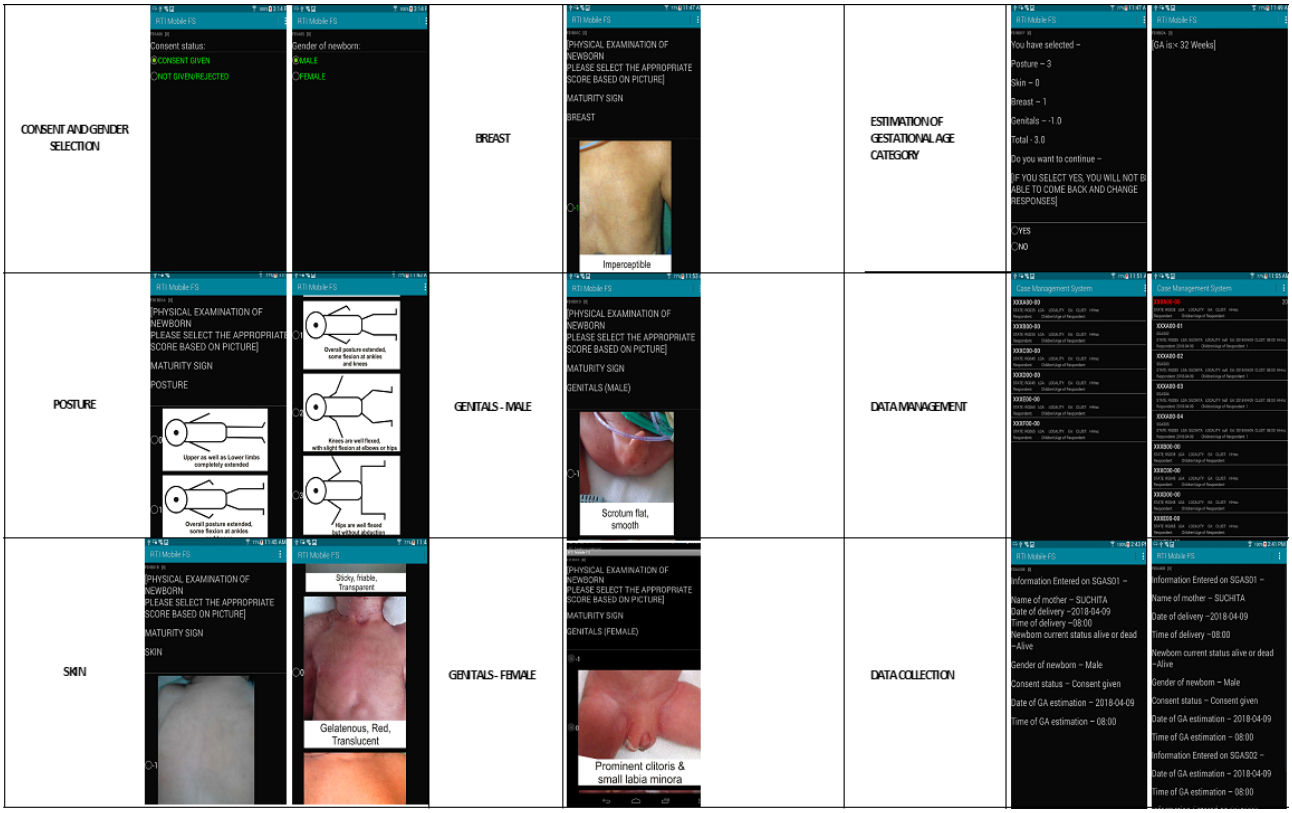
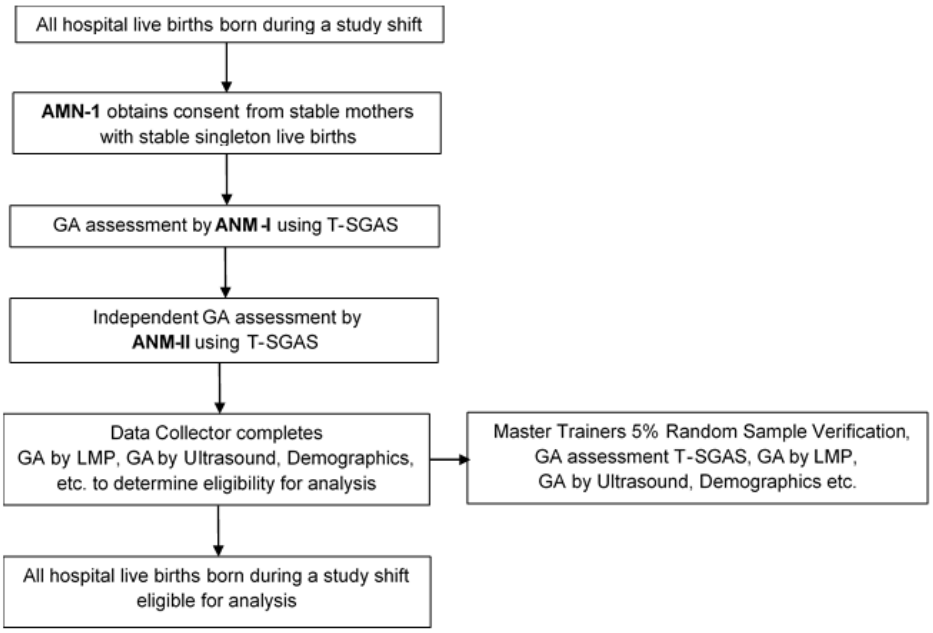


Figure 3. Overview of the T-SGAS study. ANM: auxiliary nurse midwife, GA: gestational age, T-SGAS: tablet app for the simplified gestational age scoring system, LMP: last menstrual period.



Quality Control Procedures

The master trainers will complete a GA assessment for 5% of the newborns selected at random to monitor accuracy of the ANMs' assessment of GA. These data will be entered on form SGAS04. Since the ultrasounds are done for clinical purposes and may not be available at the hospital where the baby is delivered, there are no additional quality control procedures for estimation of GA from the ultrasound. If there is more than one ultrasound available, the earliest ultrasound in the pregnancy will be selected for the GA estimate, ideally one that has been conducted within the first trimester. The accuracy of the ultrasound will likely be improved by requiring the GA by ultrasound to be within 1 week of the mother's assessment of GA based on her LMP. Form SGAS05 will be used to record any protocol deviations or unexpected events in the course of the neonate's enrollment.

Data collection and transmission will be on a real time basis to an RTI International Server (Data Coordinating Center), which will allow daily viewing of data by data managers and statisticians. Edit reports (missing data, pending forms, inconsistencies between the forms and data) will be generated on a daily basis and sent to the birthing facilities so that the data collector can verify the data and resolve inconsistencies.

Monitoring will also be conducted by the research staff and master trainers during regular planned and unplanned visits to facilities to review ANM performance.

Analysis

Sample Size

We have assumed that the prevalence of preterm births will be approximately 10% in this population. In a 2-sided test for sensitivity, a sample size of 7440 will achieve 80% power at a significance level of 0.05 when the sensitivity under the null hypothesis is 0.60 and the sensitivity under the alternative hypothesis is 0.65. This sample size will also be sufficient to achieve 80% power at a 0.05 significance level in a 2-sided test for specificity, when the specificity under the null hypothesis is 0.70 and the specificity under the alternative hypothesis is 0.75, which requires a minimum of 704 subjects.

Analysis plan

Firstly, we will use the Fleiss kappa statistic to estimate agreement between GA (as a dichotomous outcome) measured by ANM-1 and ANM-2. Since our goal is to evaluate the use of the T-SGAS by ANMs, we will not determine which AMN is "correct" (eg, by having a third AMN independently assess the GA of the baby to resolve disagreement). Instead, we will assess the screening accuracy (sensitivity, specificity, prevalence of preterm) of the T-SGAS for both ANMs using 4 different reference standards: LMP alone, ultrasound alone, either LMP or ultrasound, and both LMP and ultrasound (when GA by ultrasound is within 1 week of the GA estimated by the date of the LMP) [19]. We will also determine the predictive accuracy using the area under a receiver operator curve, based on predicted probability estimates obtained from logistic regression. We will determine from the data the optimal cutoff for the dichotomization of the T-SGAS using tree analysis. For this analysis, each of the four aforementioned reference standards will be separately considered as dependent variables and the birth weight and the T-SGAS as independent variables.

Secondly, we will use latent class analyses [20-23] to predict a preterm birth when neither the GA based on the date of the LMP nor GA based on the ultrasound are treated as a reference standard. Finally, we will conduct classification and regression tree (CART) analyses to identify specific items from the T-SGAS and combine them with birth weight to achieve an improved prediction of a preterm birth, since birth weights are universally measured in health facilities soon after birth. The CART analyses will also provide an optimum protocol for implementation of the T-SGAS in community settings, since birth weights are now universally measured in the health facilities soon after birth. Improvement in discrimination and reclassification using the T-SGAS over the traditional method that uses birth weight and LMP will be quantified using the integrated discrimination improvement index and the net reclassification index, respectively [24,25].

Results

The results of the T-SGAS development process will be as follows: (1) successful development of the Android app with iterative improvements based on feedback from end users; (2) successful training of ANMs, who are the main skilled birth attendants in Primary Health Centers and District and Regional level hospitals in India; and (3) successful implementation of the quality control procedures. Enrollment began on July 27, 2015 and ended on March 28, 2016. Results are anticipated in June 2019.

Discussion

Principal Findings

The T-SGAS and its evaluation by the research protocol has the potential to provide a new way for neonates born at first level care facilities and of unknown GA to be promptly referred to second or tertiary level care facilities, if the baby is preterm. Access to optimal care for preterm babies has the potential to improve outcomes in this at-risk population. An anticipated strength of the development of the app is the iterative development process based on user feedback. An anticipated strength of the evaluation is the large sample size of neonates that will be studied and the future analysis of the ability of ANMs to accurately assess GA using the app. If effective, the T-SGAS has the potential for rapid scale-up and the app could easily be modified to efficiently transfer medical data to referral facilities.

An important anticipated limitation of this study is that most fetal ultrasounds in India are obtained in the third trimester, instead of the ideal timing in the first trimester, in part to reduce the risk of the abortion of female fetuses. Whenever a first trimester ultrasound is done, we will obtain that report for GA dating and plan to conduct a subgroup analysis on the subset of pregnancies for which a first trimester ultrasound is available, providing there are sufficient first trimester ultrasound studies. We also recognize that prospectively collected data on the LMP

or recall of the LMP earlier in pregnancy, as well as a first trimester ultrasound, could all improve the accuracy of the GA assessment. Conversely, the inability to accurately recall the LMP can impact study enrollment and is considered to be a further limitation of this study. However, the accuracy of all ultrasounds will likely be improved by requiring the GA by ultrasound being within 1 week of the mothers' assessment of GA, based on her LMP.

Conclusions

This paper describes the development of the T-SGAS and the research protocol to evaluate its use by ANMs in 3 second (District and Regional) level hospitals in Nagpur, India. Key outcomes will include whether the ANMs can correctly identify preterm babies using the app, compared to GA assessments by ultrasound obtained during pregnancy. This approach has the potential to improve outcomes in preterm infants born in first (Primary Care Centers) level facilities where their GA at birth may not be known if ANMs can accurately use the T-SGAS to assess GA and promptly refer those babies that are born prematurely.

Conflicts of Interest

None declared.

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Abbreviations

ANM: auxiliary nurse midwife
CART: classification and regression tree
DWS: Dubowitz Score
FTP: File Transfer Protocol
GA: gestational age
ID: identification number
IRB: Institutional Review Board
LMP: last menstrual period
mHealth: mobile health
NBS: New Ballard Score
NICHD: National Institute of Child Health and Human Development
SGAS: simplified gestational age scoring system
T-SGAS: tablet app for the simplified gestational age scoring system

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Protocol

The Indigo System in Acute Lower-Limb Malperfusion (INDIAN) Registry: Protocol

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Abstract

Background: Acute lower limb ischemia (ALLI) poses a major threat to limb survival. For many years, surgical thromboembolectomy was the mainstay of treatment. Recent years have brought an endovascular revolution to the management of ALLI. It seems that the newly designed endovascular thrombectomy devices may shift treatment recommendations toward endovascular options. This protocol study aims to collect evidence supporting the latest hypothesis.

Objective: The devices under investigation are the Penumbra/Indigo Systems (Penumbra Inc). The objective of this clinical investigation is to evaluate, in a controlled setting, the early safety and effectiveness of the devices and to define the optimal technique for the use of these systems in patients with confirmed peripheral acute occlusions.

Methods: This study will be an interventional prospective trial of patients with a diagnosis of ALLI treated with Penumbra/Indigo devices. This project is intended to be a national platform where every physician invited to participate could register his or her own data procedure. The primary outcome is the technical success of thromboaspiration with the Indigo System. Assessment of vessel patency will be recorded using the Thrombolysis in Myocardial Infarction (TIMI) score classifications before and after use of the device. Clinical success at follow-up is defined as an improvement of Rutherford classification at 1-month follow-up of one class or more as compared to the preprocedure Rutherford classification. Secondary endpoints include the following: (1) safety rate at discharge, defined as the absence of any serious adverse events; (2) primary patency at 1 month, defined as a target lesion without a hemodynamically significant stenosis or reocclusion on duplex ultrasound (>50%) and without target lesion reintervention within 1 month; and (3) limb salvage at 1 month.

Results: The study is currently in the recruitment phase and the final patient is expected to be treated by the end of March 2019. A total of 150 patients will be recruited. Analyses will focus on primary and secondary endpoints.

Conclusions: These new endovascular thrombectomy devices that are specifically designed for peripheral intervention in this difficult set of patients, as those under investigation in the proposed registry, may offer improved clinical outcomes with lower rates of major systemic and local complications. Following completion of this study, it is expected that the value of the Indigo Thrombectomy System in the treatment of ALLI will be better defined. As a result, a shift of treatment recommendations toward endovascular options may be observed in the near future.

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KEYWORDS

acute limb ischemia; endovascular; mechanical thrombectomy

Introduction

Background

Acute lower limb ischemia (ALLI) poses a major threat to limb survival. For many years, surgical thromboembolectomy was the mainstay of treatment. Recent years have brought an endovascular revolution to the management of ALLI. A wide range of endovascular procedures can nowadays be employed, providing results at least as good as the traditional surgical approach.

Since the first successful embolectomy performed by Georges Labey in 1911, the treatment goal has been to restore adequate blood supply to the extremity as soon as possible [1]. After introduction of the balloon catheter by Fogarty in the mid-1960s, surgical thromboembolectomy was considered the gold standard of treatment for many years [2].

Minimally invasive techniques emerged at the beginning of the 1970s when Dotter et al first introduced the idea of clot lysis in the treatment of ALLI. After discouraging first experiences with general thrombolysis, the concept of percutaneous, catheter-directed thrombolysis (CDT) emerged [3]. Since then, many new techniques utilizing sophisticated equipment have been developed to improve treatment results and reduce complications.

Significant changes in the treatment of ALLI have been observed in recent years. Although surgery still plays an important role, endovascular techniques are gaining a more prominent role in this difficult set of patients. It seems that the newly designed endovascular thrombectomy devices may shift treatment recommendations toward endovascular options.

This protocol study aims to collect evidence supporting the latest hypothesis.

Fogarty Catheter Thromboembolectomy

Fogarty thromboembolectomy offers several advantages. In cases of limb-threatening ischemia due to large-vessel embolic occlusion, it can be promptly performed via femoral approach using local anesthesia.

The operation is relatively easy to perform even by less-experienced operators. It allows immediate therapeutic heparinization, which is considered to improve outcomes [3]. A successful operation results in an instant perfusion improvement in the ischemic limb.

In cases of below-the-knee embolism and/or arterial thrombosis, the surgical treatment is more complicated. Precise thromboembolectomy via inguinal incision is very difficult using a standard Fogarty catheter (ie, low torquability).

The walls of peripheral vessels are fragile and prone to vasospasm. Additionally, back-bleeding is not a reliable indicator of adequate thromboembolectomy [4]. Surgical approach to the popliteal artery requires general or spinal anesthesia, extensive dissection, a more experienced operator and, often, patch angioplasty. The drawbacks of a “blind” popliteal embolectomy may be reduced by using an intraoperative C-arm and application of a modified Fogarty catheter with an additional channel for guidewire navigation. Using an intraoperative C-arm, targeted thrombectomy is feasible and provides improved results [5].

Sometimes, when adequate thrombus removal cannot be achieved, especially in patients with thrombosed popliteal aneurysm or small vessel thrombosis, intra-arterial injection of a thrombolytic agent at the time of revascularization or other hybrid solutions are advocated [6,7].

Although simple thromboembolectomy still plays a significant role in the treatment of ALLI, fundamental changes in the patient population have occurred in recent decades.

Decreasing incidence of rheumatic heart disease and widespread anticoagulation therapy in patients with cardiac arrhythmias has largely reduced the frequency of peripheral embolism. Nowadays, in the majority of patients, the symptoms of ALLI are the result of either advanced atherosclerosis, complications of previous vascular procedures, or peripheral aneurysms. Surgical treatment in such cases is much more demanding and often requires additional patch angioplasty or a vascular bypass.

Moreover, surgical treatment of ALLI, although effective, has significant drawbacks. Residual thrombus, propagation of thrombi, chronic atherosclerotic disease, and vessel injuries secondary to Fogarty catheter passage may limit the clinical success rate.

Fibrinolysis

The concept of thrombolysis was introduced by Dotter in the early 1970s. Initial experience with systemic thrombolysis was not encouraging. The treatment was ineffective and burdened with a high rate of bleeding complications. Further development of thrombolysis resulted in catheter direct thrombolysis, which is currently widely utilized in clinical settings. Nowadays, although some contraindications exist, the majority of patients with less severe ischemia (ie, classes 1, 2a, and sometimes 2b, according to Rutherford’s classification) [8] can be offered CDT.

Bleeding is considered to be the most formidable complication of thrombolysis, especially in older patients and when the therapy exceeds 48 hours. Reported data suggest that approximately 5%-15% of treated patients suffer major bleeding that requires intervention. Intracranial bleeding occurs in less than 1% of patients; however, it is lethal in most cases.

Distal embolization is another serious complication of CDT. The reported frequencies vary between 0% and 37% of treated patients [9,10]. Uncontrolled disruption of the distal portion of the thrombus may pose a significant threat to the limb survival. Small thrombi tend to migrate to peripheral arteries, in which case treatment—surgical and/or endovascular—is difficult and the result is often unsatisfactory. Some authors recommend distal filter placement during CDT in order to reduce the risk [11]. Such a protocol seems effective but at the cost of possible filter-related complications and significant economic burden.

Mechanical Aspiration Thrombectomy

Mechanical thrombectomy devices are the latest advancement in the field of ALLI treatment. Aspiration thrombectomy is a

method of thrombus evacuation in patients with ALLI with some potential advantages over thrombolysis: prompt reperfusion (ie, minutes, not hours) and feasibility in patients with contraindications to thrombolysis and nonthrombotic material removal (ie, peripheral atheromatous emboli after endovascular procedures). As opposed to rheolytic thrombectomy, it does not induce hemolysis. It may be utilized in patients with contraindications to thrombolysis (ie, hepatic failure, recent surgery, trauma, or a neurovascular accident).

The Indigo System

The devices under investigation are the Penumbra/Indigo Systems (Penumbra Inc). At the start of the study, Indigo catheters 8 (straight/torq/Xtorq tip [STR/TORQ/XTORQ]), 6, 5, and 3 and Indigo Separators had obtained European Conformity (CE)-approval and are all indicated for the removal of fresh, soft emboli and thrombi from vessels of the peripheral arterial and venous systems.

The Indigo System's aspiration is generated by an external vacuum generator. The system works on the over-the-wire platform. The Indigo device is a polymer-covered, nitinol-strengthened 6 French gauge (Fr) catheter with a suction port at the tip of the device.

During the procedure, the specially designed occlusion catheter is first located proximally to the lesion. It also works as a guiding catheter for the suction unit. The suction catheter is advanced to the level just beneath the thrombus. A separator with an olive-shaped soft tip is advanced and withdrawn several times through the thrombus to disrupt it and facilitate aspiration.

The objective of this clinical investigation is to evaluate, in a controlled setting, the early safety and effectiveness of the Penumbra/Indigo aspiration thrombectomy Systems (Penumbra Inc) and to define the optimal technique for the use of these systems in patients with confirmed peripheral acute occlusions.

Methods

Patient Population and Setting

The Indigo System in Acute Lower-Limb Malperfusion (INDIAN) Registry was intended as a national platform where every physician could register his or her own data procedure.

A total of 150 patients suffering from acute lower limb malperfusion will be recruited in order to prove safety and efficacy of the Indigo System. All participating centers have extensive experience in this kind of disease. The ethical committee of each hospital was informed of the nonexperimental design of the protocol, considering that the devices under investigation have CE mark approval, and endorsed the project.

The anticipated duration of this clinical investigation is approximately 13 months. It is estimated that the inclusion period will be 12 months. The follow-up period is set to be 1 month. The actual start date of the investigation was September 2017, the estimated primary completion date is March 2019, and the estimated study completion date is May 2019.

Patients will be selected based on the investigator's assessment and evaluation of the underlying disease. Each patient's medical condition should be stable, with no underlying medical condition that would prevent them from performing the required testing or from completing the study.

Patients should be geographically stable, willing and able to cooperate in this clinical study, and remain available for midterm follow-up. Patients who do not wish to participate in this study can obtain any other standard commercially available device therapy. Refusal to participate in this study will in no way affect their care at the institution. Inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for the study.

Inclusion criteria:

- Patient presenting with an acute occlusion of lower limb arteries; thrombosis no longer than 14 days
- Patient presenting a score from 1 to 2b following Rutherford classification for acute limb ischemia
- Patient is willing to comply with specified follow-up evaluations at the specified times for the duration of the study
- Patient is >18 years old
- Patient, or their legal representative, understands the nature of the procedure and provides written informed consent, prior to enrollment in the study
- Patient is eligible for treatment with the Indigo System (Penumbra Inc)

Exclusion criteria:

- Patient has an estimated time of intraluminal thrombus of >14 days
- Patient refuses treatment
- Patient for whom antiplatelet therapy, anticoagulants, or thrombolytic drugs are contraindicated
- Patient with a history of prior life-threatening contrast medium reaction
- Patient has life expectancy of less than 6 months
- Patient is considered to be hemodynamically unstable at onset of procedure

Endpoints

The primary endpoint of the study is the technical success of the thromboaspiration with the Indigo System. Assessment of vessel patency will be recorded using the Thrombolysis in Myocardial Infarction (TIMI) score classification before and after the use of the device [12].

The following secondary endpoints will be assessed:

1. Clinical success at 1-month follow-up defined as an improvement of Rutherford classification of one class or more as compared to the preprocedure Rutherford classification.
2. Safety rate at discharge defined as absence of any serious adverse events, such as any clinical event that is fatal, life-threatening, or judged to be severe by the investigator, that resulted in persistent or significant disability.
3. Primary patency at 1 month, defined as a target lesion without a hemodynamically significant stenosis or reocclusion on duplex ultrasound (>50%) and without target lesion reintervention within 1 month.

Data Collection and Analysis

Patient data will be captured electronically using a cloud platform accessible to all investigators.

Descriptive data summaries will be used to present and summarize the collected data. For categorical variables (eg, gender), frequency distributions and cross tabulations will be given. For numeric variables (eg, patient age), minimum, maximum, mean, median, and standard deviation will be calculated. For all variables, a 95% confidence interval for the relevant parameters of the underlying distribution will be calculated. For all time-dependent events, life tables will be calculated using the Kaplan Meier estimate method for a period starting on the date of the procedure up to and including the 24-month follow-up visit. Stratification to preprocedural risk factors, Rutherford, and lesion criteria will be performed and the log rank test will be used to compare between the different outcomes; associated P values <.05 will be defined as significant.

Additionally, all peri- and postprocedural complications (<24 hours) will be evaluated and documented.

Patient Confidentiality

All information and data concerning patients or their participation in this clinical investigation will be considered confidential. Only authorized personnel will have access to these confidential files. Authorized personnel of health authorities will have the right to inspect and copy all records pertinent to this clinical investigation. All data used in the analysis and reporting of this clinical investigation will be without identifiable reference to a specific patient name.

Results

Patient enrollment started in October 2017. It is anticipated that 150 patients will be recruited to the study. The final patient is expected to be treated by the end of March 2019 and the estimated study completion date is May 2019. Data will be analyzed by the coordinating center and results will be shared with each investigating center.

Discussion

After the invention of the balloon catheter by Fogarty in 1963, surgical thromboembolectomy was considered the gold standard of treatment for many years in patients with ALLI. Still, ALLI is a dramatic event, carrying a significant risk of amputation and high perioperative morbidity and mortality. Therefore, the need for continued innovation in this area led to innovative percutaneous approaches. In the 1970s, Dotter first introduced the idea of clot lysis in the treatment of ALLI, then modified to the catheter-directed thrombolysis [2]. Since then, many new endovascular procedures utilizing sophisticated equipment have been developed to improve treatment results and reduce complications.

Currently, the majority of ALLI (approximately 70%) is arterial thrombosis, which generally occurs in the setting of pre-existing vascular lesion. This condition is very common in patients with diabetes. Clinical presentation in the case of thrombosis on atherosclerotic stenosis—so-called “acute on chronic ischemia”—may be less severe. However, treatment is generally more challenging than for ALLI due to embolism, considering the complexity in device trackability through the diseased vessels, potential vessel injury, incomplete revascularization, and need of correction of underlying vascular lesions.

Although surgery is still a significant treatment option, especially for ALLI due to embolism, endovascular techniques are gaining a more prominent role in the case of acute on chronic ischemia. Improved clinical outcomes, associated with lower rates of major complication coming from the application of newly designed endovascular thrombectomy devices in this difficult set of patients, may shift treatment recommendations toward endovascular options. In this scenario, the rapid development of technology allows physicians to choose between different approaches, techniques, and devices.

The Indigo System promotes active thrombectomy using a vacuum pump that generates substantial suction, enabling aspiration of clots of varying sizes and lengths. The device has three components: aspiration catheter, separator, and pump. The system does not contain any rotational components; therefore, the risk of vessel injury is truly minimized. The Indigo System represents a last-generation system for thromboembolic disease, being designed specifically to address the limitations of conventional technology.

Since 2005, the Penumbra System became available in Europe and the United States for the revascularization of occluded intracranial vessels in patients with acute ischemic stroke. By demonstrating that the system is safe and effective in the neurovasculature and by providing high rates of complete intracranial vessel revascularization, the Penumbra System has become the market leader in stroke treatment. Consequently, physicians who were familiar with the Penumbra System for stroke care started using it in the peripheral vasculature for acute thrombotic and embolic events. Lesions that were previously inaccessible with conventional technology were then treated by

these atraumatic, ultraflexible neurovascular devices. In 2014, Penumbra launched the Indigo System specifically for this application, redefining below-the-knee mechanical thrombectomy.

Although there are some very promising case report experiences, clinical data with this thrombectomy device in patients with ALLI is still limited. An ongoing trial, called the Penumbra and Indigo Systems for Mechanical Thrombectomy in the Periphery (PRISM) trial [13], has been designed to evaluate safety and efficacy of the Indigo thrombectomy catheter. The examined population consists of ALLI patients with thrombolysis failure. Partial results were recently published, showing promising results with safe and effective mechanical thromboembolectomy in the peripheral arterial vasculature (ie, they showed a technical success rate of 86.4%). These results were reached across a broad range of clinical applications, including acute ischemia, removal of emboli that occurred during other endovascular procedures, and after failed thrombolysis.

In conclusion, suggestive modifications in the treatment of ALLI have been proposed in recent years. While surgery still represents a significant treatment option, especially for ALLI due to embolism, endovascular techniques are acquiring a more prominent role in the case of acute on chronic ischemia.

Various mechanical endovascular systems for thrombus removal have been investigated over the last 15 years. Most of them have partially failed to be successful or have been associated with undesirable complication rates.

New endovascular thrombectomy devices specifically designed for peripheral intervention in this difficult set of patients, as the one under investigation in the proposed registry, may offer improved clinical outcomes with lower rates of major systemic and local complications.

After completion of this study, data analysis from the INDIAN Registry may clarify the value of the Indigo Thrombectomy System in the treatment of ALLI. As a result, a shift of treatment recommendations toward endovascular options may be observed in the near future.

Authors' Contributions

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Conflicts of Interest

None declared.

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Abbreviations

ALLI: acute lower limb ischemia
CDT: catheter-directed thrombolysis
CE: European Conformity
Fr: French gauge
INDIAN: Indigo System in Acute Lower-Limb Malperfusion
PRISM: Penumbra and Indigo Systems for Mechanical Thrombectomy in the Periphery
STR/TORQ/XTORQ: straight/torq/Xtorq tip
TIMI: Thrombolysis in Myocardial Infarction

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Protocol

Modern Innovative Solutions to Improve Outcomes in Asthma, Breathlessness, and Chronic Obstructive Pulmonary Disease (MISSION ABC): Protocol for a Mixed-Methods Study

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Abstract

Background: A high proportion of the costs for respiratory diseases are generated by a relatively small group of patients with severe disease (recognized or unrecognized) or complex problems that include multimorbidity, at-risk behaviors, and socioeconomic disadvantage. These patients often struggle to engage with the structured, proactive, care approaches for chronic disease management advocated for asthma and chronic obstructive pulmonary disease (COPD), resulting in repeated emergency use of both primary and secondary health care. An integrated approach for the management of complex patients, incorporating both specialist and primary care teams' expertise, may be effective in improving outcomes for such high-risk patients. However, the evidence is mixed, and there is a need for evaluation of models of integrated care in routine "real-world" clinical settings.

Objective: This mixed-methods protocol examines the implementation of a novel integrated care model for patients with airways disease and undifferentiated breathlessness by using both quantitative and qualitative evaluation of processes, patient and health care professional experiences, and clinical outcomes throughout the clinic cycles. It aims to establish whether Modern Innovative Solutions to Improve Outcomes in Asthma, Breathlessness, and Chronic Obstructive Pulmonary Disease (MISSION ABC), including innovative diagnostic and self-management tools, can deliver improvements in health service use and clinical outcomes for the different patient groups (asthma, breathlessness, and COPD) and compares the 12-month period prior to the first patient visit and the 6-month period following the last visit.

Methods: A combination of study designs is required to evaluate all aspects of the service: participatory action research approach, involving real-time evaluation at each clinic to inform subsequent clinics; before-and-after study for patient outcomes before and after clinic attendance; and qualitative methods (interviews and focus groups).

Results: The results will be compiled and published in April 2019.

Conclusions: Evaluation of the clinic cycles will include consideration of qualitative data from patients, carers, and health care professionals in addition to quantitative outcomes for service implementation and patient factors. The long-term impact of the service will be evaluated using clinical and health service outcomes.

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KEYWORDS

asthma; breathlessness; COPD; diagnosis; integration; participatory action research

Introduction

The Burden of Disease

Respiratory diseases are highly prevalent and a major cause of health care utilization in Wessex, United Kingdom. The two most common chronic respiratory diseases—asthma and chronic obstructive pulmonary disease (COPD)—are underdiagnosed, are major drivers to acute care episodes, and show poor clinical outcomes compared to other conditions in many areas of the region.

More than 1 million people in the United Kingdom are diagnosed with COPD. There is still a "prevalence gap" between the expected and actual prevalence of COPD among general practitioner (GP) practices, and in 13% of the UK population aged over 35 years, COPD is undiagnosed. These "missing millions" will likely need acute care, and 15% will only be diagnosed on admission to the hospital [1]. More than 5 million people are affected by asthma in the United Kingdom, and more than 500,000 people have severe or difficult-to-control asthma, of which 70% have an allergic subtype [2]. Patients with severe, exacerbation-prone disease are more likely to be admitted to the hospital and account for the most significant utilization of health services. Both COPD and asthma are associated with increased morbidity and mortality and can lead to disabling symptoms that impact the patient's quality of life and well-being. COPD is the fifth most common cause of death in the United Kingdom, resulting in approximately 25,000 deaths annually. It is also the second most common cause for hospital admission in the United Kingdom, and 35% of patients are readmitted within 30 days. In 2009, asthma accounted for 1,131 deaths in the United Kingdom, triggering a National Audit of Asthma Deaths. The National Review of Asthma Deaths [3] published in 2014 concluded that many areas in the diagnosis and care of patients with asthma such as access to timely and appropriate care, use of personalized action plans, and appropriate severity assessment can be improved to reduce unnecessary deaths.

The National Health Service spends £2 billion per year on the management of asthma and COPD [4]. Both conditions have direct financial costs, additional social costs through time off work and reduced productivity, and further indirect costs through reduced quality of life and well-being. The annual health care expenditure on COPD is more than £800 million (£1.3 million per 100,000 population). The treatment of severe, exacerbation-prone COPD (exacerbation is defined as an acute worsening of respiratory symptoms requiring an increase in therapy [5]) costs ten times more than that of mild disease. COPD is responsible for 24 million lost working days annually, costing the economy £2.7 billion. Nearly 80% of costs for asthma are related to the treatment of poorly controlled disease [6], which amounts to over £1 billion per annum [2] as a direct cost and £6 billion as an indirect cost to society (time off work and lost productivity). Four of the top 10 most expensive drugs covered by the National Health Service are inhaled medications for asthma and COPD.

Shortness of breath is recorded in 1% of primary care consultations [7] and 10% of the population affected by chronic breathlessness symptoms [8]. This proportion increases to one-third in the elderly, with a significant impact on the functional status and health-related quality of life [9]. Although breathlessness is a symptom of many diseases, the referral and management systems are often specific to the diagnosis. Thus, patient visits to more than one outpatient department for breathlessness may result in an onerous clinical journey and underrecognition of comorbidity [10].

A New Model of Care

A high proportion of the costs for respiratory diseases is generated by a relatively small group of patients with severe disease (recognized or unrecognized) or complex problems that include multimorbidity, at-risk behaviors, and socioeconomic disadvantage. Such patients often struggle to engage with the structured, proactive care approach to chronic disease management advocated for asthma and COPD, resulting in repeated emergency health care use of both primary and secondary care. An integrated approach for the management of complex patients, incorporating both specialist and primary care teams' expertise, may be effective in improving outcomes for such high-risk patients. However, the evidence is mixed, and there is a need for evaluations of models of integrated care in routine "real-world" clinical settings.

The Modern Innovative Solutions Improving Outcomes in Asthma, Breathlessness, and COPD (MISSION ABC) system is a new model of care that starts by identifying at-risk patients and subsequently streamlines their care, incorporating new technology to improve management of airways disease. Patients are identified using criteria that indicate poor disease control, a heavy burden of symptomatology, or unidentified disease. The patients are then delivered streamlined assessment and care in a one-stop (MISSION Rapid) or two-stop clinic journey (Rapid plus MISSION Investigation clinics). MISSION Rapid clinics, organized in the community, promote integration of primary and specialist teams, wider respiratory multidisciplinary teams, psychological and well-being services, charity, and patient group representation. Each patient's diagnosis is reviewed using spirometry, fractional exhaled nitric oxide (FeNO), and oscillometry (each provided by a specialist respiratory physiologist) along with a specialist medical review; the reasons for poor disease control are explored (unidentified comorbidity, difficulties in self-management, coexisting anxieties, or social stressors), and the medications are optimized using local and national guidelines. All patients were offered personalized self-management plans. Patients who are stable are supported in the management of their disease through education (myCOPD [11] or myAsthma [12]) and upskilling of lead health care professionals (HCPs) and champions in GP practices through competency-based training, including spirometry and comorbid disease management. The model of

patient flow through the MISSION service is shown in Figure 1 (COPD), Figure 2 (asthma), and Figure 3 (breathlessness).

Figure 1. COPD cohort flow chart with study outcomes shown in yellow boxes. COPD: chronic obstructive pulmonary disease; GRASP: Guidance on Risk Assessment in Stroke Prevention; CAT: COPD Assessment Test; ASK-12: Adherence Starts with Knowledge questionnaire-12; PAM: Patient Activation Measure; WBPA: weight-bearing physical activity; MDT: multidisciplinary team; GP: general practitioner; PIS: patient information sheet; HCP: health care professional; BMI: body mass index; SF-36: Short Form Health Survey-36; VSAQ: Veterans Specific Activity Questionnaire; EQ5d: EuroQoL-5D; WPAI: Work Productivity and Activity Impairment.

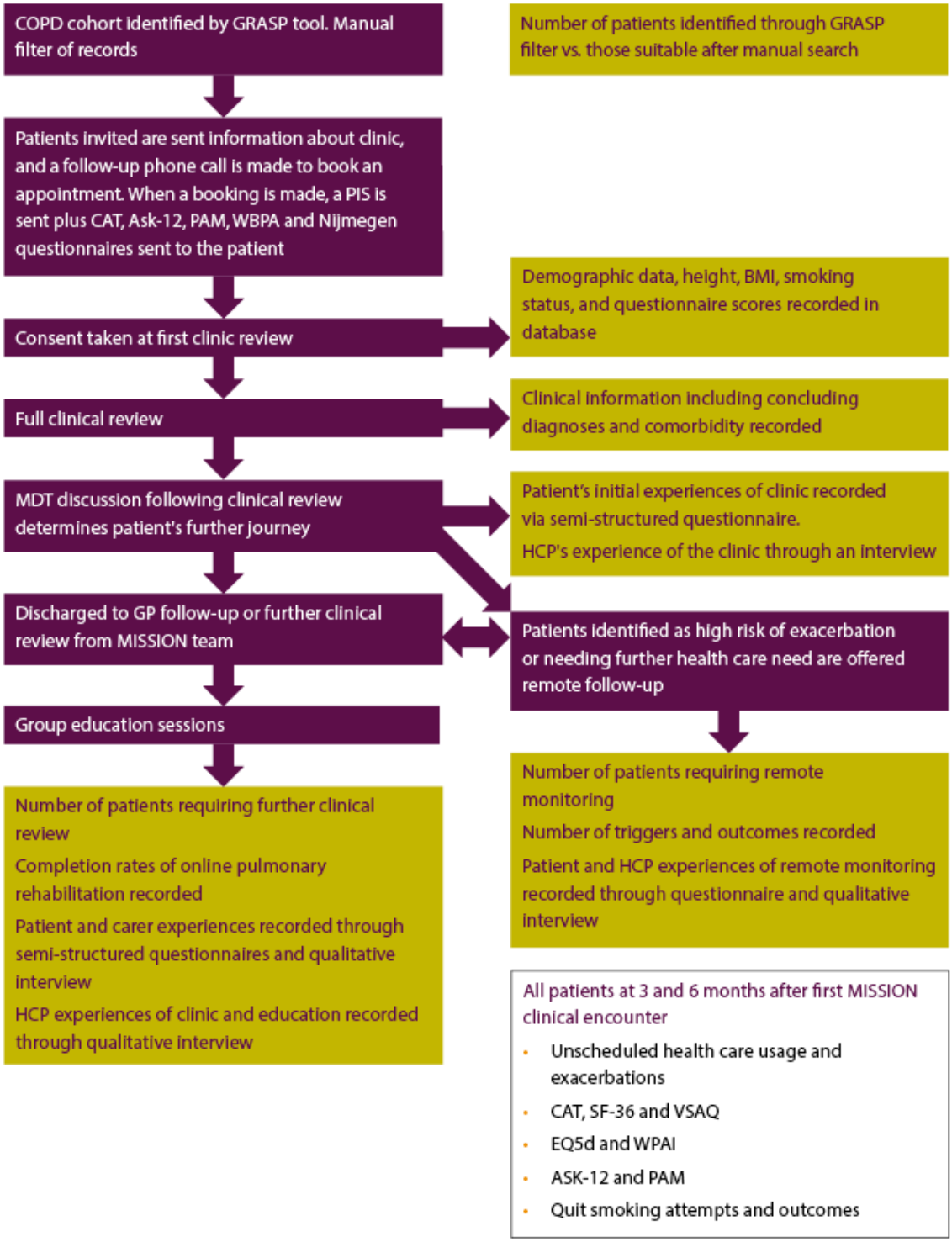


Figure 2. Asthma cohort flow chart with study outcomes shown in yellow boxes. GRASP: Guidance on Risk Assessment in Stroke Prevention; CAT: Chronic obstructive pulmonary disease Assessment Test; ASK-12: Adherence Starts with Knowledge questionnaire-12; PAM: Patient Activation Measure; WBPA: weight-bearing physical activity; MDT: multidisciplinary team; GP: general practitioner; PIS: patient information sheet; HCP: health care professional; BMI: body mass index; EQ5d: EuroQoL-5D; WPAI: Work Productivity and Activity Impairment; ACQ: Asthma Control Questionnaire; TLA: temperature-controlled laminar airflow.

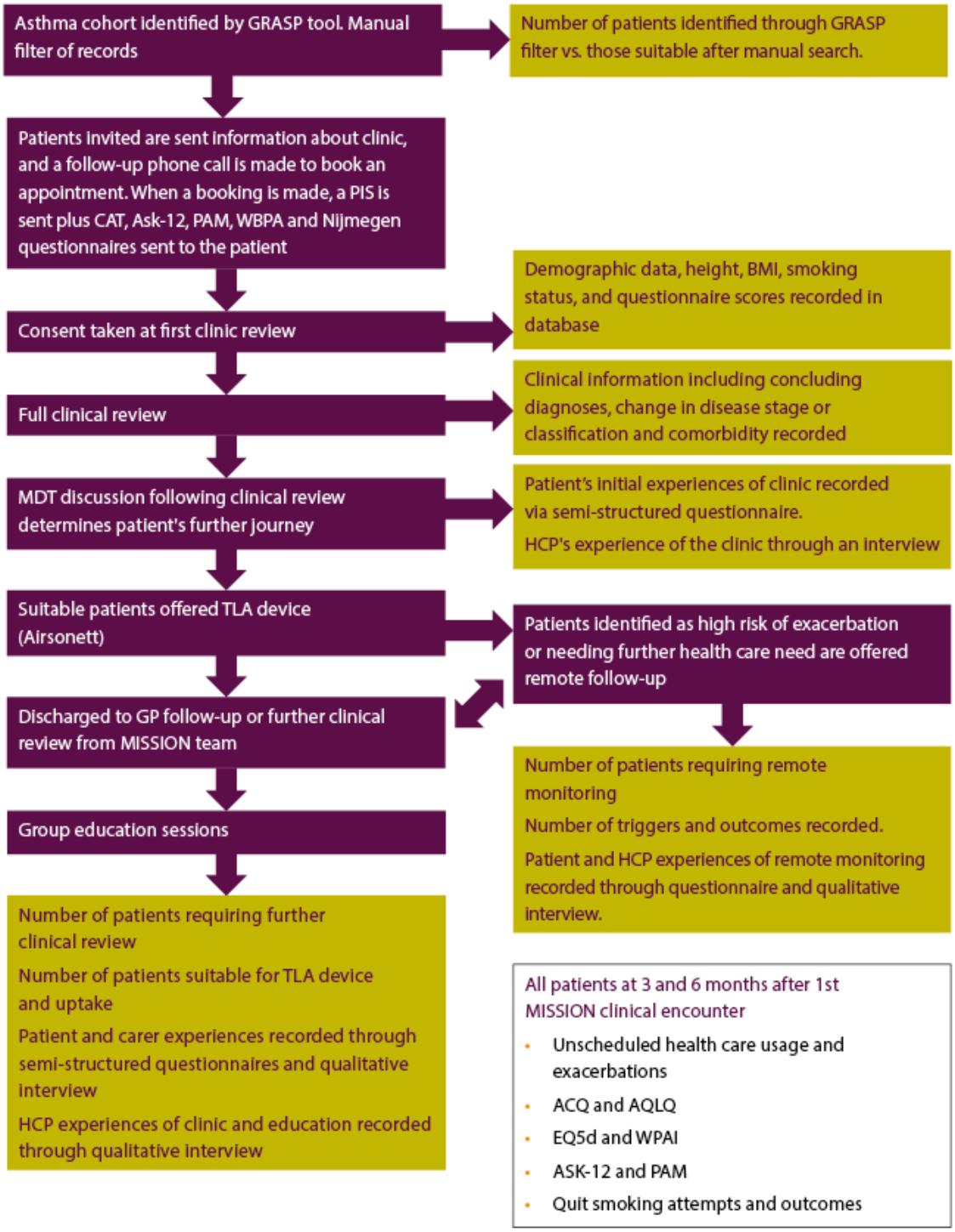
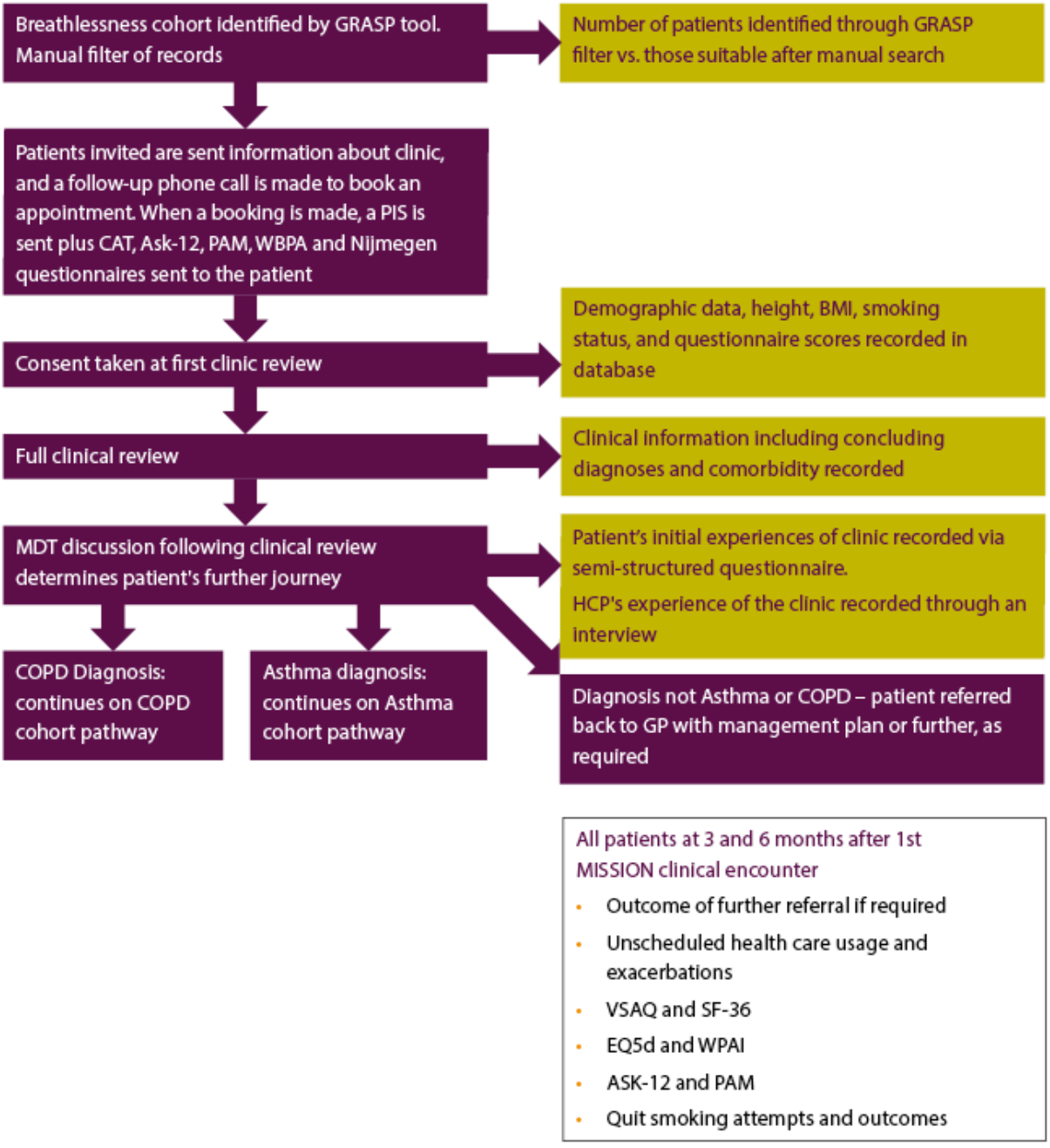


Figure 3. Breathlessness cohort flow chart with study outcomes shown in yellow boxes. COPD: chronic obstructive pulmonary disease; GRASP: Guidance on Risk Assessment in Stroke Prevention; CAT: COPD Assessment Test; ASK-12: Adherence Starts with Knowledge questionnaire-12; PAM: Patient Activation Measure; WBPA: weight-bearing physical activity; MDT: multidisciplinary team; PIS: patient information sheet; HCP: health care professional; BMI: body mass index; SF-36: Short Form Health Survey-36; VSAQ: Veterans Specific Activity Questionnaire; EQ5d: EuroQoL-5D; WPAI: Work Productivity and Activity Impairment.



A New Service for Asthma Patients

We will implement a novel clinical pathway for asthma patients that includes diagnosis, assessment, and adjustment of treatment; maintains control using complementary innovations and models of care; and draws on resources and skills from primary, secondary, and tertiary care.

We will use Guidance on Risk Assessment in Stroke Prevention (GRASP) [13] searches across Wessex Clinical Commissioning Groups to identify patients who are likely to have asthma. When a diagnosis is established, we will identify patients whose conditions are not well controlled (eg, frequent exacerbations, emergency department visits, hospital admissions, use of three or more controller medications, and use of frequent short-acting bronchodilators). These patients' records will be reviewed by specialist nurses and, if appropriate, in MISSION clinics. The clinics will provide timely diagnosis with cutting-edge technology, including FeNO and airway oscillometry, assessment of disease control and comorbidity, an education session, and a self-management plan through written and mobile- or Web-based solutions, where appropriate. Inhaler technique and adherence will be assessed, and patients will be encouraged

to maintain good practices with the Flo-Tone device and inhaler-use monitor [14]. Patients requiring more urgent care will be assessed and treated by a rapid response team.

After the patients visit the MISSION Asthma clinic, the following tools will be used to enable continuous assessment, adjustment, and maintenance of disease control: Message Dynamics portal [15], Clinitouch system [16,17], myAsthma, Airsonett [18,19], smoking cessation, and education. Message Dynamics and Clinitouch use communications technology across multiple platforms to monitor symptoms, allowing early recognition of deterioration. By combining these approaches, HCPs can target patients early in an exacerbation event by using community-based management, thereby reducing the need for admission and the cumulative burden of symptoms on the patient. MyAsthma is a self-management online platform providing education and a symptom diary to encourage patients to manage their asthma. The Airsonett device is a laminar airflow device that reduces allergen exposure in patients with severe allergic asthma and may increase control and reduce healthcare utilization.

Chronic Obstructive Pulmonary Disease

Patients will be identified through the use of GRASP COPD [13] and directed to the MISSION COPD clinics. At the clinics, patients will be reviewed according to the following the National Institute for Health and Care Excellence (NICE) quality framework standards [20]:

- Diagnosis: Thorasys [21] and exhaled nitric oxide from Niox [22]
- Medicine optimization: Flo-Tone device
- Smoking cessation
- Self-management: MISSION Self-Management Plans and myCOPD (similar to myAsthma but including online pulmonary rehabilitation program)

After the initial assessment, all patients will be encouraged and supported to keep themselves active while using myPR, the online pulmonary rehabilitation tool designed by my mHealth. Patients found to be at high risk of disease exacerbation (based on clinical characteristics or prior health care usage, decided by the senior clinician at the clinic) at the MISSION will be encouraged to report their symptoms via the Message Dynamics portal or Clinitouch system to allow early recognition and treatment of exacerbation.

Breathlessness

Assessment

Patients with breathlessness who do not have an established diagnosis will be identified from the GP and practice records by using GRASP case-finding tools and will be offered the same high-quality diagnostic service as that offered to patients with asthma and COPD. In the MISSION clinic, these patients will be assessed using our novel diagnostic tools with additional availability of electrocardiogram recordings and a point-of-care test to identify any strain on the cardiac muscle by measuring the B-natriuretic peptide level. If asthma or COPD is identified, patients will join the respective care pathways. If a cardiac cause is identified, the patient will either be referred to the heart failure clinic or discharged to their GP. If the cause is a syndrome that leads to difficulty in breathing or deconditioning, patients will be offered an appointment with a MISSION ABC physiotherapist who will deliver targeted breathing retraining and discuss the benefits of maintaining exercise.

Innovations Embedded With New Models of Care

A brief outline of the innovations is provided below, followed by a description of how these innovations are incorporated into the new service model.

Digital Platforms to Identify and Monitor Patients

GRASP is a tool created by PRIMIS (Nottingham, United Kingdom) in conjunction with the University of Nottingham, United Kingdom. The tool examines GP records based on a chosen set of read codes and generates a search list tailored to the demands of the interrogator. This tool has been successfully used to generate patient lists for a variety of projects for the Wessex Academic Health Science Network (Southampton, United Kingdom).

Patient Self-Management and Monitoring

The following tools were used for patient self-management and monitoring:

MymHealth (myCOPD and myAsthma)

MymHealth [23] is a Web-based self-management system designed to support self-care in people with COPD and asthma. The system can be easily and securely accessed online by patients and HCPs. It facilitates the effective recognition of symptoms, inhaler technique, and management of medicines. It is an easy-to-use system that promotes patients to manage their COPD or asthma at home. Patients can also access an electronic platform containing a comprehensive, guided, 6-week pulmonary rehabilitation program to improve their health and quality of life.

Message Dynamics

Message dynamics [15] is a multiaward-winning provider of low-cost telehealth solutions through an app or a traditional telephone. Patients respond to a simple questionnaire that aims to detect symptoms of exacerbation.

Clinitouch

Clinitouch [16,17] is an app-based system that uses disease-control questionnaires and Bluetooth-enabled blood pressure and oxygen-saturation monitors that allow clinicians to remotely monitor their patient cohort. The patient is supported with an online self-management plan.

Technical Innovations

Diagnosis

The following tools were used for diagnosis:

Niox

This is a point-of-care testing device that measures exhaled nitric oxide [22]. It is a marker of eosinophilic corticosteroid-responsive inflammation that can predict loss of control in patients with asthma and supports phenotyping of

patients with asthma and COPD. This tool was recently approved by NICE for the diagnosis of asthma [24].

Thorasys

This is a portable diagnostic tool that measures airways oscillometry, airway resistance, and obstruction independent of patient effort, thereby providing an accurate diagnosis with minimal effort [21,25]. Oscillometry offers an alternative method to traditional methods such as spirometry for assessing airway function. It has the potential to identify abnormal airway function that spirometry may be unable to detect, especially defects residing in the smaller airways. Oscillometry is particularly useful in patients who are unwilling or unable to adequately comply with the technical requirements of spirometry or when spirometry is considered inappropriate or contraindicated.

Treatment Improvement

For improving treatment, the following tools were used:

Clement-Clark Flo-Tone

This is a simple device that fits within the mouthpiece of any inhaler [26]. When the optimum inspiratory flow rate is achieved for that device, a musical note is heard. This immediately provides feedback to the patient but can also be recorded via a mobile phone app to inform the HCP.

Airsonett

The Airsonett device [19] can improve care of patients with severe allergic asthma and poorly controlled symptoms. The laminar airflow system, placed above the patient during sleep, vastly reduces aeroallergen exposure, resulting in fewer symptoms and improves disease control.

Service Model Innovations - MISSION COPD and MISSION Asthma

This is an award-winning, novel way of delivering highly specialized multidisciplinary asthma and COPD care in the community, providing specialist clinics to rapidly identify patients with asthma and COPD and then to assess and adjust management plans and empower patients through education [27]. A pathway has been designed to improve patient care and safety and prevent hospital admissions and nonelective visits in primary care.

Aims and Objectives

This study aimed to examine (1) the implementation of a novel integrated care model for patients with airways disease and undifferentiated breathlessness using both quantitative and qualitative evaluation of processes and patient and HCP experiences and (2) clinical outcomes throughout the clinic cycles driving a continuous improvement process, evaluated through participatory action research. We also aimed to establish whether MISSION ABC, including innovative diagnostic and self-management tools, can deliver improvements in health service use and clinical outcomes for different patient groups (asthma, breathlessness, and COPD) by comparing the 12-month period prior to the first patient attendance and the 6-month period following attendance, by using regressional analyses to control for seasonal variation bias.

Methods

Study Design

Summary

The main focus of this project is to deliver a quality-improvement project—MISSION ABC—that has been informed by three prior projects. This protocol of predominantly Participatory Action Research [28] accompanies the project to record the delivery, iterative changes to the project, and outcomes and ensure rigor in the reporting of these parameters.

Accompanying innovations are embedded in the project to encourage a culture of growth amongst small- and medium-sized enterprises within the health care system. Outcomes related to these innovations are exploratory, not designed to be powered, and will not be presented with a control group.

A combination of study designs are required to evaluate all aspects of the service:

1. Participatory Action Research approach involving real-time evaluation at each clinic to inform subsequent clinics
2. Cohort (longitudinal) data approach for clinic- and patient-level service use and outcome indicators
3. Before-and-after study of patient outcomes before and after the clinic visit
4. Qualitative methods (interviews and focus groups)

Participatory Action Research Approach

Data Evaluation

A list of all the data that will be evaluated on a cyclical basis is provided below. These include quantitative data and themes that will be explored qualitatively with HCPs, patients, and carers to inform the next clinic. Issues for improvement, changes to the clinic process, and the rationale for changes will be recorded in a learning log. The impact of changes will be reviewed following the subsequent clinic visit and from any further feedback from qualitative interviews and focus groups. Fidelity to the original project plans and reasons for the changes made will be reported as part of the project analysis.

This list of outcomes is not exhaustive, as the cyclical approach may identify other key areas that are important to monitor. If additional questionnaires or methods of data collection from patients are required, they will be submitted to the ethics committee as an amendment.

Clinic Process

- Acceptability of clinic delivery model by patients, carers, and HCPs including host GP surgeries
- Perceived appropriateness of the clinic by the patient group, judged by HCPs delivering the clinic services and the host surgeries
- Primary care staff attendance at the clinic (number and position)
- Number of patients identified as appropriate for the clinic
- Attendance rates at each offered session

Diagnostics

- Number of new or modified diagnoses made at the clinic

- Number of patients where the British Thoracic Society Asthma stage or Global Obstructive Lung Disease (GOLD) COPD classification [5] is changed following discussion by the multidisciplinary team
- Number of new comorbidities newly identified

Education and Supported Self-Management

- Uptake of the education sessions when offered and reasons for decline, when given
- Acceptability of education sessions by participants and carers
- Confidence in self-management measured before and after the clinic visit and after subsequent education sessions
- Changes in treatment adherence before and after the intervention, measured using the Adherence Starts with Knowledge questionnaire-12 (ASK-12) [29,30] and a prescription reconciliation
- Uptake of the HCP education program
- Acceptability of the HCP education program by participants

Use of Treatment Tools

- Number of patients who showed improved inhaler technique, as judged after the first clinical encounter
- Number of patients with improved technique who sustained the improvement at subsequent review when prompted by clinical need
- Number of quit-for-life reviews that resulted in a quit attempt, and if these quit attempts resulted in sustained cessation at 6 months
- Number and type of inhalers prescribed before and after the intervention

Remote Monitoring

- Number of patients identified for remote monitoring
- Number of triggers on remote monitoring that progress to a clinically significant exacerbation
- Number of reported delays in reporting exacerbation due to the presence of remote monitoring
- Incidences where the carer of a family member is required to facilitate use of remote monitoring

Additional Balancing Measures

- Number of GP or practice nurse sessions changed or cancelled to host the clinic
- Additional costs such as childcare or extra travel incurred by the delivery team when care is delivered remote to their usual place of work or outside the usual working week
- Number of GP, community nurse, or emergency department episodes resulting from remote monitoring
- Number of secondary care referrals resulting from the program

Patient and Health Service Use Outcomes (Longitudinal Follow-Up)

Changes in quality-of-life measures prior to the clinic visits and at 3 and 6 months were measured with generic or disease-specific quality-of-life questionnaires. These questionnaires evaluated the following:

- Changes in productivity and activation measures prior to the clinic visit and at 6 months
- Changes in disease control, quality of life, and comorbidity measured by disease-specific questionnaires and unscheduled health care utilization (eg, emergency GP visits, out-of-hours/111 calls, hospital admissions, and emergency department attendances).
- Exacerbations in the 6 months before and after MISSION attendance
- Cost of delivery of the clinic model

Innovations

Thorasys

- Number of new diagnoses of airways disease made after use of the Thorasys device
- Number of patients who are unable to complete reproducible spirometry who have reproducible results with Thorasys
- Number of unusable results
- Perceived ease of use by health care professionals

Flo-Tone

- Number of patients given the Flo-Tone device
- Number of patients using the Flo-Tone device following reviews, when prompted by clinical need
- Number of patients deemed to have improved the pressurized metered dose inhaler technique through use of Flo-Tone

Airsonett

- Number of patients suitable for use of the Airsonett temperature-controlled laminar airflow device
- Number of patients offered the device who accepted its use
- Change in exacerbation frequency in the 6 months before and after the use of the Airsonett device
- Number of patients who elect for ongoing use of the device after 6 months

MyCOPD and MyAsthma

- Uptake of online, supported self-management provided by my mHealth
- Acceptability of online-supported self-management by the patient and family or carer
- Number of patients using online pulmonary rehabilitation
- Number of patients who access the online self-management plan

Message Dynamics

- Acceptability of the treatment by patient
- Acceptability of the treatment by HCPs
- Number of positive triggers that can be managed by advice only
- Number of positive triggers that require clinical review, and type of review chosen
- Number of triggers that result in a clinically significant exacerbation
- Duration of monitoring required by the patient, as judged by the clinical team

Clinitouch

- Acceptability of the treatment by patient
- Acceptability of the treatment by HCPs

- Number of positive triggers generated by Bluetooth device readings
- Number of positive triggers generated by symptom scores
- Number of positive triggers that can be managed by advice only
- Number of positive triggers that require clinical review, and type of review chosen
- Number of triggers that result in a clinically significant exacerbation
- Duration of monitoring required by the patient, as judged by the clinical team

Study Participants

Study Setting

MISSION Clinics will be held in at least 10 surgeries within the Wessex region. The clinic services will be delivered by an integrated team of primary (primary care nurses and GPs), secondary (respiratory nurses, physiotherapists, physiologists, and registrars), and tertiary (regional specialist asthma service) care providers with delivery of care across all three sectors.

Overall Description of Study Participants

Adult patients (aged ≥ 16 years) with poorly controlled asthma or COPD as well as those with undifferentiated breathlessness will be identified using GRASP tools; referred from a community pharmacist or by their primary care team; and invited to a local MISSION clinic with a relative, friend, or carer in attendance, if they wish. All eligible attendees will be invited to participate in the study. The sample size will be determined by the uptake of appointments and clinic capacity but is projected to be 500 patients and 15 HCPs.

Eligibility Criteria

All patients who have attended the MISSION ABC clinic will be considered eligible to partake in the study if they are able to provide informed consent. Family or carers will be asked to participate in the qualitative research if they have accompanied the patient to an educational event. Health care participants from host surgeries or visiting from outside organizations will also be eligible for participation in the participatory action research and qualitative aspects of the study. An individual's participation in any applicable aspect of the MISSION will be unaffected by their decision to consent.

Study Procedures

Screening and Enrollment

All potential participants will be sent a Participant Information Sheet by post or email after initial contact. If they are suitable for the clinic, they will be screened for their ability to give informed consent. If they are able to consent and wish to do so, they will be enrolled at a clinic. It will be made clear to each participant that their care is unaffected by their decision to enroll in the study.

Randomization

There will be no randomization.

Study Assessments

The study assessments are summarized in Figures 1, 2, and 3 (COPD, asthma, and breathlessness, respectively).

Patient Assessments

Patient Characteristics

- Age, height, weight, and body mass index recorded at the first clinic visit
- New or changed diagnoses recorded for each patient seen
- Any change in British Thoracic Society Asthma Stage or GOLD COPD classification, as judged by the multidisciplinary team for those with newly diagnosed or established asthma or COPD
- Number and type of comorbidities pre-existing and identified through the MISSION process
- Occupation, employment status, and postal code
- Smoking status

Disease Control, Disease-Related Quality of Life, and Activation Measures

All baseline questionnaires will be sent to patients before the first clinical encounter. If they choose not to participate in the research study, these questionnaires will still aid in clinical decision-making and will be retained in the clinical record. If patients need assistance in completing these questionnaires, it will be offered at the first clinic visit. The questionnaires used are listed below:

- A baseline exploratory semistructured questionnaire designed by the team to explore disease impact and behaviors
- Disease-specific control questionnaires (Asthma Control Questionnaire [31] and COPD Assessment Test [32]): Baseline measure and then repeated at 3 and 6 months after the first clinical encounter
- Exercise tolerance and symptom measures: Veterans Specific Activity Questionnaire [33], Nijmegen questionnaire [34], and Self Evaluation of Breathing Questionnaire [35] at baseline and repeated at 3 and 6 months
- Use of unscheduled care (including GP visits), steroids or antibiotics for exacerbations, and hospital admissions recorded for each patient at 3 and 6 months compared to their 6 and 12 months visits prior to the MISSION process
- Measures of activation and medicine compliance (ASK-12 and Patient Activation Measure [36]) at baseline and 3 and 6 months
- Productivity measures (EuroQoL-5D [37] and Work Productivity and Activity Impairment [38]) at baseline and 6 months
- Quality of life scores: Short Form Health Survey-36 (generic) [39], Asthma Quality of Life Questionnaire (AQLQ) for asthma [40], and St George's Respiratory Questionnaire for COPD [41]
- Number of quit-for-life reviews that have resulted in a quit attempt at 3 and 6 months
- Prescription reconciliation at 6 months before and after the clinic visit to assess medication usage

Patient's Experience of MISSION ABC

- Semistructured questionnaires exploring patient experiences, completed after each clinical encounter
- Qualitative interviews will be completed with 10% of patients who participate in the study, exploring factual, structural, interpersonal, intrapersonal, and contextual influences on the experience of receiving the new service. Discussions will be transcribed using a transcription service and analyzed using a thematic analysis to compare themes. A second researcher will review the analysis to ensure all themes are captured.

Assessment of Innovations

Devices

- Acceptability of use of the new diagnostic devices (Niox, FeNO, and Thorasys) as well as the management tools (Flo-Tone and Airsonett) will be analyzed through structured questionnaires given to the clinic staff.
- Instances where a diagnosis is made as a result of the use of these devices, which would not be identified by standard investigation, will be recorded. If these events are unclear, the decision of the senior clinician present will be considered.
- Equipment breakdowns or technical difficulties will be recorded as a clinic process outcome.
- Proportion of patients who have continued to use supportive devices at the follow-up review will be calculated.

Digital Platforms

- HCPs' and patients' experiences of the use of digital platforms will be assessed using semistructured questionnaires.

Assessment of Monitored, Supported Follow-Up

- Number of patients offered remote monitoring, and proportion of patients who accept
- Proportion of patients with access to smartphones or home internet
- Number of triggers generated on remote monitoring
- Proportion of triggers that result in a clinically significant exacerbation
- Proportion of triggers that require a patient review
- Proportion of clinically significant exacerbations that are managed in the community
- Proportion of responses to remote monitoring that are completed by the patient
- Rate of drop outs from remote monitoring and the stated reason
- Patient and primary care experiences of using remote monitoring measured by a semistructured questionnaire

Assessment of Health Care Professionals' Experiences

In addition to the assessments listed above, a sample of 10 HCPs will be invited to participate in a focus group that will explore their views on the acceptability, appropriateness, and feasibility of the program. An independent interviewer will ask them to comment on their perceived barriers and drivers for further implementation of the program. The focus group will be recorded, but the responses will be anonymized. After transcription, the interviews will be analyzed for themes.

Participatory Action Research Outcomes

The core team will meet monthly to evaluate the clinic delivery process. Using patient and HCP feedback questionnaires, pitfalls and issues of the clinical process will be examined using Plan-Do-Study-Act analysis. When changes are made, a further review will take place in the following meeting until the change is deemed to have provided a positive impact on the process. These analyses will be recorded in a learning log.

Additional Process Outcomes

- Rate of uptake of the clinic by primary care providers when offered
- Expenditure in delivery of the clinic services including staffing costs, consumables, and unexpected expenses

Balancing Measures

We acknowledge that enhanced investigation and intervention may increase costs to health care providers in the short-to-medium term. The following balancing measures will be included as a project outcome:

- Number of GP or practice nurse sessions changed or cancelled to host the clinic
- Additional costs such as childcare or extra travel incurred by the delivery team when care is delivered remote to their usual place of work or outside the usual working week
- Number of additional GP, community nurse, or emergency department episodes resulting from remote monitoring
- Number of additional secondary care referrals resulting from the program

Discontinuation or Withdrawal of Participants from Study Treatment

Participants may withdraw at any point in the study.

Definition of End of Study

The end of study is the 6-month follow-up after the questionnaires are received from the last participant.

Data Analysis

Description of Analysis Populations

All patients recruited in the study will be included in the analysis population.

Analysis of Quantitative Outcome Data

The objective of all analyses is to examine differences in measured variables between time points.

The following comparisons will be made:

- Asthma Control Questionnaire, CAT, and AQLQ: baseline as compared to 3 and 6 months
- Emergency care outcomes: 3 and 6 months prior to study as compared to the 3- and 6-month study period
- Activation or medicine compliance (ASK-12 and Patient Activation Measure): baseline as compared to 3 and 6 months

- EuroQoL-5D and weight-bearing physical activity: baseline as compared to 3 and 6 months

All the abovementioned variables are continuous measures. Comparisons between time points will be made using the paired *t* test or the Wilcoxon matched-pairs test, depending on the distribution of the changes in outcome between time points.

Summaries of the measures of monitoring and supported follow-up will be prepared (measures outlined above). Patient satisfaction measures will be summarized descriptively. Numbers and percentages will be used for categorical variables, whereas mean and SD or median and interquartile range will be used for continuous variables. Uncertainty in percentages, means, and medians will be quantified by calculating the appropriate 95% CIs.

Participatory Action Research

Periodic reviews of process measures and feedback may result in iterative changes of the clinical model. The fidelity of clinic delivery to the original plan will be presented and analyzed.

Procedure for Dealing With Missing, Unused, and Spurious Data

Each outcome will be analyzed using measured data values of all patients. Patients with missing data will be excluded from the analyses. Suspicious data values will be checked against the source data. If there are outlying values, the analyses will be performed twice—once with the outlying values and once without the outlying values.

Interim Analysis and Criteria for Early Study Termination

No interim analyses are planned. A single analysis will be performed when all patients have completed the study. The study will not be terminated early based on any study data.

Patient Public Involvement

Study Design

The MISSION ABC clinic has been formed by feedback from patients' involvement in the prior pilots (MISSION Asthma and MISSION COPD). All relevant outcomes of patients will be recorded. All paperwork, such as Participant Information Sheets and educational literature, is reviewed by our patient participants before distribution.

Study Implementation

The steering group for MISSION ABC includes the chair of a local Patient Action Group and patients from the MISSION COPD pilot project and local Breathe Easy Groups. Ongoing data such as those generated from the cyclical evaluation of clinics will be reviewed, and the group will contribute to informing and delivering change.

Dissemination

Lay summaries of the results of the research will be written together with the Patient and Public Involvement members, disseminated both in verbal and written formats to local groups such as Breathe Easy groups, and written in appropriate formats for the Trust social media accounts. The Patient and Public Involvement members will be invited to present data locally and nationally, where appropriate.

Results

The project was funded in 2017 and enrollment was completed in 2018. Data analysis is currently underway, and the first results are expected to be submitted for publication in April 2019.

Discussion

This is a unique participatory action research study using both qualitative and qualitative methodology involving patients, carers, and HCPs. The longer-term impact of the service will be evaluated using clinical and health service outcomes that will inform decisions on future service implementation.

Conflicts of Interest

None declared.

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Abbreviations

ASK-12: Adherence Starts with Knowledge questionnaire-12
AQLQ: Asthma Quality of Life Questionnaire
COPD: chronic obstructive pulmonary disease
FeNO: fractional exhaled nitric oxide
GP: general practitioner
GOLD: Global Obstructive Lung Disease
GRASP: Guidance on Risk Assessment in Stroke Prevention
HCP: health care professional
MISSION ABC: Modern Innovative Solution Improving Outcomes in Asthma, Breathlessness, and COPD
NICE: National Institute for Health and Care Excellence

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Protocol

Genetic Determinants of Ototoxicity During and After Childhood Cancer Treatment: Protocol for the PanCareLIFE Study

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Abstract

Background: Survival rates after childhood cancer now reach nearly 80% in developed countries. However, treatments that lead to survival and cure can cause serious adverse effects with lifelong negative impacts on survivor quality of life. Hearing impairment is a common adverse effect in children treated with cisplatin-based chemotherapy or cranial radiotherapy. Ototoxicity can extend from high-tone hearing impairment to involvement of speech frequencies. Hearing impairment can impede speech and language and neurocognitive development. Although treatment-related risk factors for hearing loss following childhood cancer treatment have been identified, the individual variability in toxicity of adverse effects after similar treatment between childhood cancer patients suggests a role for genetic susceptibility. Currently, 12 candidate gene approach studies have been performed to identify polymorphisms predisposing to platinum-induced ototoxicity in children being treated for cancer. However, results were inconsistent and most studies were underpowered and/or lacked replication.

Objective: We describe the design of the PanCareLIFE consortium's work packages that address the genetic susceptibility of platinum-induced ototoxicity.

Methods: As a part of the PanCareLIFE study within the framework of the PanCare consortium, we addressed genetic susceptibility of treatment-induced ototoxicity during and after childhood cancer treatment in a large European cohort by a candidate gene approach and a genome-wide association screening.

Results: This study included 1124 survivors treated with cisplatin, carboplatin, or cranial radiotherapy for childhood cancer, resulting in the largest clinical European cohort assembled for this late effect to date. Within this large cohort we defined a group of 598 cisplatin-treated childhood cancer patients not confounded by cranial radiotherapy. The PanCareLIFE initiative provided, for the first time, a unique opportunity to confirm already identified determinants for hearing impairment during childhood cancer using a candidate gene approach and set up the first international genome-wide association study of cisplatin-induced direct ototoxicity in childhood cancer patients to identify novel allelic variants. Results will be validated in an independent replication cohort. Patient recruitment started in January 2015 and final inclusion was October 2017. We are currently performing the analyses and the first results are expected by the end of 2019 or the beginning of 2020.

Conclusions: Genetic factors identified as part of this pan-European project, PanCareLIFE, may contribute to future risk prediction models that can be incorporated in future clinical trials of platinum-based therapies for cancer and may help with the development of prevention strategies.

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KEYWORDS

ototoxicity; hearing loss; childhood cancer survivors; cisplatin; genetics; GWAS; candidate genes; polymorphisms

Introduction

Survival outcomes after childhood cancer have improved considerably over the last decades, now reaching approximately 80%. This marked increase is a result of advanced diagnostic and treatment procedures, improved stratification options, and optimized supportive care [1]. Nevertheless, more than 25% of all childhood cancer survivors (CCS) are affected with severe or life-threatening long-term side effects of treatment (eg, heart failure, secondary malignant neoplasms, and cognitive dysfunction), and approximately 75% of all CCS experience at least one long-term side effect [2,3]. Ototoxicity is a side effect of childhood cancer treatment and is defined by damage to the cochlea resulting in hearing loss, tinnitus, and/or vertigo [4].

Hearing loss is frequently encountered in childhood cancer patients and survivors treated with platinum derivatives such as cisplatin and carboplatin [5-9]. Studies have shown that 45% to 60% of CCS treated with cisplatin develop irreversible hearing loss and almost half of them may require hearing aids [10,11]. Platinum-induced hearing loss usually starts in the high frequencies but can eventually affect the lower frequencies, including speech frequencies [12].

Even though hearing loss is not a life-threatening disorder, it is a serious adverse effect of treatment, especially in children at ages before and during language acquisition. It can cause distress, anxiety, and depression leading to problems with speech development, neurocognitive functioning, school performance, and social life [6,9,12-14]. Hence, hearing loss can have a large negative and lifelong impact on quality of life [15]. Currently, novel therapeutics such as sodium thiosulfate have proven to be otoprotective, yet they cannot be applied in clinical practice since these novel therapeutics can reduce the efficacy of anticancer treatment [16].

Apart from platinum compounds, several other risk factors for hearing loss during and after childhood cancer therapy have been identified. These include a high platinum dose, renal dysfunction, young age at diagnosis, concomitant use of other potentially ototoxic drugs, and cranial irradiation. However, in total these factors only partially explain the interindividual variability in ototoxic responses to platinum [17]. This suggests that genetic susceptibility may contribute to the occurrence of hearing loss in CCS. Although several genetic association studies have been performed so far, their results are uncertain due to study design, selection of particular candidate genes, failure of independent replications, and/or the small sample size, which limits statistical power. In addition, some studies were heterogeneous with respect to ethnicity and/or the nongenetic risk profile, particularly the inclusion of cranial irradiated cases and the types of platinum compounds [6,18,19]. All but one of the previous studies in pediatric cancer survivors

focused on genetic associations within prespecified genes of interest (ie, candidate gene approach), yet it is unclear whether previous studies indeed have considered the most relevant candidate genes.

Prerequisites for a satisfactory approach to identification of genetic determinants of platinum-induced hearing loss would be adequate numbers of research subjects and well-documented clinical and treatment data. The multinational PanCareLIFE (PCL) study provides a unique opportunity to investigate preexisting and novel genetic markers for treatment-related hearing loss in CCS [20]. PCL is funded by the European Union's Seventh Framework Programme from 2013-2018 and originated from the PanCare network [21]. Investigators from 10 European countries collected data from over 12,000 CCS in order to investigate the determinants of long-term health in this population. PCL addresses three main outcomes: ototoxicity, fertility impairment, and quality of life.

This study is part of the PCL project and addresses the genetic susceptibility of platinum-induced hearing loss. Specifically, the aims were to identify clinical and genetic risk markers in a large cohort of CCS and identify additional genetic risk markers of hearing loss by genome-wide association screening (GWAS) in a carefully characterized subgroup.

Methods

In total, 8 work packages (WPs) are included in the PanCareLIFE study, of which 5 are scientific WPs. In this study, WP5 and WP4b will be addressed.

Study Population and Inclusion Criteria

WP5 aimed to identify clinical and genetic risk markers in a large cohort of CCS. For eligibility in the PCL WP5 genetic study, the following inclusion criteria were applied: (1) patients were younger than age 18 years at cancer diagnosis; (2) patients had been treated for cancer with cisplatin, carboplatin, or both; (3) patients were off therapy and had at least one pure tone audiometric evaluation available after the end of chemotherapy; and (4) patients had provided biomaterial (saliva or blood) for DNA extraction (Figure 1). Subjects were excluded from the study if they had permanent hearing loss identified before the start of cancer therapy.

WP4b used a subset of research subjects from WP5 and aimed to identify additional genetic risk markers of hearing loss by GWAS with better control of nongenetic risk factors. An additional set of inclusion criteria was imposed to reduce potentially confounding factors and focus on the influence of cisplatin. These were (1) cancer treatment included upfront cisplatin, either cisplatin as the single platinum drug throughout the entire course of treatment or change from cisplatin to carboplatin during treatment, and (2) no radiotherapy administration to the brain or inner ear (Figure 1). Research subjects whose initial treatment included carboplatin were excluded.

Ethics Approval and Consent to Participate

The PanCareLIFE study has been approved by the local ethics committees: Kantonale Ethikkommission Bern, 362/2015; Comitate Etico Regionale, 507REG2014; Ethical Committee University Hospital Brno, June 11, 2016; Ethics Committee Fakultni Nemocnice v Motole, Prague; De Videnskabsetiske Komiteer Region Hovedstaden, H-1-2014-125; Ethikkommission Medizinische Universität Graz, 27-015 ex 14/15; Ethikkommission der Universität Ulm, 160/17; Ethikkommission der Universität zu Lübeck, 14/181; Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster, 2014-619; Medische Ethische Toetsings Commissie Erasmus MC; Medisch Ethische Toetsingscommissie, 2015_202. Informed consent was obtained from the patient or their the legal representatives.

Data Collection, Storage, and Anonymization

CCS were recruited through an institutional network from several countries in Europe. The participating institutions are referred to as data providers. Each data provider collected retrospective demographic, diagnostic, treatment, and audiometric data from their medical record files and registries. Diagnostic data included the *International Classification of Disease* –coded diagnosis and date of diagnosis (for each tumor). Treatment-related data included information on platinum treatment (eg, platinum compound, dose per cycle, cumulative dose, date of start and stop treatment, and infusion duration) and potentially ototoxic comedication (eg, amikacin, gentamycin, tobramycin, furosemide, vincristine, vancomycin). The data were stripped of all identifiers and assigned a unique PCL-ID number, rendering the data pseudonymous for the investigators of this study. Data providers sent their data to the PCL data center in Mainz (German Childhood Cancer Registry, University Medical Center Mainz, Germany), which also collected and archived the genetic, clinical, and audiological data from the lab and the audiometry center.

Outcome

The main outcome of this study was hearing function following platinum treatment in pediatric cancer survivors. Diagnosis of hearing loss was based on pure tone audiometry performed at frequencies of 250, 500, 1000, 2000, 4000, 6000, and 8000 Hz [22]. Data providers sent the pseudonymized original audiograms to the audiometry center (Department of Phoniatry and Pediatric Audiology, University Hospital Muenster, Germany) for standardized review. The audiogram assessors were blinded to patient characteristics including their treatment, such as platinum compound, platinum dose, or cranial irradiation. The assessors graded the severity of hearing loss using the Muenster criteria [23,24]. The Muenster criteria considers minimal hearing loss (Muenster grade 1: >10 to ≤20 dB) and allows the detection of early post-cisplatin hearing loss. Clinically relevant hearing loss was defined as Muenster grade ≥2b [24]. The International Society of Pediatric Oncology (SIOP) Boston criteria [25,26] was used as an independent, secondary grading. Clinically relevant hearing loss was defined as SIOP grade ≥2 (Table 1).

Figure 1. Description of WP4b and WP5 study cohorts.

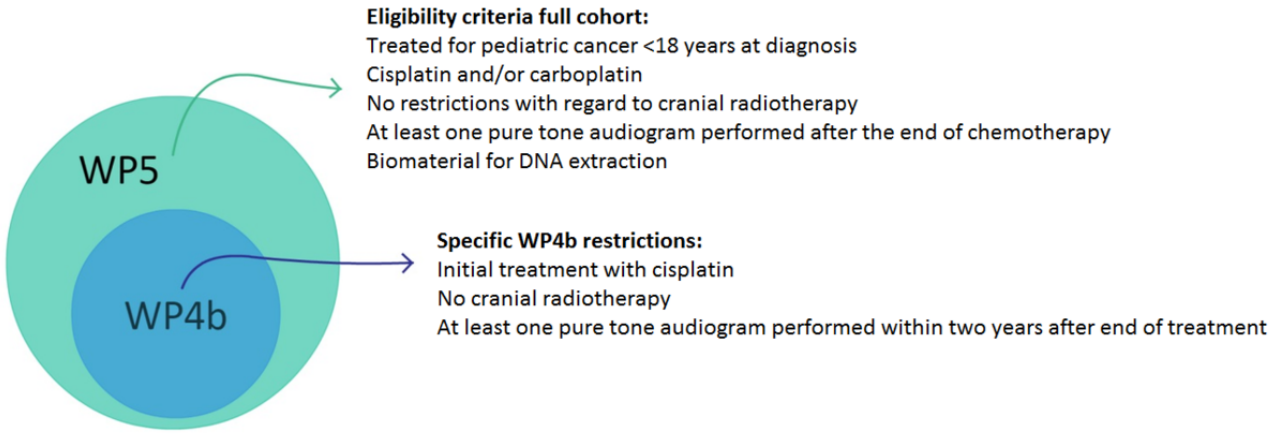


Table 1. Applied ototoxicity criteria.

Grade	Muenster criteria	SIOP[a] Boston criteria
0	≤10 dB HL[b] at all frequencies	≤20 dB HL at all frequencies
1	>10 to ≤20 dB HL at one or more frequencies or tinnitus	>20 dB HL above 4 kHz
2	>20 dB HL at 4 kHz and above	>20 dB HL at 4 kHz and above
	2a: >20 to ≤40 dB	
	2b: >40 to ≤60 dB	
	2c: >60 dB	
3	>20 dB HL at <4 kHz	>20 dB HL at 2 kHz and above
	3a: >20 to ≤40 dB	
	3b: >40 to ≤60 dB	
	3c: >60 dB	
4	≥80 dB at <4 kHz	>40 dB HL at 2 kHz and above

[a]SIOP: International Society of Pediatric Oncology.

[b]HL: hearing loss.

DNA Collection and Genotyping

Detailed methods for DNA collection and genotyping are described elsewhere [27]. For the first aim of the genotype study, a candidate gene approach was applied to validate 10 previously identified single nucleotide polymorphisms (SNPs) associated with hearing loss in childhood cancer patients and survivors [19,28-40]: *ACYP2*, *LRP2*, *NFE2L2*, *OTOS*, *TPMT*, *SOD2*, *SLC22A2*, *GSTP1*, *ABCC3*, and *SLC16A5* [30,32,35,38,40-43]. In WP4b, array-based genotyping data was used. Thereafter, these data were merged with data from TaqMan PCR generated in WP5. Next, novel SNPs that were independently associated with treatment-related hearing loss in childhood cancer patients were explored within WP4b by GWAS. For maximum standardization, array genotyping in the PCL consortium was conducted by one partner (genetic laboratory of the Department of Internal Medicine in the Erasmus Medical Center, Rotterdam, the Netherlands) [44]. The Infinium Global Screening Array (Illumina, Inc), which contains >770,000 SNPs, was used [45].

Quality Control and Imputations

A stringent quality control protocol was applied where multiple filters were used to ensure the quality of the genetic data prior to either imputations or analysis. The quality control procedure is described elsewhere [27]. To remove poorly genotyped SNPs and individuals from the data, a call rate of 97.5% was applied. In addition, a Hardy-Weinberg equilibrium test ($P<1*10^{-7}$) was assessed to identify potential genotyping errors. Samples with gender mismatches, familial relationships, and extreme heterozygosity were removed to ensure sample quality. After the quality control, principal components were calculated in order to adjust for population heterogeneity and technical confounders in all subsequent analyses [46]. Imputations were performed using the Michigan Imputation Server with default settings [47]. The reference panel chosen for imputations was the Haplotype Reference Consortium (HRC r1.1) [48]. This panel has also been used in large-scale population-based studies such as the Rotterdam Study [49] and Generation R [50].

Statistical Power

To estimate the number of cases required for the GWAS analyses, a sample size calculation was performed. Assuming a risk allele frequency of 0.2, a case to control ratio of 1:1, and a *P* value threshold of $P<5*10^{-8}$ for the GWAS analysis, a cohort of 574 patients was considered sufficient to detect an odds ratio of at least 2.8 with a statistical power of 80% in the design of the study.

Genetic Susceptibility Analysis

For both candidate gene and GWAS analyses, genetic profiles from children who were treated with cisplatin and have hearing impairment were compared to those of children treated with cisplatin who did not develop hearing impairment. Relationships of categorical data were compared using the chi-square and Fisher exact tests. Comparison of distribution between groups with continuous data was tested with the Mann-Whitney and Kruskal-Wallis tests. Standard logistic regression models adjusting for age at diagnosis, gender, total cumulative cisplatin dose, and principal components were employed to calculate odds ratios with 95% confidence intervals in order to assess the risk of hearing loss. Principal component analysis, a common tool that has been widely used for the combined analysis of correlated phenotypes in genetic linkage and association studies, was used to correct for population stratification by modeling ancestry differences between cases and controls. Bonferroni correction was used in the candidate gene analysis to adjust for multiple testing. In the GWAS, a suggestive significance threshold of $P<1*10^{-6}$ was used to identify relevant SNPs that could be important but did not reach genome-wide significance ($P<5*10^{-8}$). All statistical analyses were performed by investigators of WP4b and WP5 in close collaboration with the Biostatistical Support Group of UMC Mainz and Ulm.

For both the WP4b candidate gene approach and WP4b GWAS, replication analysis is planned within an independent Canadian cohort from the Canadian Pharmacogenomics Network for Drug Safety (CPNDS).

Results

Study participants were recruited through a network of 14 institutions from 7 countries: Switzerland, Italy, Czech Republic, Denmark, Germany, Austria, and the Netherlands. The data providers and number of patients per data provider are shown in Table 2; data providers and locations are depicted on a map in Figure 2. WP5 ultimately enrolled a total of 1124 patients. Compared to WP5, WP4b investigated a more restricted study population of 598 patients. Germline DNA, extracted from EDTA blood or saliva samples, was used for genotype studies. To reduce patient discomfort and boost study enrollment, saliva was allowed as an alternative to blood. In total, the data providers collected a similar number of blood and saliva samples. Biosamples were stored and processed at the University Medical Center Ulm, Germany, and at the Erasmus Medical Center Rotterdam, the Netherlands, until analysis. Blood samples were stored at –20°C or lower; saliva samples were stored at room temperature. Germline DNA was extracted using the salting-out method and served as a template for TaqMan polymerase chain reaction (PCR; WP5) and array-based genotyping (WP4b).

Patient recruitment started in January 2015 and final inclusion was October 2017. We are currently performing the analyses and the first results are expected by the end of 2019 or the beginning of 2020.

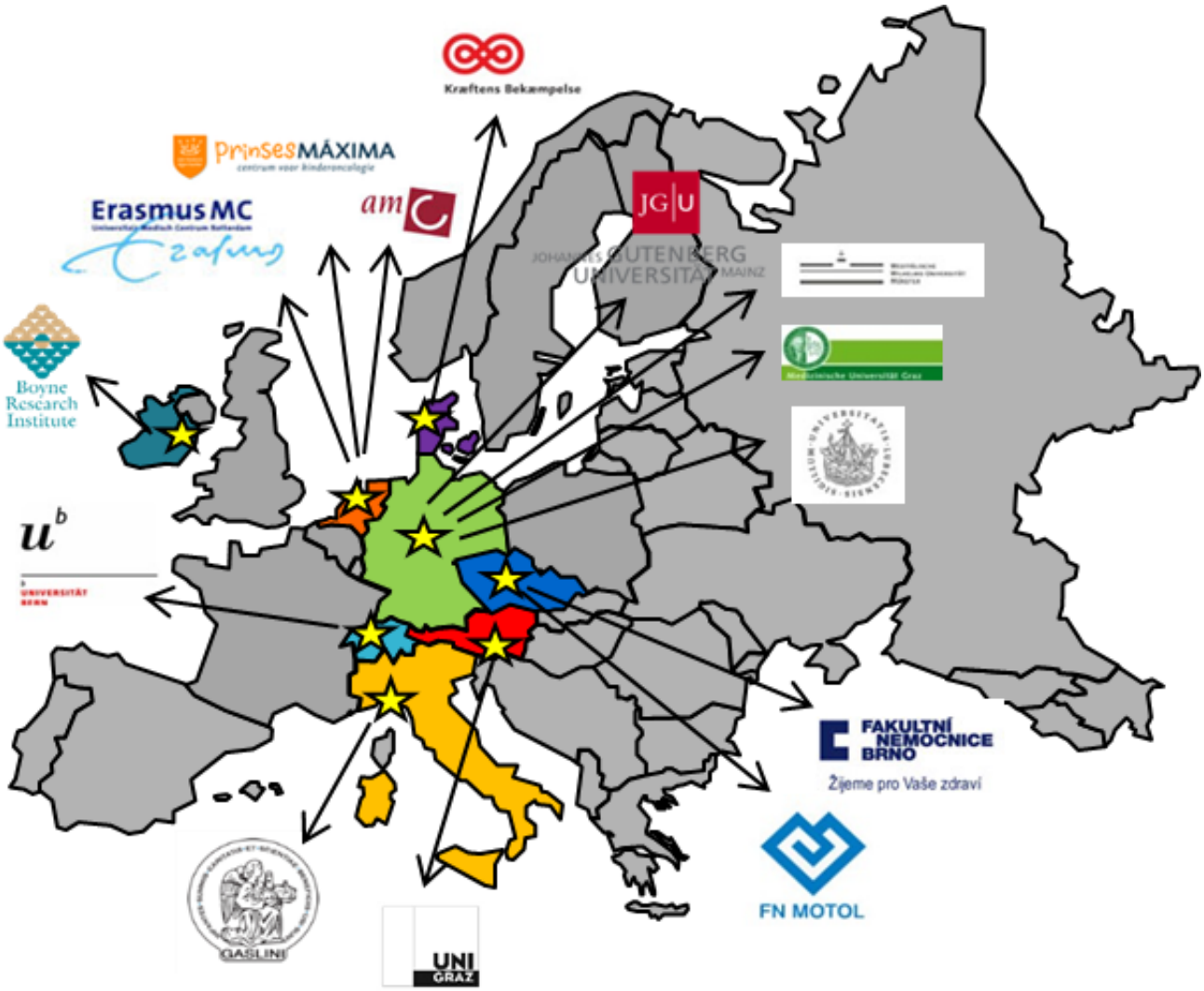
Table 2. Data providers included in the genetics study.

Data provider	Country	Patients enrolled in WP5[a]	Patients enrolled in WP4b[b]
University of Bern, Bern	Switzerland	153	73
Istituto Giannina Gaslini, Genova	Italy	8	8
University Hospital Brno, Brno	Czech Republic	173	54
Motol Teaching Hospital Prague, Prague	Czech Republic	86	41
Kraeftens Bekaempelse, Copenhagen	Denmark	94	35
Osteosarcoma clinical trial	Germany	124	107
University Hospital Muenster, Muenster	Germany	297	111
Euramos clinical trial	Germany	36	34
University Lübeck, Lübeck	Germany	30	12
University Graz, Graz	Austria	29	10
Academical Medical Center Amsterdam, Amsterdam	The Netherlands	17	22
Erasmus Medical Center, Rotterdam	The Netherlands	32	32
University Medical Center Groningen, Groningen	The Netherlands	18	18
Princess Máxima Center for Pediatric Oncology, Utrecht	The Netherlands	27	27

[a]WP5: work package 5.

[b]WP4b: work package 4b.

Figure 2. Data providers participating in WP4b and WP5 of PanCareLIFE: University of Bern, Instituto Giannina Gaslini, University Hospital Brno, Motol Teaching Hospital Prague, Kraeftens Bekaempelse, University Graz, Osteosarcoma clinical trial, University Hospital Muenster, Euramos clinical trial, University Lübeck, Academical Medical Center Amsterdam, Erasmus Medical Center Rotterdam, University Medical Center Groningen and Princess Máxima Center for Pediatric Oncology Utrecht. PanCareLIFE study management: Boyne Research Institute Drogheda and German Childhood Cancer Registry Mainz.



Discussion

Principal Findings

This paper describes the design of the PCL ototoxicity genetics study aiming to identify clinical and genetic risk markers in a large and heterogeneous cohort of CCS and identify additional genetic risk markers of hearing loss by GWAS with better control of nongenetic risk factors in a more homogenous subcohort of CCS. Data were collected from 1124 CCS from 7 different European countries. Some of the previously identified genetic variants for hearing loss were validated by a candidate gene approach. In addition, the first international GWAS of cisplatin-induced hearing loss sets out to identify novel allelic variants in the largest European cohort assembled for such a genome-wide pharmacogenetics association study so far.

For this study, a subcohort was recruited consisting of patients who were treated with cisplatin and did not receive cranial irradiation, a well-known independent risk factor for sensorineural hearing loss. From 14% to 27% of children who received radiotherapy without ototoxic chemotherapy suffered from high-frequency hearing loss [51,52]. This risk of hearing loss increases in patients who require platinum-based chemotherapy combined with radiation. Whether the same genetic markers are associated with platinum- and radiation-induced hearing loss is unknown. To limit contamination by the presence of confounding factors such as cranial irradiation, a more homogenous subcohort of patients was selected for WP4b.

Appropriately sized cohorts are required to identify genetic determinants of platinum-induced hearing loss. The many associations that are tested in a GWAS require a very low significance threshold to prevent an inflated genome-wide type I error. This reduces the probability of identifying SNPs with small effect size, unless sample sizes are large enough to achieve sufficient power to identify such SNPs. The large combined cohort within the PCL consortium is expected to provide adequate statistical power.

Many classification systems of drug-induced hearing loss have been developed—Brock grading system [53], American Speech-Language-Hearing Association (ASHA) criteria [54],

Chang classification [55], Muenster classification [24], and the SIOP Boston Ototoxicity Grading Scale [26]—yet an international standard for ototoxicity reporting is still lacking. Choice of the classification system and definitions of hearing loss may have an impact on the frequency of occurrence in childhood cancer survivors [56], as shown in a recent study that investigated the influence of several classification methods in a large prospective cohort of platinum-treated children and adolescents. Estimates of the overall occurrence of hearing loss (40% to 56%) and severe hearing loss (7% to 22%) cover a wide range [57]. Compared to other methods, Muenster grade 1 is considered a strong predictor for the need of hearing support in CCS, with reported sensitivity and specificity levels of 67% and 87%, respectively [58]. In addition, the SIOP Boston scale might be superior to determine hearing loss compared to the ASHA, Brock, and Common Terminology Criteria for Adverse Events (CTCAE) methods, based on the high number of evaluable assessments, sensitivity, and earliest time to detect hearing loss [57]. In order to strengthen our study, both the Muenster classification and SIOP Boston scale were used for a valid interpretation of the severity of platinum-induced hearing loss in this cohort.

The availability of a large European set of clinical, audiometric, and genetic data provides the PCL consortium excellent opportunities for further collaboration, including replication studies in independent transatlantic cohorts or meta-analyses. In order to validate findings from the initial discovery cohort, it is standard practice to include an independent replication cohort. A collaboration with the CPNDS for replication of results of this study has been initiated. The patients enrolled in our replication cohort were recruited from 11 hospitals and health care centers in Canada. Hearing loss in the CPNDS cohort was originally graded according to the CTCAE [29]. Applying a standardized definition for hearing loss facilitates a combined analysis of the CPNDS and PCL data. For that purpose, end point harmonization was pursued by reevaluating all audiograms (EC) of the CPNDS cohort according to Muenster and SIOP criteria. Additional replication cohorts could be needed for future international collaborations.

Limitations

The PanCareLIFE ototoxicity studies have some limitations. As a result of missing or unclassifiable audiograms, some patients cannot be included due to a missing phenotype. Because many of the patients with missing audiograms might have good hearing function, they might therefore no longer be followed up for audiometric testing, As a consequence, the risk of ototoxicity based on the results of this study might be an overestimation of the true risk. Currently, the International Late Effects of Childhood Cancer Guideline Harmonization Group is developing recommendations for audiological monitoring in CCS. The guideline unifies existing recommendations and provides optimum follow-up practices, which is important for consensus on the frequency and timing of audiological evaluations after childhood cancer [59].

Conclusions

In summary, our paper described the design of a genetic susceptibility study that addresses an important late effect of cancer therapy (ie, platinum-induced hearing loss in survivors of cancer diagnosed and treated during childhood). Identification of genetic risk factors may assist in the development of more accurate prediction models that can be incorporated in future clinical trials of platinum-based therapies for cancer. Increased knowledge of nongenetic and genetic risk factors of cisplatin-induced hearing loss may contribute to the development of preventive methods to improve quality of life in CCS.

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Authors' Contributions

EC, AM, and MMvdHE wrote the manuscript. EC, ALFvdK, and MMvdHE coordinated the study and were responsible for study logistics. TL, CEK, MLG, TK, JK, JFW, WJET, AaZD, and OZ coordinated the study nationally and were responsible for study logistics, patient recruitment, and data collection from the various institutions. JB, DG, HB, and PK were involved in coordination and management of the central data center and/or PanCareLIFE. LB, OZ, EC, and ALFvdK were involved in aspects of genetic statistical analyses. EC, AM, MMvdHE, and OZ contributed to the conception and the design of the study. MMvdHE, AU, LB, and OZ were involved in aspects of conceptualization and study design. MMvdHE and AdV are the principal investigators. All authors critically read and revised the manuscript. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ASHA: American Speech-Language-Hearing Association
CCS: childhood cancer survivors
CPNDS: Canadian Pharmacogenomics Network for Drug Safety
CTCAE: US National Cancer Institute Common Terminology Criteria for Adverse Events
GWAS: genome-wide association screening

PCR: polymerase chain reaction
PCL: PanCareLIFE
SIOP: International Society of Pediatric Oncology
SNP: single nucleotide polymorphism
WP: work package
WP4b: Work Package 4b
WP5: Work Package 5

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Original Paper

Identification of Complex Health Interventions Suitable for Evaluation: Development and Validation of the 8-Step Scoping Framework

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Abstract

Background: There is extensive literature on the methodology of evaluation research and the development and evaluation of complex interventions but little guidance on the formative stages before evaluation and how to work with partner organizations that wish to have their provision evaluated. It is important to be able to identify suitable projects for evaluation from a range of provision and describe the steps required, often with academic institutions working in partnership with external organizations, in order to set up an evaluation. However, research evaluating programs or interventions rarely discusses these stages.

Objective: This study aimed to extend work on evaluability assessment and pre-evaluation planning by proposing an 8-Step Scoping Framework to enable the appraisal of multiple programs in order to identify interventions suitable for evaluation. We aimed to add to the literature on evaluability assessment and more recent evaluation guidance by describing the processes involved in working with partner organizations.

Methods: This paper documents the steps required to identify multiple complex interventions suitable for process and outcome evaluation. The steps were developed using an iterative approach by working alongside staff in a local government organization, to build an evidence base to demonstrate which interventions improve children's outcomes. The process of identifying suitable programs for evaluation, thereby establishing the pre-evaluation steps, was tested using all Flying Start provision.

Results: The 8-Step Scoping Framework was described using the example of the local government organization Flying Start to illustrate how each step contributes to finding projects suitable for process and outcome evaluation: (1) formulating overarching key questions that encompass all programs offered by an organization, (2) gaining an in-depth understanding of the work and provision of an organization and engaging staff, (3) completing a data template per project/program offered, (4) assessing the robustness/validity of data across all programs, (5) deciding on projects suitable for evaluation and those requiring additional data, (6) negotiating with chosen project leads, both within and outside the organization, (7) developing individual project evaluation protocols, and (8) applying for ethical approval from the university and partner organization.

Conclusions: This paper describes the processes involved in identifying suitable projects for evaluation. It adds to the existing literature on the assessment of specific programs suitable for evaluation and guidance for conducting evaluations by establishing the formative steps required to identify suitable programs from a range of provision. This scoping framework particularly relates to academic partners and organizations tasked with delivering evidence-based services designed to meet local needs. The steps identified have been described in the context of early years provision but can be applied to a range of community-based evaluations, or more generally, to cases where an academic partner is working with external stakeholders to identify projects suitable for academic evaluation.

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KEYWORDS

complex interventions; early years; evaluation; multistakeholder provision

Introduction

There is extensive literature on evaluation research methodology and development and evaluation of complex interventions, from identifying existing evidence to measuring outcomes and understanding processes [1-7]. However, there is little guidance on the formative stages of identifying suitable services/programs for evaluation and the ways to work with partner organizations that wish to have their provision evaluated in order to build an evidence base related to their particular local, geographical or cultural context beyond basic advice [8-10]. A possible disadvantage of conducting a robust evaluation is the risk of finding no change or negative results, potentially influencing future funding decisions and reputations.

Research on program evaluation rarely discusses the steps involved prior to evaluation in order to identify suitable projects, often with academic institutions working in partnership with external organizations to set up an evaluation. Guidance assumes that projects have already been identified, providing detailed instructions to plan and conduct evaluations. For example, Newcomer et al assumed that the projects to be evaluated were already chosen, and evaluators and organization staff had planned their evaluation approach [11]. They described the fundamental considerations that evaluators and organizations should address before beginning any evaluation activities, starting with matching evaluation approach to key questions, producing methodological rigor and appropriate evaluation design, or identifying ways to apply an evaluation framework in a particular disciplinary context [12].

Pre-evaluation activities are mostly discussed in the literature on evaluability assessment, which was first conceptualized in the late 70s [13] after the costly, large-scale evaluations of major social interventions in the United States in that period reported no benefit. Poor evaluation approaches and ultimately, disappointing results, were thought to be the result of inadequate program definition and lack of development and specification of causal links between intervention actions and expected results. In response, a "pre-assessment of evaluability" was developed to improve evaluation methodology, not by assessing whether a program can be evaluated, "but [by] whether the program is ready to be managed to achieve desired performance and outcomes, what changes are needed to allow results-oriented management, and whether evaluation is likely to contribute to improved program performance" [14]. Evaluability assessment has been revived in recent years, because the demand for evidence-based practice of has increased [15].

Evaluability assessment is a systematic method to plan robust evaluations as well as a "low-cost pre-evaluation activity to prepare better for conventional evaluations of programmes" [16] in order to make sound decisions on evaluation methodology before funds are committed. The approach is viewed as a way to balance the growing demand for evidence through evaluation when limited resources are available [15]. A recent rapid scoping review showed the range of interventions that have been assessed by evaluability assessment methodology to determine their suitability for evaluation, such as the State Asthma Programme [17], the Healthy Community Challenge Fund [18], and National Driver Retraining Programme [19].

Evaluability assessment focuses on the feasibility of evaluating a specific intervention and usually involves the following key stages: structured engagement with stakeholders to understand the context of a particular intervention and ensure evaluation findings are meaningful, development of a theory of change to inform implementation and identify key outcomes, review of existing literature and data to establish quality of evidence already available, and recommendations for proposed evaluation designs. Evaluability assessment allows researchers to assess the suitability of a specific intervention for evaluation by working through the aforementioned four stages.

As it is designed to assess the suitability of a particular intervention for evaluation, it assumes that organizations that want to have their provision evaluated have the expertise to identify projects suitable for evaluation. The 8-Step Scoping Framework detailed here guides researchers and stakeholders through the stages prior to evaluability assessment, where the appetite for evaluation exists but the scope is ill defined. The 8 steps described are discussed using an example of a local government organization, Flying Start, to illustrate how each step contributes to the ultimate aim of identifying projects suitable for a process and outcome evaluation.

Flying Start [20] is part of Luton Borough Council, which is a part of the UK local government. It is a unitary local authority; as such, it provides all local services including health and social care, education, and learning. Flying Start aims to improve social, emotional, and health outcomes for children from the point of pregnancy to the age of 5 years. The importance of the early years and inequality in developmental outcomes is well documented [21-26]. Flying Start and the University of Bedfordshire are developing a process and outcome-evaluation framework to establish the efficacy of their multistakeholder provision, find evidence of what works, and ensure the provision offered meets local needs [27].

In this paper, the term "provision" most often refers to all the work of an organization to discern what it offers; "programs" or "services" are terms more likely used by an organization to describe the services they offer to the public or clients; and "intervention" is the more scientific term researchers favor to describe a project, program, or service that is subject to a process and outcome evaluation.

There is limited information in the literature about the steps required to identify suitable interventions before conducting an evaluation. This paper therefore aims (1) to extend work on evaluability assessment and pre-evaluation scoping by proposing an 8-Step Scoping Framework to be applied prior to evaluability assessment to enable the appraisal of multiple programs in order to identify interventions suitable for evaluation and (2) to add to the literature on evaluability assessment and more recent

evaluation guidance by describing the processes involved when working with partner organizations.

Methods

This paper documents the steps involved in identifying multiple complex interventions suitable for process and outcome evaluations. We developed an 8-Step Scoping Framework to identify complex health interventions. The framework guides the selection of suitable interventions for evaluation from a range of projects. Evaluability assessment allows in-depth appraisal of one project and is particularly important when considering the evaluation of larger, costly interventions before making a decision to commission an evaluation and begin detailed evaluation planning (Figure 1).

To refine these stages, an iterative approach was taken in order to develop the steps described below. The process was developed through regular meetings between an academic institution and stakeholders, which allowed a collaborative and reflexive process where researchers reported progress and were able to form a critical understanding of stakeholder priorities, and practical considerations were balanced with research objectives. A log was maintained to document progress during the process of identifying projects suitable for evaluation.

The 8-Step Scoping Framework was developed over an 11-month period through a series of meetings with Flying Start, Luton Borough Council, and associated stakeholders. Table 1 details the nature of the meetings, attendee numbers, affiliations, and their roles in the development of the pre-evaluation framework. The meetings were conducted concurrently during the development of the framework. All meetings, except the Scoping Framework planning meetings, were ongoing as part of Flying Start's activities. The Flying Start staff meetings allowed researchers to gain an in-depth understanding of Flying Start provision, range, number, and development of services. The Partnership Board and Project Evaluation Group meetings allowed the input of a range of professionals on evaluation scoping strategy, identification of framework steps, and feedback on framework development through various iterations. The Scoping Framework-planning meetings were devoted to reporting framework progress and allowed researchers to apply the developing scoping criteria to Flying Start projects.

Formulation of the steps was led by the following key aims: to determine ways to obtain a full understanding of the provision offered by an organization; to arrive at a consensus on the type of questions to be asked in order to assess suitability of provision for evaluation; to find the best way to obtain such information from stakeholders; to refine the scoping process to allow a decision on suitable projects, space for negotiation with project leads, and development of stand-alone project-evaluation protocols per chosen project.

Meeting minutes with decisions made were typed up and circulated for comment and discussion as the framework steps were defined and clarified. The process of identifying suitable programs for evaluation, thereby establishing the 8 scoping steps, was tested using all Flying Start provision. During the framework-development period, 36 programs/services were offered by Flying Start to families in Luton. First and successive drafts of the Scoping Framework were presented to Flying Start, council staff, researchers, and associated stakeholders over time.

Figure 1. Context of 8-Step Scoping Framework in relation to evaluability assessment and evaluation planning.

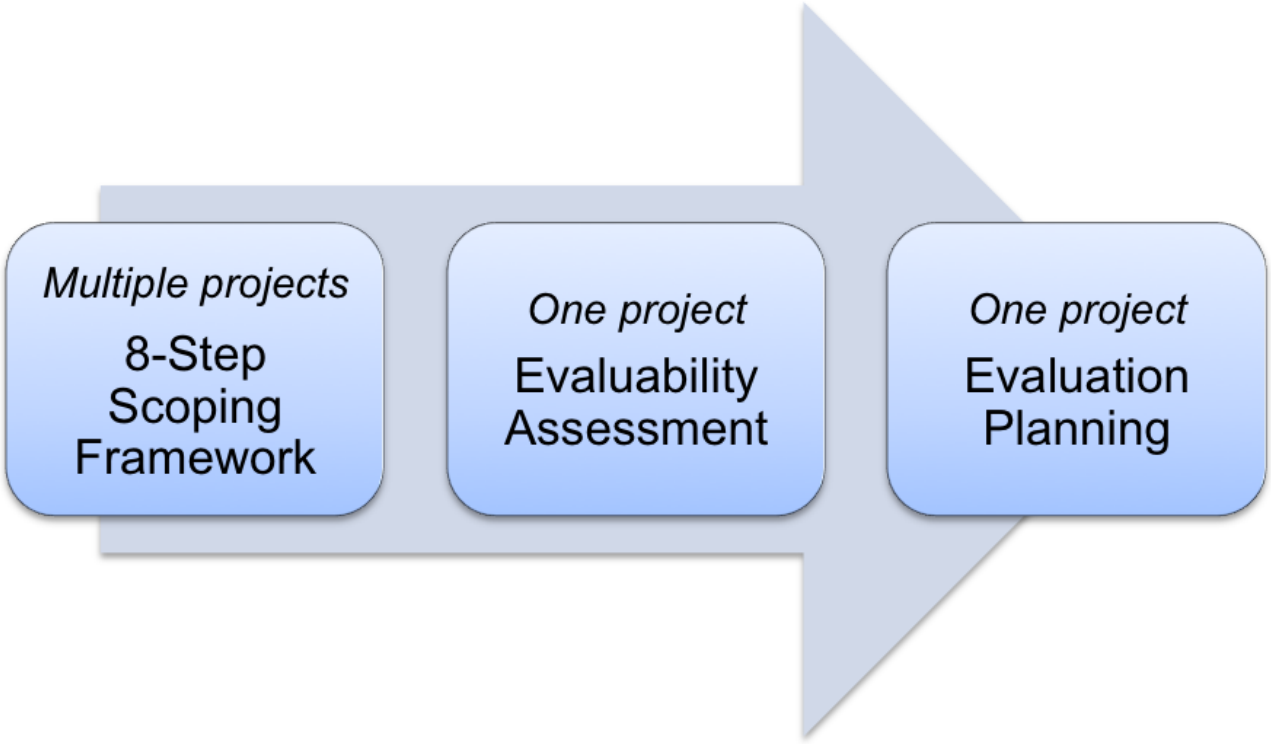


Table 1. Characteristics of the meetings used to develop the 8-Step Scoping Framework.

Characteristic	LBC[a] and Flying Start Partnership Board	Flying Start Project-Evaluation Group	Flying Start staff	Scoping Framework planning
Number of meetings held over the framework-development period	5 (bimonthly)	8 (every 4-5 weeks)	10 (monthly)	16 (every 2-3 weeks)
Purpose	Multiagency meeting to discuss issues related to early years services	Forum to discuss evaluation approaches for Flying Start services	Staff to update on progress and discuss any arising matters	Mapping of Scoping Framework progress
Attendees	Council heads of services, Flying Start staff, early years and public sector organizations, midwives, nutritionists, general practitioners, and councilors	Flying Start staff, LBC staff, and University of Bedfordshire staff	Flying Start staff, practitioners working in early years services, and university evaluation team	Flying Start senior staff and university evaluation team
Approximate number of attendees	15-20 stakeholders	8-12	15-20	3-5
Role in framework development	Input from a range of professionals and feedback on framework development	Identifying framework steps through various iterations	Gaining in-depth understanding of Flying Start provision, range, and number of services	Applying scoping criteria to all Flying Start services/programs offered

[a]LBC: Luton Borough Council.

Results

The steps in the 8-Step Scoping Framework are presented in Figure 2. The steps are discussed using a specific example of the local government organization Flying Start to illustrate how each step contributes to the ultimate aim of finding projects suitable for process and outcome evaluation.

Step 1 – Formulating Overarching Key Questions That Encompass All Programs Offered by an Organization

This may sound like an obvious first step, but it is important to determine whether the organization has an overarching aim guiding the content and purpose of their provision. Can this be translated into a research question to guide an evaluation? When considering multiple projects, is there a coherent research question that encompasses all projects? Most organizations will have key aims or a mission statement that can be reframed as a research question, which serves as a useful guide to ensure the overall evaluation strategy retains its focus and that the research question aligns with the objectives of the organization. In the case of Flying Start, a part of the Luton Borough Council, the overarching research question to guide the evaluation strategy was “What impact does an integrated early year’s strategy make on a life ready for learning at age five in a unitary authority?” This question was divided further into three subquestions:

- Has Flying Start succeeded in improving child/family outcomes?
- Was Flying Start more successful with certain groups and why?
- What aspects of Flying Start did participants (families) find most beneficial?

Irrespective of whether the organization has specific programs it wishes to evaluate or is led in consultation with an academic partner, the next step is vital.

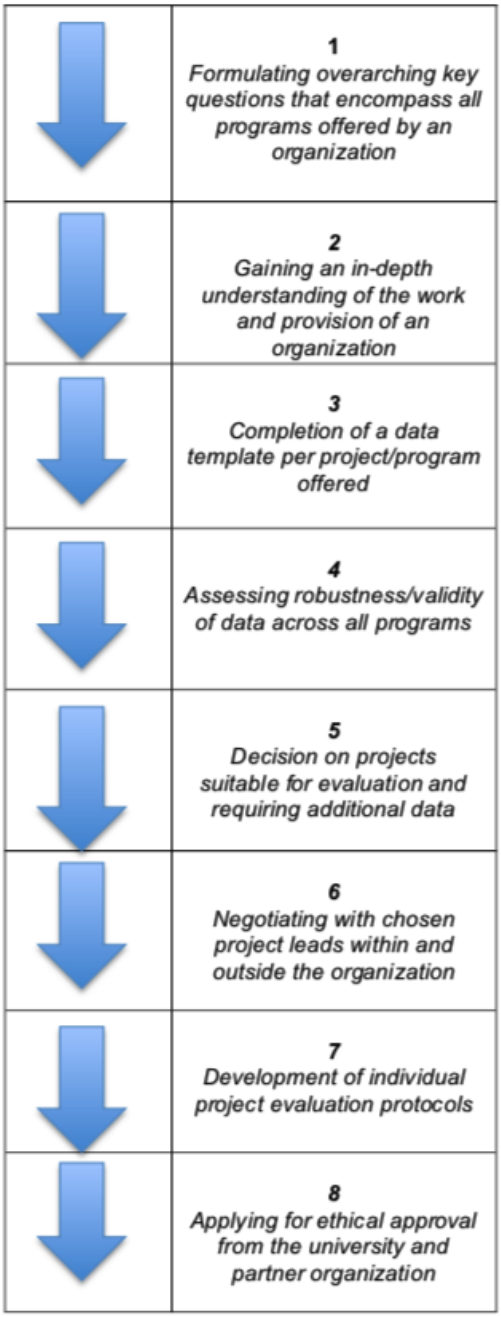
Step 2 – Gaining an In-Depth Understanding of the Work and Provision of an Organization

In the case of Flying Start, the requirement to evaluate their provision was a priority, but what was to be evaluated was unclear. Through a series of meetings, a logic model was developed to identify a set of questions that would help to both understand the provision and assess its suitability for evaluation [28]. What services would lend themselves to a robust process and outcome evaluation, which could then be published in peer-reviewed academic journals, thereby building a credible evidence base for their work? How to be strategic with the evaluation, given the finite resources and research capacity? In order to answer these questions, it is essential to negotiate access to the organization and be available to attend meetings, particularly where staff are given a forum to discuss their work and current progress. What may seem to be one organization from the outset is, in fact, a complex structure consisting of staff working in a considerable range of ways to deliver services. The researcher can begin understanding in detail how provision fits together, who it is aimed at, and the level of need it attempts to address.

Underlying all these issues, however, is an understanding of the pressures an organization faces, such as lack of staff, limited resources, responding to diverse and changing needs of a community, government guidelines, policy steers with ebbs and flows in funding, getting services up and running, and reaching those who need help most but are least likely to access services. Attending meetings and building relationships cement trust [1] and allays fears around being the subject of an evaluation. If a researcher is available to answer questions and give advice more generally about research and evaluation, it is possible to be a

valuable resource to the organization in terms of embedding evaluation methodology across all services, not only the interventions chosen for evaluation.

Figure 2. The 8-Step Scoping Framework for identifying complex health interventions suitable for evaluation.



Step 3 – Completion of a Data Template per Project/Program Offered

Understanding the range and content of an organization's provision is different from establishing suitability for evaluation. With Flying Start, a template was developed for project/service leads to complete requesting information on target audience for service; service aims; whether any baseline data was collected prior to inception; key performance indicators linked to outcomes (eg, communication and language, nutrition and diet, and social and emotional development); the data available and what it signifies; who owns the data (is it in the public domain?); who the data custodian is; how often data is collected; opportunities for tracking cohorts, size, and scale of the intervention; coverage (population, town wide, or ward level); whether participants (parents/families) are likely to be involved in more than one program; and the start date and length of intervention (Multimedia Appendix 1).

Researchers also agreed on key terminology during the process to avoid misunderstandings. For example, the term "provision" was used to describe the range of work an organization does to discern what was offered; "programs" or "services" were used to describe what was offered to the public or clients; and

"intervention" was the scientific term used to describe a project, program, or service that lends itself to a process and outcome evaluation.

An evaluation workshop was then organized with all project leads and other key Flying Start staff with the aim of encouraging staff to think about ways to evaluate their provision, answer evaluation and research questions, and provide guidance on how to fill in the data templates. A total of 36 programs/services were offered by Flying Start to families in Luton. The staff divided them into 8 domains: Antenatal/baby, Communication, Life course approach to healthy weight, Child mental health, Strong and supportive parents, System changes, Child safety, and Other. The event helped engage stakeholders in meaningful ways [29], foster partnerships, agree on the remit of different programs [6], support staff on ways to build an evidence base demonstrating the efficacy of their provision, and offer overall criteria to refer to in order to understand why some provision may be more suitable for evaluation. Possession of the completed data templates allowed different projects to be assessed and compared, leading to the next step.

Step 4 – Assessing Robustness/Validity of Data Across All Programs

With the completed data templates, the task of assessing suitability of projects for evaluation could be approached systematically. It was easier to approach project leads with any follow-up questions after referring to the templates. Key criteria (Table 2) for deciding on projects were assessment of quality of data (ie, use of validated outcome tools/scales for data collection); presence of an explicit statement on the causal assumptions of how the intervention will work [1]; presence of a robust existing theory underpinning the intervention [29]; whether a theory can be identified or developed if no theory is evident [2]; presence of any other factors that drive the program, such as experience and professional practice [1]; whether the intervention is developed to a point that it can reasonably be expected to have a worthwhile effect [2]; whether there are systems or protocols already built in to projects to collect the process and outcome data required; and whether it is possible to make comparisons with control groups in order to measure progress of those using a service or participating in an intervention. Practical considerations were paramount; for example, had a project already started [9]? How long would the project/intervention run for? What were the funding restrictions? Strategically, a project may appear to be on a smaller scale, but may run for a sufficient amount of time to produce multiple cohorts of participants and therefore yield the quantity and depth of data required.

Services that appear suitable for evaluation on first inspection may, in fact, be in the early stages of implementation or facing implementation problems such as issues with recruitment or referral processes. Such problems are particularly significant when working with vulnerable families to, for example, assess the level of support required and willingness to engage with or attend services. Strategic decisions may have to be made to focus attention and resources elsewhere if an otherwise suitable program is facing problems with, for example, implementation, recruitment, or referrals of suitable participants. An exception may be made if a decision is taken to focus only on an early stage process study of an intervention that may not take off but may have strategic importance to an organization and contribute to academic debate. Such negotiations are most constructive when the preceding steps have been followed, allowing for face-to-face discussions and fruitful working relationships.

Step 5 – Decision on Projects Suitable for Evaluation and Requiring Additional Data

By applying the abovementioned criteria in step 4, the projects lending themselves to evaluation were identified. Research capacity [1] was then used as a guiding factor to ascertain what was possible to take on, by producing an evaluation timetable with timelines for each project under evaluation. As Flying Start offers a wide range of early years provision, it was also important, where practicably possible, to reflect diversity in the projects chosen. The provision/ interventions chosen were Sign 4 Little Talkers/Big Feelings [30,31], which uses sign language to support the development of language, vocabulary, and positive behavior in children below 5 years of age; Healthy Exercise Nutrition for the Really Young (HENRY) [32-34], an obesity-prevention program for families with children below 5 years of age; Incredible Years [35-37], a parenting program for high risk socioeconomically disadvantaged families with children aged 3-5 years old having behavioral problems; and Parents as Partners [38,39], which offers counselling to improve couple relationships in order to improve child well-being and developmental outcomes (Table 3).

Table 2. Criteria for assessing data related to projects/interventions.

Criteria	Sign 4	HENRY[a]	Incredible Years	Parents as Partners
Data quality/outcome data	Sufficient	Sufficient	Sufficient	Sufficient
Theoretical basis	Yes	Yes	Yes	Yes
In-built evaluation tools	Yes	Yes	Yes	Yes
Prior evidence of positive effect	Pilot data	Yes	Yes	Yes
Control group comparisons	Retrospective and baseline data	Baseline data	Baseline data	Baseline data
Has the project started?	Yes	Yes	Yes	Under negotiation
Funding terms	Funded	Funded	Funded	Under negotiation
Is it scalable or does it involve multiple cohorts?	Yes	Yes	Yes	Yes

[a]HENRY: Healthy Exercise Nutrition for the Really Young.

Table 3. Complex interventions identified by application of the 8-Step Scoping Framework.

Project characteristics	Sign 4	HENRY[a]	Incredible Years	Parents as Partners
Scope	• To improve vocabulary and communication in preschool children	• Obesity prevention for parents of preschool children	• To address early onset behavioral problems in preschool children	• To improve couple relationship quality impacting children's outcomes
Aims	• To investigate the impact of Sign 4 on early years outcomes and implementation, and lay and professional views	• To investigate pre- and postintervention impact on self-reported outcomes and implementation, and lay and professional views	• To investigate pre- and postintervention impact on self-reported outcomes and implementation, and lay and professional views	• To investigate pre- and postintervention impact on self-reported outcomes and implementation, and lay and professional views
Number of participants (n)	• Preschool children (1500) • Parents (20) • Staff (30) • Stakeholders (5)	• Parents (200) • Facilitators (10) • Stakeholders (5)	• Parents (140) • Facilitators (10) • Stakeholders (5)	• Parents (100) • Facilitators (12) • Stakeholders (5)
Data type	• Early years outcomes, well-being scales, interviews	• Self-report measures and interviews	• Self-report measures, parenting questionnaires, and interviews	• Self-report measures, parenting questionnaires, and interviews

[a]HENRY: Healthy Exercise Nutrition for the Really Young.

These projects already have systems in place to collect outcome data pre- and postintervention, with some opportunities to compare outcome data with existing larger datasets. Two of the four chosen are established programs running elsewhere in the United Kingdom or internationally, with published evidence demonstrating improved outcomes.

In terms of conducting evaluation research in Luton, we identified further cross-cutting questions resulting from the development of an in-depth knowledge of both provision and context, such as how established programs perform when implemented in highly ethnically and culturally diverse populations and the extent to which these complex interventions can be tailored to local circumstances or allow a degree of adaptation [2]; whether Flying Start is able to replicate the positive results reported from pilot studies or improve on outcomes published elsewhere; and collecting qualitative process data to understand *how* such improved outcomes were achieved (or not), which is an aspect of particular value to Flying Start, given that projects initially tend to be rolled out on a small scale.

Consequently, an overarching process-evaluation model was developed, which could be applied and tailored, where appropriate, to all the projects to be evaluated:

- Observations of staff and facilitator training sessions
- Observations of intervention sessions with facilitators working with families and children
- Individual interviews (or focus groups, where deemed appropriate) with staff once interventions are running as well as with project leads and Flying Start leads/commissioners
- Interviews with families after completing the sessions with follow-up interviews at 6 and 12 months

The five steps described then lead to the sixth step, developing individual evaluation protocols.

Step 6 – Negotiating With Chosen Project Leads Both Within and Outside the Organization

In order to develop a separate, specific evaluation protocol per project, it was necessary to liaise with project leads from within and outside Flying Start. From an academic point of view, the protocols were intended to stand alone as a plan to conduct a robust process and outcome evaluation; however, it was vital to receive regular feedback from Flying Start staff on what was achievable. This would include negotiating access to observe particular staff training sessions, meetings, mentoring, and shadowing routine visits and key program sessions with families; quantifying as precisely as possible the level of involvement required from all stakeholders named in each evaluation to allay the anxieties of stressed staff with challenging workloads; and actively listening to personnel involved at all levels about their concerns and aspects/dimensions of the programs that they particularly wanted to know more about, given their expertise of the local context and population demographics. While working in detail to map out the evaluation stages required for each intervention, it was necessary to remain aware of the organization's provision as a whole, specifically, the potential themes underlying all projects delivered.

In the case of Flying Start provision, a training course attended by a large proportion of Luton's early years workforce—Five to Thrive [40,41]—was of particular interest; this course coaches staff to apply evidence-based neuroscientific approaches in their practice to support families to strengthen attachment bonds by responding, talking, playing, relaxing, and cuddling their children. Representing a cornerstone of the Flying Start strategy, all study protocols included the aim of investigating the impact of this training on staff as a part of each process evaluation.

Step 7 – Development of Individual Project Evaluation Protocols

Protocol drafts were revised on numerous occasions, as Flying Start staff commented and questioned the evaluation approach

and content. For particular projects where Flying Start had subcontracted part of the delivery to a partner organization offering the intervention, the protocols were also sent out externally for feedback and clarification as well as to academic colleagues based in other universities with prior/continuing involvement with the development of the original intervention or evaluations thereof. Once protocol drafts were approved, topic guide questions were formulated for the proposed process evaluation for each project. These questions were tailored for interviews with different stakeholders—Flying Start leads/commissioners, project leads, frontline staff/session facilitators, and families. Again, the draft questions were circulated to all Flying Start staff (and key external program staff, where appropriate) involved in the delivery of each project in order to draw upon their expertise and ensure key topics were explored sufficiently and no aspects were overlooked. With agreement on the content of the topic guides, information sheets, and consent forms, it was possible to apply for ethical approval.

Step 8 – Applying for Ethical Approval From the University and Partner Organization

Although the National Health Service in the United Kingdom, for example, has systems in place as a result of systematic and ongoing evaluations of health interventions, a local authority working with an academic partner is less common. Ethical approval was sought from both the University of Bedfordshire and Luton Borough Council. Applications had to fulfil requirements of both the Institute for Health Research and Luton Borough Council for participant informed consent, data protection, and data storage. We worked with the Council's Information Governance Team to ensure the requirements of their Tier 3 Information Sharing Agreement, detailing data-sharing processes for each Flying Start project under evaluation, were met as well as to write a master Information Sharing Agreement outlining the overarching principles all parties must adhere to as part of the evaluation research process. Additional time was required to ensure that the Council's data-sharing and informed consent guidance was met, which must also adhere to European Union law in this area. Finally, each research protocol was registered in the ISRCTN (International Standard Registered Clinical/soCial sTudy Number) registry to maximize awareness of the evaluations to other researchers, clinicians, and the public as well as to promote transparency and reduce duplication and selective reporting [27,42-44].

Discussion

Overview

This paper describes the preparation and work required to identify multiple complex projects/interventions suitable for process and outcome evaluation from a range of provision offered by an organization (in this case, services), designed to improve early years outcomes as part of local council provision in the United Kingdom. It details the complexities of academic partners working with a local authority to lay the foundation for a robust evaluation, with the aim of sharing this learning with others who are considering working within a similar model. We outline these steps in relation to previous guidance on conducting evaluations and the preassessment of specific interventions, namely, evaluability assessment, prior to embarking on evaluation research.

Our work adds to existing literature on evaluation methodology by setting out the steps required, particularly related to academic partners and organizations tasked with delivering services designed to meet local needs. After the 8 steps are completed, or the process is in the latter stages, a detailed evaluability assessment may be carried out. This may be particularly important if the projects identified are large scale, costly interventions requiring considerable resources to evaluate and pressure to produce conclusive results. Furthermore, an advantage of using the 8 steps prior to evaluability assessment is that many of the questions about an intervention's performance and expected outcomes have already been explored before a more detailed appraisal can be made about intervention management and performance. For smaller scale interventions, the use of the 8-Step Scoping Framework may be sufficient to allow progression to the evaluation-planning stage.

Limitations

The 8-Step Pre-evaluation Framework covers the early stages of evaluation planning to identify complex interventions suitable for evaluation. Therefore, this paper does not address economic aspects such as a cost-benefit analysis of late intervention [45,46] and how including such expertise may strengthen an evaluation and offer a business case for future funding or commissioning decisions [47]. Further work should be undertaken to address how and when economic expertise would fit in to evaluation planning and how additional resources would be factored in to allow for this.

The 8 steps described are tested in relation to academic institutions working with local government in order to build an evidence base but is intended to be applied in other contexts where the goal is to develop a program of evaluation to identify what works. This could be, for example, healthcare, national government, or educational settings. Key criteria are that some form of program, provision, or service be offered with a defined purpose to change or improve a particular outcome(s). Therefore, at this stage, it could be argued that the 8-Step Scoping Framework may be applied in a wide variety of settings and contexts where academic evaluation is required. However, further refinement will likely be required, as others apply the 8-Step Framework and report on its generalizability and their experiences of identifying projects/interventions for evaluation.

The 8 steps are contingent upon an organization being open to having their provision evaluated and to change or modify procedures to ensure that data collection can take place. It requires researchers with good interpersonal and communication skills who are able to ask the pertinent questions and develop positive working relationships [47]. It is also important to note that the process of identifying suitable interventions is, in part, iterative and dependent on context, with some stages overlapping and feeding into each other in order to maintain momentum and ensure the most efficient use of time while considering a wide range of provision.

Evaluation Challenges, and Future Plans

The 8-Step Scoping Framework will be refined by continuing to work with Flying Start to identify further projects for evaluation in 2019 as well as seeking detailed feedback on how the organization has found the experience of working with an academic partner and being the subject of evaluation activities. As the evaluation of the chosen projects progresses, it will be possible to reflect further and refine the steps set out in this paper. The ongoing impact of evaluation work is a dynamic process. As early results emerge, positive effects will reinforce original decisions to build an evidence base, whereas less conclusive or negative results may lead to skepticism and disappointment. Considering the weight of expectations around evaluation, a regular dialogue about the impact of results, coupled with a reminder of how process findings should help improve different aspects of provision, may help resolve any arising issues. We highlight the importance of developing positive working relationships and harnessing the expertise of organizations to ensure an evaluation asks the pertinent questions and explores the key issues.

Four Flying Start projects were found to be suitable for evaluation: Sign 4, HENRY, Incredible Years, and Parents as Partners. The selected projects fulfil our evaluation criteria to varying degrees: They collect key outcome data, allow comparisons with control groups, are established or imminent, are sizeable and scalable to allow for a mixed-methods approach, and use databases to allow tracking over time and have scope for inclusion of follow-ups. Our process and outcome-evaluation framework will enable us to assess what works and why it works. The steps identified have been described in the context of early years provision but can be applied to broader community-based evaluations. The process of formulating key evaluation questions in step 1 will ensure that the overarching evaluation strategy will retain its focus and we continue to be aligned with the objectives the organization.

Our subsequent evaluation of Flying Start provision must set realistic and achievable goals with the help of a detailed timetable, including contingency plans and a degree of slippage. Consideration must be given to issues of fidelity, whereby interventions may differ substantially between areas/settings, as projects need to adapt and take into account the needs of different communities. The evaluations must also consider difficult-to-reach groups who are less likely to access Flying Start services and that in the process of working with diverse communities, people do not fit into nicely packaged intervention and evaluation “boxes”.

Authors' Contributions

RD was the project coordinator for the study and collated completed data templates, assessed data quality, identified projects for evaluation, liaised with project leads, developed and drafted individual project-evaluation protocols, applied for ethical approval, and drafted the manuscript. GR was the principal investigator and provided oversight for the study and comments on the entire manuscript. SC provided oversight for the study, designed the data templates, organized the evaluation workshop, and provided comments and edits on the entire manuscript.

Conflicts of Interest

RD received funding from the University of Bedfordshire and Flying Start Luton, UK, for this study.

Multimedia Appendix 1

Data template for the project/program offered.

[PDF File (Adobe PDF File), 38KB - resprot_v8i3e10075_app1.pdf]

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Abbreviations

HENRY: Healthy Exercise Nutrition for the Really Young
LBC: Luton Borough Council

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Corrigenda and Addenda

Correction: The Integration of Interlinkages Between Nature and Human Health in Primary Health Care: Protocol for a Scoping Review

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During typesetting and proofreading for "The Integration of Interlinkages Between Nature and Human Health in Primary Health Care: Protocol for a Scoping Review" (JMIR Res Protoc 2019;8(1):e12510), the following sentence was erroneously deleted from the Acknowledgments section:

> *This study results from the project "Green light" (in Dutch: Licht op Groen), hosted by the University of Antwerp and funded by the Province of Antwerp in Belgium.*

The aforementioned sentence has now been reinstated.

The correction will appear in the online version of the paper on the JMIR website on March 7, 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.

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Corrigenda and Addenda

Metadata Correction: Performance, Acceptability, and Usability of Respiratory Rate Timers and Pulse Oximeters When Used by Frontline Health Workers to Detect Symptoms of Pneumonia in Sub-Saharan Africa and Southeast Asia: Protocol for a Two-Phase, Multisite, Mixed-Methods Trial

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Related Article:

Correction of: http://www.researchprotocols.org/2018/10/e10191/

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The authors of the paper "Performance, Acceptability, and Usability of Respiratory Rate Timers and Pulse Oximeters When Used by Frontline Health Workers to Detect Symptoms of Pneumonia in Sub-Saharan Africa and Southeast Asia: Protocol for a Two-Phase, Multisite, Mixed-Methods Trial" (JMIR Res Protoc 2018;7(10):e10191), made a mistake in the final stage of proofreading. Kevin Baker should have been listed as affiliated with the Karolinska Institute in Stockholm, Sweden. This affiliation has also been updated to include the Department of Public Health Sciences for all affiliated authors and now reads as follows:

Department of Public Health Sciences, Karolinska Institute, Stockholm, Sweden

Additionally, Kevin Baker's address as the corresponding author for this paper has been changed to reflect this new affiliation.

The correction will appear in the online version of the paper on the JMIR website on March 7, 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.

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Protocol

Triggered Escalating Real-Time Adherence Intervention to Promote Rapid HIV Viral Suppression Among Youth Living With HIV Failing Antiretroviral Therapy: Protocol for a Triggered Escalating Real-Time Adherence Intervention

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Abstract

Background: Youth living with HIV (YLWH) are confronted with many self-care challenges that can be experienced as overwhelming in the context of normal developmental processes that characterize adolescence and young adulthood. A sizable minority of YLWH have unsuppressed viral loads in the United States attributable to antiretroviral therapy (ART) nonadherence. Interventions to promote sustained viral suppression in YLWH are needed.

Objective: The aim of this study is to evaluate the efficacy of the Triggered Escalating Real-Time Adherence (TERA) intervention in comparison with standard of care (SOC) in YLWH (aged 13-24 years) failing ART on (1) primary outcome measures—HIV viral suppression (VLS), defined as both <200 copies/ml and <50 copies/ml at 12 weeks, and (2) secondary outcome measures—VLS rates and rates of ART adherence at 24, 36, and 48 weeks as well as patterns of adherence over time as measured by an electronic dose monitoring (EDM) device.

Methods: The TERA study is a phase 2, multisite clinical trial conducted with 120 YLWH failing ART (randomized 1:1 to TERA or SOC) at participating clinical sites within the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). Participants are followed for a total of 48 weeks. For TERA arm participants, the first 12 weeks involve delivery of the intervention. For all participants, clinical outcomes are collected throughout follow-up, and adherence is assessed using EDM over the full 48 weeks. During the 12-week intervention period, TERA arm participants receive 3 remote coaching sessions delivered in clinic via videoconferencing timed to coincide with baseline and follow-up clinical visits, text message reminders when the EDM has

not been opened at dose time (which escalate to 2-way theory-informed short message service coaching interactions in response to real-time nonadherence), and review of dosing graphs produced by EDM at follow-up visits.

Results: Launch dates for enrollment varied by site. Enrollment began in April 2018 and is expected to be completed by August 2019, with results presented by the second quarter of 2021.

Conclusions: Effective, generalizable, and scalable approaches to rapidly assist YLWH failing to achieve and sustain VLS may have a substantial impact on individual health and efforts to curb transmission. Coaching for a brief but intensive period from remote coaches and using communication channels common to youth may offer multiple unique advantages in promoting self-care.

Trial Registration: ClinicalTrials.gov NCT03292432; https://clinicaltrials.gov/ct2/show/NCT03292432 (Archived by WebCite at http://www.webcitation.org/768J8ijjp).

International Registered Report Identifier (IRRID): DERR1-10.2196/11416

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KEYWORDS

HIV; adolescents; medication adherence; telemedicine

Introduction

Background

Among the 35 million people living with HIV worldwide, 7 million are below the age of 24 years. With the concerted efforts to increase viral suppression globally and through strategic national plans, the unique demands and challenges facing youth living with HIV (YLWH) must be addressed to reach viral suppression goals. Successful progression through the continuum of HIV care is poorer among adolescents than adults in the United States, with as many as 46% of those started on antiretroviral therapy (ART) not achieving viral suppression (VLS) in large part due to difficulties with medication adherence [1]. Recent reviews suggest that the subset of youth who achieve VLS after 48 weeks of ART can be alarmingly low (27% to 89%) [2]. Sustaining VLS is critical both for the individual health and to curb transmission. As those failing ART for adherence reasons are at an increased risk of subsequent ART failure [3,4] and problems with adherence appear to be relatively common [5,6], interventions to improve adherence and disrupt patterns of nonadherence are critically needed.

A dearth of evidence exists on the issues, approaches, and facilitators/barriers for YLWH failing to achieve or sustain VLS [7,8]. Literature specific to adults failing first-line ART suggests that sex (female) and delayed start of second-line therapy predict lack of suppression by 24 weeks [9], and although the evidence base in characterizing first-line ART failures and second-line outcomes in resource-limited settings is growing [10], this may not generalize to YLWH in the United States.

YLWH between the ages of 13 and 24 years are a unique cohort. Developmental tasks during this period of life create both challenges and resources [11] that impact daily living. Youth would likely benefit most from strategies that specifically bridge the gaps common during adolescence caused by normal neuro-cognitive and emotional development [12]. Brain maturation in the limbic system and prefrontal cortex, amongst other changing hormonal and environmental dynamics, can be expressed in poor decision-making, impulsivity, lower self-care, and higher engagement in risk behavior [13]. Challenges in executive functioning and cognitive abilities that limit abilities to plan, organize, focus attention, or manage rewards have been identified in HIV-infected youth, even before ART initiation [14]. Psychologically, identity development tasks heighten awareness and sensitivity to belonging and fitting in, which may exacerbate feelings of stigma among youth negotiating adherence [15]. Support for YLWH struggling with adherence must extend beyond and in-between clinical care visits, which can be achieved through technology-based modalities. Interventions that offer continuous contact and implement as-and-when-needed outreach may be well matched to the dynamics of everyday life for youth in the United States. Furthermore, with most youth also using cell phones in the United States, delivering support between visits can be facilitated through texting. The Triggered Escalating Real-Time Adherence (TERA) study (the Adolescent Medicine Trials Network for HIV/AIDS Interventions [ATN] 152) seeks to evaluate an intervention package that leverages several of these components: real-time electronic dose monitoring (EDM) that signals potential intervention opportunities, texting to explore needs and context surrounding such events, and phone-delivered outreach to offer patient-centered coaching from remotely located coaches.

Rationale for Triggered Escalating Real-Time Adherence Intervention

The rationale for each of the active components of the TERA intervention (coaching, EDM, short message service [SMS], phone-based outreach, and time-limited with remote placement of coaches) is presented separately below, whereas the manner in which TERA combines these components is provided in the description of the implementation of the intervention.

Coaching has been defined as a patient-centered, strength-based approach that tends to be time-limited, focused on problem-solving and health and wellness, and goal oriented, which differs from counseling predominantly in its explicit focus on current lifestyle and more narrow scope and depth [16]. Coaches tend to provide when and as needed support and check-ins [16], and the approach has gained support in addressing diverse health behaviors, including weight management, exercise, and overall physical health [17]. In a review of coaching interventions, approaches that included goal setting and motivational interviewing demonstrated stronger outcomes [18]. Despite the promise for marginalized groups

[19] and for adolescents [20], coaching work to date has largely focused on adults. TERA will be one of the first studies to evaluate coaching tied to EDM monitoring for youth struggling with ART adherence.

An additional core component of the TERA intervention package is the use of EDM. Evidence supports the use of technology-enhanced interventions to promote medication adherence among those living with HIV [21]. A recent study does, however, caution that reminders tethered to EDM identified that missed doses may lack impact. A study with adults in Cape Town, South Africa, evaluated an intervention that used SMS text messages to signal late doses according to a Wisepill device for first-line therapy ART [22]. Although a slight reduction in treatment interruptions was reported, overall adherence, retention in care, and VLS did not improve, which may have been due to reliance on "one-way" texting. One-way texting (with no expectation or opportunity to reply or engage in a conversation) appears to have an inconsistent impact on adherence, whereas interactive texting (where replies are expected and conversation is possible) has consistent support [23-25].

SMS text-based strategies [26,27], which are not yoked to monitoring but are systematically sent, require a response from participants and also seem to suggest that an interactive component is particularly beneficial [28,29]. Garofalo et al's recent study in this area with 105 adolescents and young adults where 2-way daily SMS texts were provided to nonadherent youth demonstrated a significant improvement in self-reported adherence and high satisfaction scores [30]. Furthermore, a pilot study using personalized, interactive, daily SMS text messages demonstrated significant improvement among 14- to 29-year-olds living with HIV with poor self-reported adherence rates [31]. Coupled with consistent support for text-based "well-checks," where patients receive an interactive text weekly simply asking how they are doing [26,27], using SMS interactive texting with a population who uses texting as part of the fabric of their daily lives was identified as a critical component to incorporate in the TERA intervention. For the TERA intervention, texting with patients about an EDM-identified late dose or simply checking in on their well-being had a strong basis for a potentially effective avenue of communication between coaches and participants. Finally, another promising aspect of collecting EDM data is the use of these data to present dosing patterns to patients and offer opportunities to discuss, problem solve, and reflect on adherence patterns. Previous research using this strategy with adults has demonstrated an impact on adherence [32,33] and could be appropriate for youth as well.

Moreover, related to EDM-identified late dosing, phone-based follow-up was identified as a promising strategy to connect with youth when and as needed. Evidence has supported the utility of phone-based outreach using a problem-solving approach [34,35]. In a recent review, harnessing mobile phone technology was identified as a promising area for future interventions encouraging optimal adherence among YLWH [30]. Furthermore, evidence suggests that using phone-based technology to engage adolescent social support networks may promote optimal engagement in care and adherence to medications [36,37]. A recent study of a phone-based support intervention among nonadherent YLWH found that it was acceptable and feasible among youth and clinic staff [38].

Finally, the rationale for using remote coaches and a time-limited intervention reflects efforts to develop interventions that are generalizable and can be brought to scale if effective. Despite the urgent need for services to assist youth failing ART to reach and sustain viral suppression, most clinics in the United States report this group as a small portion of the patient population. Thus, even if intensive interventions such as TERA are effective in improving disease outcomes, large investments to hire a full-time coach or offer dose monitoring off-hours and on weekends will have limited return for clinical care sites at the patient population level. Locating coaches remotely allows a single coach to work remotely and intensively with identified youth from multiple clinics across the United States. The TERA intervention brings the intervention to those who could benefit from it, rather than having patients physically present themselves to a specific location to receive support. In addition, because the approach is intensive, limiting its implementation to a discrete period is intended to optimize feasibility and acceptability of the approach. If effective, TERA could be developed as an independent service, available for youth across the United States, prescribed by providers and potentially covered by insurance. Together, remote and time-limited features of the intervention are intended to facilitate the viability and speed of scale-up.

Study Objectives

To support YLWH failing ART due to nonadherence, the TERA study will evaluate a novel, evidence-informed, triggered, escalating, real-time adherence intervention among 120 youth with unsuppressed virus. The study objectives and hypotheses are listed in Table 1.

Table 1. Objectives, outcomes, and hypotheses.

Level	Objective[a]	Measure(s)	Hypothesis
Primary objective #1a	To estimate and compare HIV viral suppression rates in YLWH[b] 12 weeks after initiating TERA[c] or continuing SOC[d]	HIV-1 RNA <50 copies/ml	Youth in the TERA arm will be more likely to achieve viral suppression (VLS) at week 12 compared with youth in the SOC arm[e]
Primary objective #1b	To estimate and compare HIV viral suppression rates in YLWH 12 weeks after initiating TERA or continuing SOC	HIV-1 RNA <200 copies/ml	Youth in the TERA arm will be more likely to achieve VLS at week 12 compared with youth in the SOC arm[a]
Secondary objective #1	To estimate and compare viral suppression rates in YLWH 24, 36, and 48 weeks after initiating TERA or continuing SOC	HIV-1 RNA <50 copies/ml and HIV-1 RNA <200 copies/ml	Youth in the TERA arm will be more likely to achieve VLS at weeks 24, 36 and 48 compared with youth in the SOC arm[f]
Secondary objective #2	To estimate and compare proportions of participants initiating TERA or continuing SOC who achieve viral suppression (HIV-1 RNA <200 copies/ml) by 12 weeks and maintain viral suppression through 48 weeks	HIV-1 RNA <200 copies/ml at weeks 12, 24, 36, and 48	Youth in the TERA arm will be more likely to achieve and sustain VLS than those in the SOC arm[g]
Secondary objective #3	To summarize and compare adherence patterns in YLWH initiating TERA or continuing SOC during the intervention period (weeks 0-12) and the postintervention period (weeks 12-48)	EDM[h] on-time adherence and nonpersistence (between week 0-12, 12-24, 24-36, and 36-48)	Youth in the TERA arm will have higher rates of weekly dosing as measured by EDM over 48 weeks than those in the SOC arm

[a]Other and exploratory objectives, which focus on social psychological changes over time and between arms, classification of patterns of adherence per EDM data, mixed methods characterization of acceptability and feasibility of the TERA intervention and study participants, and costing data, are also included in the protocol.

[b]YLWH: youth living with HIV.

[c]TERA: Triggered Escalating Real-Time Adherence.

[d]SOC: standard of care

[e]Participants with no HIV-1 RNA measurement within the allocated week 12 study visit window (± 14 days) will be classified as failures.

[f]Participants with no HIV-1 RNA measurement within the allocated study visit window for weeks 24, 36, or 48 (±28 days) will be classified as failures.

[g]Participants will be classified as virologic successes if both the week 12 (±14 days) and week 48 (±28 days) HIV-1 RNA measurements are <200 copies/ml and at least one of the week 24 (± 28 days) or week 36 (± 28 days) HIV-1 RNA measurements is <200 copies/ml.

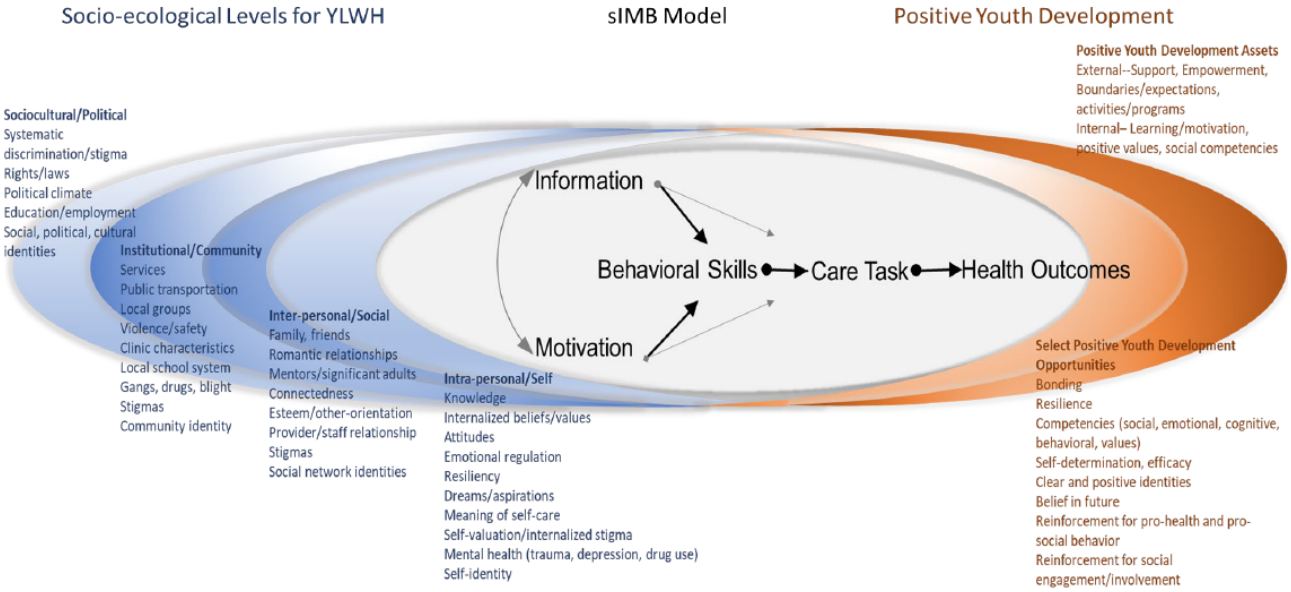
[h]EDM: electronic dose monitoring.

The primary objective, 12-week viral suppression, will be measured at the week 12 visit when the final coaching session occurs, thus representing the effects at the end of the intervention. Both the US Department of Health and Human Services viral load cutoff of 200 copies/ml used to define virologic failure [39] as well as the cutoff of 50 copies/ml increasingly used in research studies to define undetectable HIV viral load are used to describe the viral load–based primary and secondary outcome measures. Note that our use of both a stringent definition of VLS (<50 copies/ml) as well as a less restrictive but well-recognized cutoff of <200 copies/ml reflects evidence suggesting that each criterion may offer unique insights into control of virus, risk for viral rebound, and potential for development of resistance [40] and is consistent with the most recent Antiretroviral Guidelines for Adults and Adolescents [39]. The secondary objectives include viral suppression at subsequent time points to evaluate the longitudinal efficacy of the coaching sessions on viral suppression, and similarly use the <50 copies/ml as well as the <200 copies/ml cutoffs at weeks 24, 36, and 48, and the "durability" of intervention effects through characterizing the percentage of youth in each arm who achieved and maintained each operationalization of viral suppression. Finally, collected EDM data will be explored to determine whether EDM-identified adherence through week 12 and from weeks 12 to 48 was better in the intervention condition.

Theoretical Basis for Intervention

The TERA intervention uses EDM to signal coaching opportunities, whereas the implementation of coaching draws heavily from the Information, Motivation, and Behavioral Skills (IMB) model situated within socio-ecological and positive youth development frameworks (Figure 1).

Figure 1. Theoretical underpinning of triggered escalating real-time adherence (TERA) intervention.



The IMB model of ART adherence [41], which has been used extensively in interventional adherence enhancement research [42,43] and has a developed evidence base in diverse groups of adults [43-45], is used as the basis for understanding specific adherence and nonadherence events. We use the situated application of the Information Motivation Behavioral Skills model (sIMB) [46] to further embed the kinds of knowledge; personal and social consequences of adherence and nonadherence in the context of daily life; and skill sets needed for youth to navigate adherence in the context of self, others, and systems. Tailored understanding of each of the core IMB model constructs as expressed within and between the layers of the socio-ecological model (Figure 1 far left) is further refined with a Positive Youth Development lens (Figure 1 far right), which calls attention to the resources and opportunities unique to adolescents and young adults and is critical in fostering positive awareness of, attitudes toward, and skills in promoting self-care. The coaching intervention uses this synthesized model to guide efforts to engage youth in their current context, within their particular landscape of resources and gaps. Coaches are trained in the social-ecological approach and incorporate these constructs in their discussions focused on factors influencing adherence. Although the models in Figure 1 form the backbone of understanding for how adherence may be optimized or derailed, implementation of coaching discussions are guided by Next Step Counseling (NSC), which draws on Motivational Interviewing (MI). NSC, MI, and specifics for coaching in terms of theory and implementation are detailed in the intervention section. In summary, the aim of the TERA study is to evaluate a novel, evidence-informed triggered, escalating, real-time adherence intervention that leverages coaching and contemporary technology to promote viral suppression among YLWH who have failed on ART.

Methods

Trial Design Overview

TERA is a phase 2, randomized, open-label study evaluating the efficacy of the TERA coaching 12- week intervention in YLWH failing ART. A total of 120 YLWH between the ages of 13 and 24 years will be randomized with equal probability to the TERA intervention or continuing SOC, with stratification by age (<18 years vs ≥18 years). At entry, 40 participants (20 from each arm) will be randomly selected to engage in additional in-depth interviews, at study weeks 12 and 48, about their experiences around adherence and self-care as well as their experiences being in the study.

Study Setting

Clinical research sites within the ATN and the International Maternal, Pediatric, Adolescent AIDS Clinical Trials network in the United States were solicited for interest in participation in ATN 152. A total of 8 clinical research sites are engaged in the trial, including sites in Colorado, Florida, Georgia, Maryland, Michigan, New York, and Tennessee. Clinical research sites differ in the demography of clinic populations, reflecting the specific characteristics of the HIV epidemic within youth in their region. Total anticipated targets for enrollment also vary between clinical research sites, ranging from 5 to 20 youth. All sites are experienced research sites that also operate as clinical care centers for youth. For the TERA study, a minimum of a site-level principal investigator and a study coordinator are required. The University of North Carolina at Chapel Hill (UNC-CH) serves as the single Institutional Review Board (sIRB) and has reviewed and approved the study for study sites.

Participants

A total of 120 participants will be enrolled. Inclusion and exclusion criteria are listed in Textboxes 1 and 2, respectively.

Textbox 1. Inclusion criteria of participants.

Inclusion criteria:

1. Age: 13 to 24 years.
2. Confirmed HIV positive status: Confirmation of HIV-1 infection as documented in the participant's medical record by at least 2 criteria.
3. Aware of HIV status: Site staff determined.
4. Viremic: Documented plasma HIV-1 RNA plasma ≥200 copies/ml within 45 days of enrollment visit.
5. On antiretroviral therapy (ART): Prescribed ART at least 24 weeks or more before documented plasma HIV-1 RNA plasma ≥200 copies/ml; prescribed a once-a-day (one or more pills once a day) ART regimen with at least 2 active agents (per clinician judgment or genotype evidence) at enrollment.
6. Language: Able to communicate in spoken and written English.
7. Technology access: Currently has a cellular phone that is able to send and receive short message service text messages.
8. Retention: Willing and able to provide at least 1 additional contact phone number (preferably 2) to be able to contact participant.
9. Consent or assent: Able and willing to provide written informed assent or consent and able to obtain written parental or guardian permission to screen and to enroll in this study.

Textbox 2. Exclusion criteria of participants.

Exclusion criteria:

1. Cognitive capacity: Gross cognitive limitations, acute emotional instability, or medical or mental health illness that would impair the individual's ability to provide informed consent or interfere with the protocol's objectives.
2. Concurrent participation: Concurrent participation in interventional studies addressing adherence, unless approved in advance by the study team.
3. Pregnancy: Positive pregnancy test at the time of enrollment; however, if participant becomes pregnant while on study, they may continue the study.
4. Current use of electronic dose monitoring: Currently using or planning to use an electronic dose monitoring and reminder device outside of the study.

Sample Size

Approximately 54% of youth on ART in the United States are estimated to be virally suppressed [1]. The study was designed to have 85% power to detect a difference of 25% in VLS rates at week 12 between the TERA and SOC arms (assuming a success rate of 60% on SOC). Participants lost to follow-up before week 12 will be classified as failures; hence, no adjustment was made for loss to follow-up in the sample size.

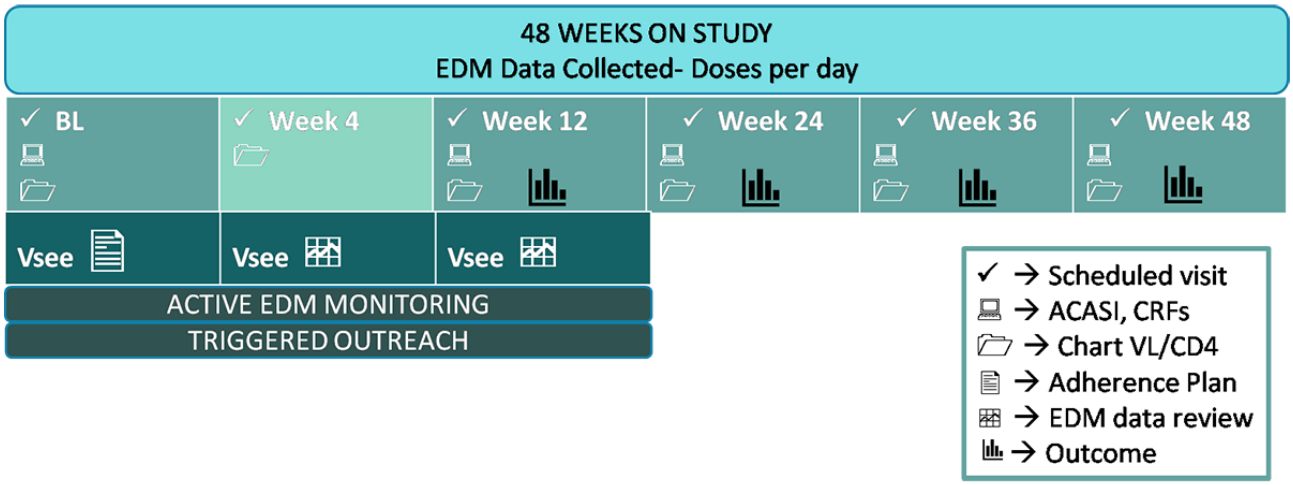
Randomization

Participants will be randomized to the TERA or SOC study arms with equal probability using Medidata Rave EDC (Electronic Data Capture) software managed by an external data management team. Randomization will be stratified by age to ensure balance in treatment assignments, and institutional balancing will be used to help ensure roughly equal balance in intervention assignments within each site. Once randomized to study arm, the system then randomly determines if the participant is eligible for 1 of the 40 interview slots (20 in each study arm). Those selected are offered participation in in-depth interviews, which will occur at weeks 12 and 48. If refusal rates for interview participation at week 12 are higher than expected, probabilities of selection will be increased during accrual.

Participant Timeline

Participants are enrolled for 48 weeks of study participation. Those assigned to the intervention condition will receive the intervention during their first 12 weeks of participation, followed by 36 weeks of observation for a total of 48 weeks. All participants are asked to attend clinic study visits at weeks 4, 12, 24, 36, and 48. All participants are asked to dose from an EDM (AdhereTech's smart bottle) for their full 48 weeks of study participation. The participant experience is depicted in Figure 2. All participants have the "light feature" activated on the smart bottle. This soft blue light band on the bottom of the bottle pulses and then turns to solid light as dose times approach (1 hour before scheduled dose time) and pass (1 hour after dose time) without the bottle being opened. The light feature is a default for all participants throughout the entire period of participation, because early discussions with youth at clinical care sites suggested this feature made the bottle more attractive to use. Although this may inflate adherence, we anticipate habituation over time and any influence would be evenly distributed between the study arms. The feature can be disabled upon request.

Figure 2. Participant experience.



Compensation

Compensation will be provided for participants at each study visit. The amount of compensation is determined by the local study site staff, is considered appropriate by the site Institutional Review Board (IRB) and will be confirmed with the sIRB, and will be reflected in the site-specific informed consent form. Recommended incentives include US $75 per visit through week 12 (first 3 study visits); US $40 per visit for weeks 24, 36, and 48; and added incentives for the final week 48 visit (US $100) for a possible total of US $445 over the full 48 weeks. In addition, participants randomly selected for the qualitative interviews receive US $50 per interview for a possible total of US $100. Participants in the intervention are not provided incentives for engagement in intervention sessions or outreach.

Virtual Youth Advisory Boards

Each participating clinical research site is asked to identify and engage at least 2 YLWH (between the ages of 13 and 24 years) to participate in virtual youth advisory board (vYAB) meetings for the study. These advisory meetings are hosted at the clinic site and use the interactive remote coaching/counseling software program (VSee) with all site youth advisory boards (YABs). Topics discussed include impressions of main challenges for YLWH, vetting ideas about intervention components and study implementation factors, and ensuring that the study and intervention are remaining relevant to the issues germane to YLWH in the regions engaged in the study. vYAB members are reimbursed for their contributions as consultants per meeting attended. Suggested reimbursement is US $50 per meeting, and clinical research sites are provided with food/beverage resources for hosting these meetings. The vYAB meets a minimum of quarterly and as needed.

Study Conditions–Standard of Care

SOC relative to adherence support will be recorded for each participant during their study participation. In a previous study, we have developed an SOC measure for ART adherence support [47] that follows international recommendations for strategies [48] as well as strategies known to have positive effects [49] in some populations. There are no restrictions on participant SOC adherence support during the study for participants; however, the use of another EDM is not allowed while enrolled.

Study Conditions–Intervention

Components of the intervention implemented over the 12-week intervention period include the following: (1) remote "face to face" coaching with the assigned adherence coach (delivered via computer connection and through VSee videoconferencing software in a private location at the clinical research site) at baseline and weeks 4 and 12; (2) 1-way, discrete SMS text message ("What's up?") at dose time when bottle has not yet been opened for that dosing window (users can disable this upon request); (3) 2-way interactive outreach SMS from the coach if the EDM bottle remains unopened after 1.5 hours post dose time ("What's the plan?" Reply a. taking now, b. took already, c. taking later, or d. pass) with related coach follow-up; and (4) incorporation of dosing data collected via the electronic dose monitoring into follow-up visits (weeks 4 and 12) to help youth visualize, reflect on, and problem solve around dosing patterns. Tracking and monitoring progress for each of these components occurs in a TERA Implementation Dashboard created for the study. Study implementation material also includes a detailed intervention manual and TERA Implementation Dashboard monitoring guide. Study material will be made available at the completion of the study.

TERA coaches, located at the University of Michigan, are bachelor or graduate level trained staff with experience working with youth. Coaches are not required to match the demographics of participants or be living with HIV. Each coach completes and maintains training on human subjects research ethics and specific training on brief counseling techniques and intervention-specific skills and protocol material. Interactions with participants are intended to draw from problem-solving [50], MI [51], NSC [52,53], Positive Youth Development theory [11], and sIMB [46]. Coaches complete 2 MI [51] workshops and 1 NSC workshop and participate in several simulated sessions to practice techniques and skills before meeting with participants. MI [51] has a long history of use in brief interventions, with promising results on improving adherence for YLWH [54], and NSC [52,53] has been adapted to ART adherence among youth for this study. Intervention material is contained in an intervention manual, with basic steps articulated

for each planned face-to-face virtual session, infographics and visuals that are used through the sharing screen function during sessions, and full training on the use of the TERA Implementation Dashboard. Thus, coaches receive training in not only the theories underpinning the intervention approach, basic coaching, MI, and NSC but also on using the technology and software used to deliver the intervention and monitor implementation.

Youth assigned to the TERA intervention condition at baseline will interact with their assigned adherence coach in a private clinic location through Web-enabled remote coaching (VSee software program). These trained coaches are not part of the clinic team; rather, they are centrally located at the University of Michigan. The general content and flow of each of the 3 planned remote face-to-face sessions are depicted in Figure 3; however, coaches can revise this based on specific needs and context for each participant. Sessions are recorded and transcribed for fidelity checks and supervision. Material created during the session (such as drawing and writing out important factors and people in the participant's life) on the "white board" feature of VSee is saved for use in subsequent sessions in a secure location.

Information about dose time, preferences, and contacts, in addition to a case note summary of the content of coaching sessions, is entered after the visit in the TERA Implementation Dashboard.

In addition to the coaching remote face-to-face interactions, daily dosing is monitored for participants in the intervention condition to identify when text- or phone-based outreach from coaches should be initiated. Between-visit contacts are detailed in Figure 4 and include outreach around late dosing, check-in texts, and other strategies to engage youth who have been difficult to contact. For each outreach around challenges with dosing, the goal is to engage youth before the dose is "missed" to see if dosing may be possible in a supportive manner. A dose is considered missed for intervention purposes only if the EDM remains unopened through to the following day, although we recognize that some participants who have dose times late in the day may in fact still be within an appropriate window to take the dose. Coaches work with participants on a case-by-case basis when conducting follow-up and assisting participants in determining next steps. Each late dose (1.5 hours after dose time without a bottle opening) sends a planning question to the youth's phone (What's the plan?) and an alert to the coach or the monitor watching the TERA Implementation Dashboard after hours. The alert creates a "ticket" in the TERA Implementation Dashboard that is followed until closed through successful contact or determined on a case-by-case basis to be resolved.

Coaches and monitors (research staff who are trained to monitor and triage tickets in the TERA Implementation Dashboard after workday hours and on weekends) track and document implementation of the TERA intervention package in the TERA Implementation Dashboard. The TERA Implementation Dashboard was developed for this study and receives direct input from the EDM device's proprietary dashboard (AdhereTech). The main components of the EDM manufacturer's dashboard for the TERA study and the TERA Implementation Dashboard it communicates with are presented in Figure 5. Each secure site plays an important role in the implementation of between-session contacts.

Figure 3. Remote face-to-face coaching sessions.

Remote Coaching Scheduled Sessions		
Session 1 (~60min)	***Session 2 (~30min)***	***Session 3 (~45min)***
Rapport building and orientation to technology and intervention components with graphics and smart bottle review	Rapport building and review of experiences with smart bottle and/or coach since baseline session	Check in and rapport building
Preferences for contact times and contact tree information	Review and Update Lifespace	Reflect on the participant's adherence plan by discussing potential barriers and ways to sustainable adhere to medication as prescribed
Exploration of Lifespace through co-creating a personalized graphic representation on the "white board" (a function of the telemedicine platform)	Present and discuss data captured by the EDM dashboard (color-coded dosing data mapped by month), contextualizing consecutive dosing days and non-dosing days	Review Lifespace by projecting any future adherence obstacles and identifying personal improvements made while in TERA
Discussion of experiences living with HIV	Review and revise (as needed) the adherence plan using NSC and other MI-based strategies	Reflecting on the benefits and challenges of participating in TERA and using MI-based strategies to capture the participant's motivation and readiness to adhere to their medication
Exploration of experiences with ART adherence using NSC, a theory-based model (see Figure 2)	Reflect on the participants experiences in TERA as they relate to self, adherence motivation and general satisfaction	Explaining what the program does and does not entail following the Coaching-phase
Development and agreement on the adherence plan	Reinforce remaining time in the Coaching-phase of the intervention, specifically having one remote visit left	Thank participant for their time and effort and wish them well in all that is to come

EDM: Electronic Dose Monitoring
Lifespace: A visual depiction of areas of interest, personal characteristics, personal goals and other defining attributes that is created during sessions
MI: Motivational Interviewing
NSC: Next Step Counseling
White board: A feature in Vsee video conferencing where images can be shared, manipulated and marked

Figure 4. Between session contacts.

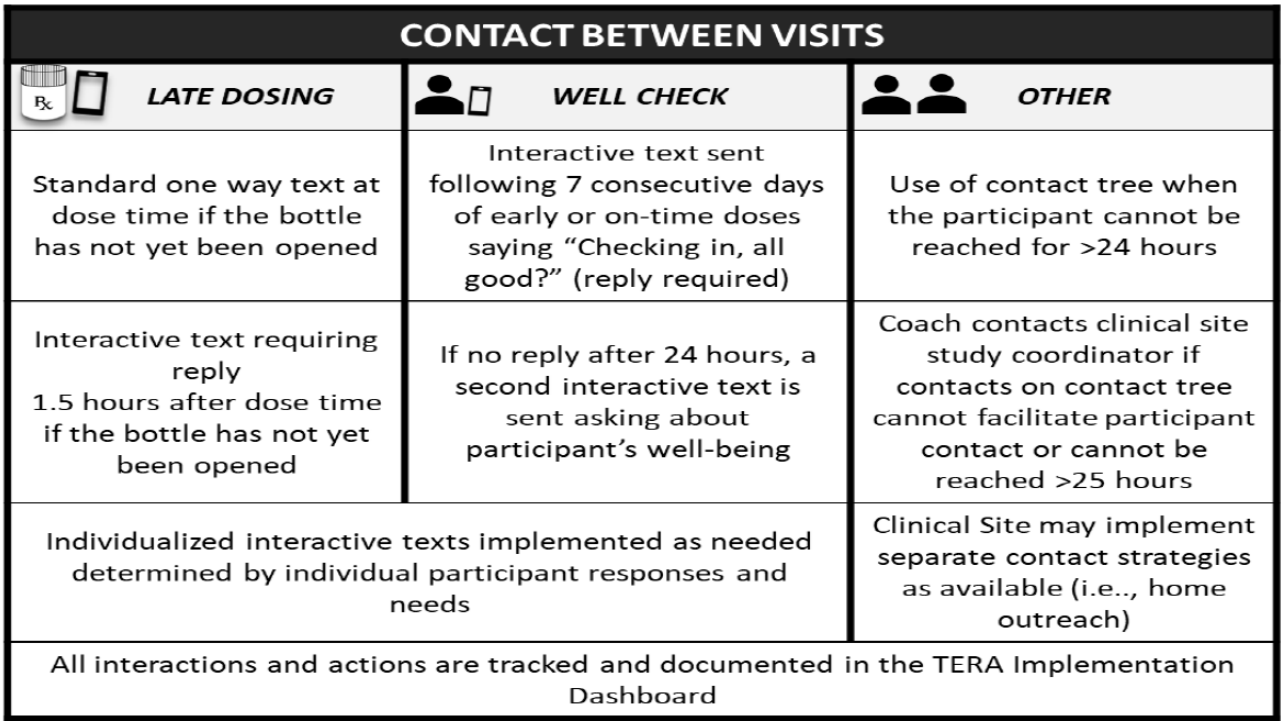
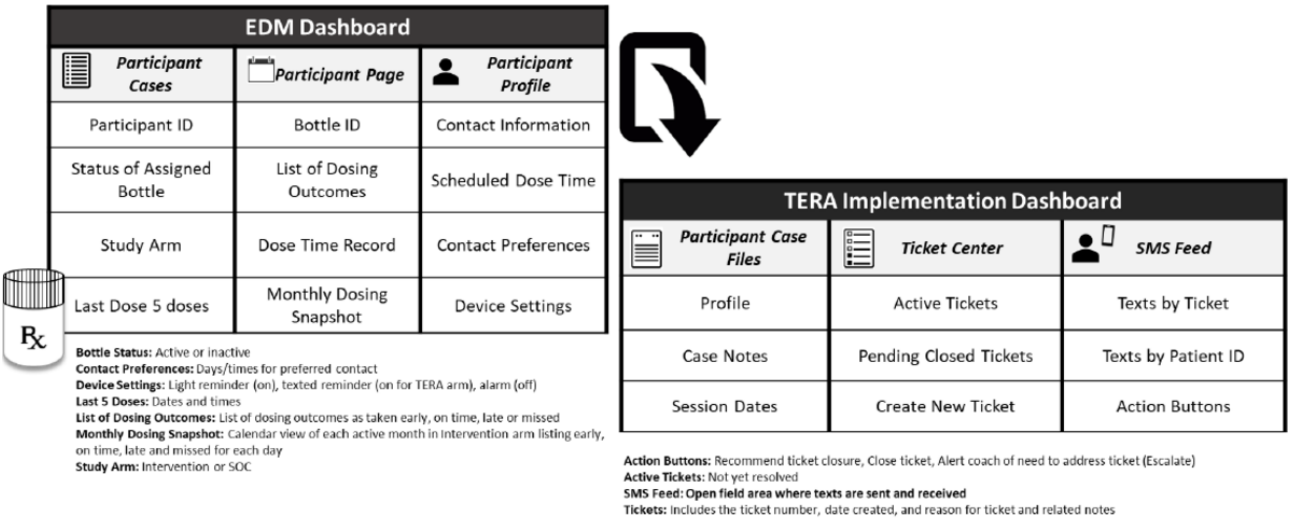


Figure 5. Electronic dose monitoring device dashboard and triggered escalating real-time adherence (TERA) Implementation Dashboard.



As depicted in Figure 5, the EDM dashboard has daily data specific to whether or not the bottle was opened relative to dose time as well as functionality checks on battery and cell signal strength. The additional details collected and presented in this dashboard allow coaches and monitors to quickly assess dosing patterns as well as the status of dosing (opening events) currently and historically. This dashboard also presents dosing data pictorially with colored marks on each calendar day for *taken early*, *on time*, *late*, or *missed* (no opening in a 12-hour period) dosing. As previously noted, coaches use this graphic in their review of dosing patterns at the week 4 and week 12 remote face-to-face coaching visits.

The detailed tracking of the implementation components of the TERA intervention are collected in the TERA Implementation Dashboard for use in real time to work with youth to prevent missed dosing as well as for use at the end of the study to characterize actual intervention implementation. As can be seen in Figure 5, each participant in the intervention arm has an area for basic details such as contact information and preferences for contact times, case notes to document interactions by date and time (much like an electronic medical record), dates and windows for remote coaching visits, and details surrounding current and historical tickets (virtual medical file). The ticket center lists all open tickets that are in process (active) or pending closure. Tickets are created automatically when the EDM dashboard signals a late dose (1.5 hours after dose time), when participants are automatically texted a check-in message after 7 days of on-time dosing, and can be manually created by coaches for any other type of communication with participants via text or phone. Tickets are also created if a participant texts the coach outside of a communication chain already initiated in response to a specific ticket. Thus, all communications with

participants between the scheduled remote face-to-face visits are associated with a ticket number. Texting, both sent and received, is conducted in a specific area of the TERA Implementation Dashboard. All SMS texts are stored in the dashboard. SMS texts sent and received in a communication chain and related case notes are connected to the originating ticket number. This allows data collection and capture of each interaction in the 12-week intervention period. When a participant has been contacted or the issue that started the ticket has otherwise been resolved, supervisors can move tickets from "pending" to "closed," which provides an added layer of oversight on intervention implementation. In addition to providing a tool for coaches and monitors to implement the intervention, the TERA Intervention Dashboard also serves to collect data (such as number of and content of texts and reasons for or outcomes of outreach attempts) that will be used to characterize intervention implementation.

Measures

Data collected include responses to Audio Computer-Assisted Self-Interviews (ACASI) scales and items, estimated adherence through collection of "opening events" from the EDM, and chart extracted data. In addition, implementation data are collected to provide costing data. Finally, qualitative interviews are conducted to explore feasibility, acceptability, and overall experiences in the study immediately at the end of the active intervention phase (week 12) and again at the end of participation in the study (week 48). Interview collected data are not used to modify the intervention during TERA but will be used in considering future implementation of this and related intervention approaches.

ACASI data are collected at baseline, week 12, week 24, week 36, and week 48. Table 2 describes each measure used in the ACASI as well as the schedule for data collection and brief description of the measure. The ACASI should take approximately 30 minutes or less to complete.

Statistical Methods

The primary and secondary objectives of this study are to estimate and compare VLS rates and adherence over 48 weeks between the TERA and SOC arms. Analyses will be intent-to-treat (ITT) using all participants as-randomized to control or intervention arm. Participants lost to follow-up before key time points or with no HIV-1 RNA measurement within allowable windows will be classified as failures at that time point. Categorical outcomes will be summarized using proportions (95% confidence intervals), and continuous outcomes will be summarized using means/medians as appropriate. In adjusted analyses, the number of covariates used in the models will be limited because of the relatively small sample size. Factors that could be associated with the outcome measures and could affect the magnitude of differences between the TERA and SOC arms include age, race, gender, route of HIV infection, years living with HIV, regimen line (eg, first and second), and substance use. A significance level of $P<.05$ will be used with no adjustments for multiple comparisons or interim analyses.

The EDM will provide daily information on adherence in each participant. Overall, 2 outcomes (percentage of days correctly dosed per week and percentage of days dosed within the targeted time frame per week) will be summarized by arm weekly, in 12-week intervals, and between the intervention and postintervention time periods. Differences may be largest during the initial 12 weeks, as that is when the intervention is administered, with differences waning over time. To address possible informative censoring induced by losses to follow-up, analyses will include (1) available data and (2) imputing weekly adherence of 0% if a participant is lost to follow-up.

To characterize TERA implementation, ability to enroll to the study, drop-out rates by week 12 and throughout the study, numbers of participants escalating to different alerts and outreach at least once, numbers of alerts per participant (TERA arm only), and themes from qualitative interview content related to experiences in the intervention will be summarized.

Ethics

The ATN Coordinating Center at UNC-CH provides sIRB approval, guidance, and monitoring. All clinical research sites ceded regulatory oversight to the IRB at UNC-CH. All sites adapt an sIRB approved consent template to meet the specific requirements of their site. Waivers of parental consent for those under the age of 18 years were considered by all sites and adopted by those with local regulatory approval.

Study and Data Monitoring

On-site monitors from the ATN Coordinating Center will review a selected portion of the individual participant records, including assent/consent forms, case report forms (CRFs), and supporting source documentation to ensure the protection of study participants, compliance with the protocol, and accuracy and completeness of records. Regulatory files, as required, will also be inspected to ensure that regulatory requirements are being followed.

The Protocol Team will review accrual, retention, and data quality on monthly team calls, with data combined across study arms. An independent Study Monitoring Committee (SMC) will review the study at scheduled, planned points to monitor participant safety as well as data integrity. At each review, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide specific operational recommendations to help address any study implementation challenges identified during their reviews. Untoward events will be recorded by the site and reported to the ATN Coordinating Center, study team, and the sIRB.

Table 2. List of study measures and collection time points.

Measures[a]	Collection method	Study visit week					Description
		BL[b]	12	24	36	48	
Adherence support during participation	ACASI[c]	—[d]	X[e]	—	—	X	Checklist of receipt of specific kinds of support during the first 12 weeks and at week 48
Information Motivation Behavior Skills ART[f] Adherence Questionnaire [55,56]	ACASI	X	X	X	X	X	Measure of adherence barriers identified by the Information, Motivation, Behavioral Skills Model of adherence
The HIV Adherence Self-Efficacy Scale [57]	ACASI	X	X	X	X	X	Measures self-efficacy for adherence to HIV treatment plans, including, but not limited to, taking HIV medications
Adolescent Decision-Making Questionnaire (ADMQ) [58]	ACASI	X	X	X	X	X	Revised version of the ADMQ that measures decision-making patterns in adolescence: avoidance, self-confidence, panic, and impulsive/thoughtless
Center for Epidemiological Studies Depression Scale (CESD-10) [59]	ACASI	X	—	—	—	X	Self-reported 10-item screener for depressed mood in respondents
Demographics	ACASI	X	—	—	—	—	Study developed and ATN-harmonized items assessing sociodemographic characteristics
Emotional Regulation Questionnaire [60]	ACASI	X	X	X	X	X	10-items scale designed to measure cognitive reappraisal and expressive/suppressive regulation
EuroQOL Five Dimensions Questionnaire for Youth (EQ-5D-Y) (overall health status) [61]	ACASI	X	X	X	—	X	Standardized measure of overall health status: mobility, looking after myself, doing usual activities, having pain/discomfort, and sad or happy, using a visual analog scale
HIV cascade measure (ATN Coordinating Center)	ACASI	X	—	—	—	—	ATN-harmonized items related to engagement in HIV-related care
HIV stigma mechanisms [62]	ACASI	X	X	X	X	X	Stigma framework including measures of internalized, anticipated, and enacted HIV stigma
Life Events Survey	ACASI	X	X	—	—	X	Study-adapted measure of significant or traumatic life events
Satisfaction scale (developed for study)	ACASI	—	X	—	—	X	Study-developed measure of participants' satisfaction with the TERA[g] intervention
Self-reported adherence [63]	ACASI	X	X	X	X	X	3-items: *doses taken* (0 to 30), *frequency* of doses taken in last 30 days, and *rating* of how good of job taking medications
Sex behavior	ACASI	X	X	—	—	X	Brief item set to assess rates of condomless sex
Social Support Scale (Medical Outcomes Study) [64]	ACASI	X	X	X	X	X	Overall functional social support and emotional/information and tangible, affectionate, and positive social interaction support
Substance use (Alcohol, Smoking and Substance Involvement Screening Test) [65]	ACASI	X	X	—	—	X	Problem or risky use of tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, sedatives, hallucinogens, inhalants, opioids, and "other drugs" that do not fall into the previous categories
Adherence support services utilization checklist	Participant visits and interviews	X	X	X	X	X	Study-developed checklist completed by study staff to document standard of care adherence support services received by participant

Measures[a]	Collection method	Study visit week					Description
		BL[b]	12	24	36	48	
Medical history	Chart abstraction	X	X	X	X	X	Date of HIV diagnosis, route of HIV transmission, previous ART regimens, opportunistic infections since diagnosis, comorbidities, and concomitant medications
Qualitative interviews	Remote (VSee) interview	X	—	—	—	X	Main themes youth report for adherence support needed, received, and valued

[a]EDM adherence data are collected throughout study participation, that is, from baseline to the 48-week visit. Chart-abstracted data for all HIV-VL and CD4 tests conducted while on study will be extracted; VL test results at baseline, week 12, and week 48 are required and resourced by the study if clinical care did not involve a VL test at those visits.

[b]Baseline.

[c]ACASI: Audio Computer-Assisted Self-Interviews.

[d]Not included in visit.

[e]Conducted or included in the visit.

[f]ART: antiretroviral therapy.

[g]TERA: triggered escalating real-time adherence.

Results

To date, all clinical research sites have ceded to the UNC-CH sIRB and are in the process of opening for enrollment. First enrollments occurred in April 2018 with a planned 12-month period to reach the target enrollment of 120 youth. Original timelines anticipated enrollment to begin in January 2018, allowing enrollment to end in January 2019. An adjusted timeline, allowing enrollment to extend to August 2019, would allow completion of data collection by August 2020 and dissemination of results in the second quarter of 2021. Presently, 8 sites are open to enrollment and 46 youth have been enrolled in the study.

Discussion

Summary

The TERA study will contribute to the developing evidence base focused on better understanding the dynamics that influence ART adherence in youth. This study advances the number of options for highly generalizable strategies to optimize adherence among YLWH known to have struggled with ART in the past. As the approach uses centralized coaches and electronic dose monitoring that are separate from the clinical care team and related resources, if effective, the program could be brought to scale as a support service offered to youth throughout the United States resourced by insurers or stakeholders invested in optimal adherence. Interventions that are matched to maturational issues and demands of youth are critically needed [7,37]. TERA results should contribute to advancing both the science and practice of providing optimized support to YLWH.

Limitations

There are several limitations that are important to consider. The EDM device tracks opening events and not consumption of medications. Days with opening events cannot assure consumption, and days passing without opening events cannot confirm nonconsumption. We do note that EDM data do perform well as a proxy for adherence. Evaluations of EDM-collected opening events do provide evidence for a consistent association with viral load and when compared with other measurement approaches (self-report, pill-count, and pharmacy refill) tend to demonstrate higher associations with clinical outcomes [66-68]. Another assumption of the TERA intervention is that failure to achieve and/or sustain viral suppression is secondary to adherence problems. Working with youth in the United States where resistance testing is a part of clinical care, especially with documented treatment failure, we feel this may be a reasonable assumption. In addition, among youth with perinatal infection, a recent study has suggested that drug resistance is less frequently the cause of virologic failure to new ART regimens than nonadherence [69,70]. Clearly, one would not expect the TERA intervention to be effective in assisting youth with viral suppression if the root cause for failure is resistance. In addition, the intervention uses SMS texting as a method for contacting youth. If participants' cell phones become discontinued or numbers are changed, lost, or replaced, there is no way of knowing on the basis of texting. To mitigate this, coaches include specific discussions on what to do in these situations with each intervention arm participant at the initial and subsequent remote coaching sessions. In addition, coach procedures allow contacting site coordinators to investigate this in the event that they have had several days without participant reply or response to outreach.

Conclusions

EDM, real-time triggered interventions, and interactive and real-person phone-based outreach with the use of a contact-tree are all novel components to adherence support that promise high impact. The existing evidence base will be leveraged to create a high-intensity, responsive, time-limited intervention approach. Although texting has a strong evidence base for adults [26,28,41], use with youth, although intuitively appealing given the widespread use of texting, remains supported largely only by pilot studies [31]. Similarly, phone-based problem-solving discussion with adherence coaches has preliminary evidence [34] demonstrated in a pilot study. This study leverages the wealth of pilot evidence to create an intervention approach with demonstrated promise but not yet rigorously evaluated. Of

particular interest, our goal is to mesh together an evidence-informed approach that can also be generalizable. Given that sites and clinics working with youth will have limitations in resources, we adapted interventions implemented over an extended period to a discreet, intensive approach implemented over a 12-week period and intensified in response to delayed dosing. This creates a more generalizable program as resources required are similarly time-limited. The key pieces that make up the TERA intervention are largely in place; YLWH overwhelmingly have cell phones and clinic team members already use or will be trained in problem-solving. A system for sending and receiving texts can be automated, with costs allocated toward building the system and minor costs for maintenance of system. If the intervention is effective, it could have an immediate impact on care services provided to YLWH failing ART and future applications to other points in the continuum of HIV prevention and care that depend on youth adhering to the applicable interventions.

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Conflicts of Interest

None declared.

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Abbreviations

ACASI: Audio Computer-Assisted Self-Interview
ADMQ: Adolescent Decision-Making Questionnaire
ART: antiretroviral therapy
ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions

CRF: case report forms
EDM: electronic dose monitoring
EQ-5D-Y: EuroQol 5 dimensions Questionnaire-Youth
IMB: Information, Motivation, Behavioral Skills Model
IRB: Institutional Review Board
MI: motivational interviewing
NSC: Next Step Counseling
SDAC: statistical data analysis center
sIMB: situated application of the Information Motivation Behavioral Skills model
sIRB: single Institutional Review Board
SMC: Study Monitoring Committee
SMS: short message service
SOC: standard of care
TERA: triggered escalating real-time adherence
UNC-CH: The University of North Carolina at Chapel Hill
VLS: viral suppression
vYAB: virtual youth advisory board
YAB: youth advisory board
YLWH: youth living with HIV

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Protocol

Community-Based, Point-of-Care Sexually Transmitted Infection Screening Among High-Risk Adolescents in Los Angeles and New Orleans: Protocol for a Mixed-Methods Study

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Abstract

Background: Sexually transmitted infection (STI) rates are increasing in the United States, with approximately half of new infections occurring among adolescents aged 15-24 years. Gay, bisexual, and transgender youth (GBTY), homeless youth, and youth with histories of drug use, mental health disorders, and incarceration are all at uniquely high risk for STIs. However, these adolescents often lack access to sexual health services.

Objective: This study aims to use point-of-care STI tests in community-based settings to screen for and treat STIs in adolescents.

Methods: We are recruiting 1500 HIV-uninfected youth and 220 HIV-infected youth from homeless shelters, GBTY organizations, and community health centers in Los Angeles, California and New Orleans, Louisiana. Study participants will receive STI screening every 4 months for 24 months. STI screening includes rapid HIV, syphilis, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and Hepatitis C virus testing. Trained paraprofessionals will conduct all STI testing. When a participant screens positive for an STI, they are either linked to a partner medical clinic or provided with same-day antibiotic therapy and expedited partner therapy. We will monitor STI prevalence among study participants as well as point-of-care test performance, linkage to care, and treatment outcomes.

Results: The project was funded in 2016, and enrollment will be completed in 2019. Preliminary data analysis is currently underway.

Conclusions: As STI rates continue to rise, it is important to improve access to screening and treatment services, particularly for high-risk adolescents. In this study, we aim to evaluate the use of point-of-care STI diagnostic tests in community-based organizations. We hope to determine the prevalence of STIs among these adolescents and evaluate the acceptability and feasibility of community-based STI screening and treatment.

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International Registered Report Identifier (IRRID): DERR1-10.2196/10795

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KEYWORDS

sexually transmitted infections; adolescents; point-of-care testing

Introduction

There are approximately 20 million new sexually transmitted infections (STIs) every year in the United States. Half of these infections occur among adolescents aged 15-24 years [1]. STI rates have been steadily increasing over the past few years, with adolescent rates of *Chlamydia trachomatis* (CT) infection, *Neisseria gonorrhoeae* (NG) infection, and syphilis infection on the rise (Figure 1) [2,3].

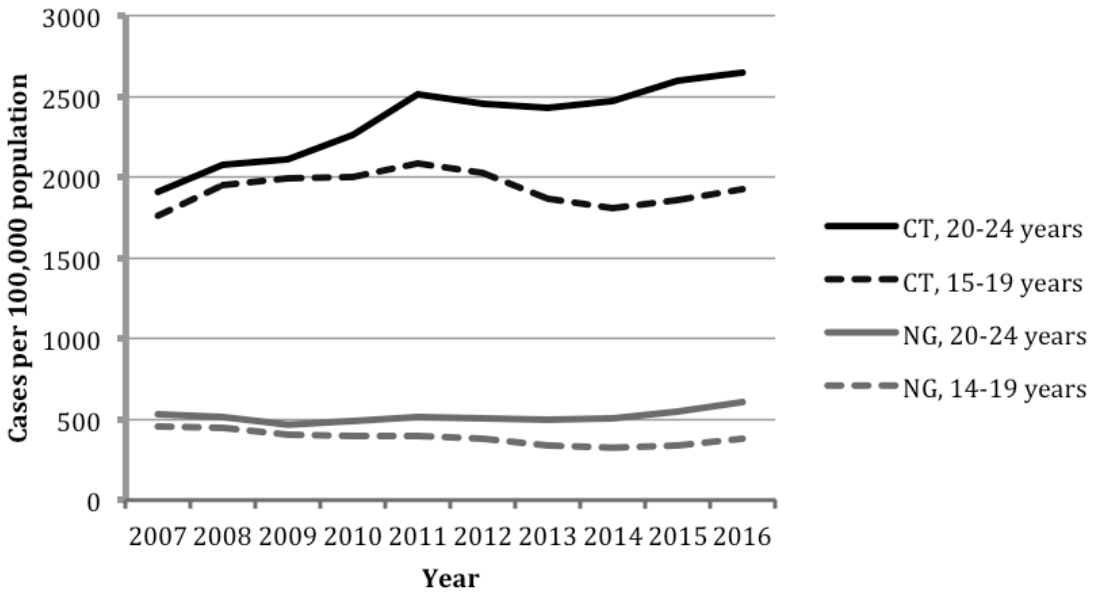
Adolescents are at particularly high risk for STIs due to a combination of behavioral, biological, and social factors. Behaviorally, adolescents are more likely to engage in higher-risk sexual behaviors such as concurrent partners or sex without a condom. Biologically, adolescent females are often more susceptible than adult women to contracting an infection if exposed [2,4]. Socially, adolescents often lack access to sexual health services or do not pursue STI testing due to confidentiality concerns [5].

STI prevalence is highest in the southern and western United States, with black and Latino adolescents at particularly high risk [2]. Social and geographic differences in STI prevalence are likely due to systemic inequalities leading to limited access to sexual health services and reduced rates of STI screening [6]. The stigma surrounding sexual health may also contribute to reduced screening uptake. Gay, bisexual male, and transgender female youth are at an increased risk for STIs due to a combination of risk factors, such as condomless sex, concurrent partners, and sex with older partners [2]. Receptive anal intercourse also has a higher STI transmissibility than other forms of intercourse. Among gay, bisexual, and transgender youth (GBTY), parental rejection, stigma, discrimination by peers, and increased stress associated with being a member of a minority, whether that minority status comes from race, ethnicity, socioeconomic status, or sexual orientation, may increase sexual risk-taking behaviors and STI rates. Finally, several studies have shown that homelessness, a history of incarceration, and illicit drug use are also associated with increased STI risk in adolescents [7-9]. Reduced access to sexual health services, high levels of stigma, and increased rates of risk-taking behaviors may all contribute to lower rates of screening and higher prevalence of STIs in these populations.

It is critical to diagnose and treat adolescent STIs for a number of reasons. Left untreated, many STIs can lead to long-term health consequences. Bacterial STIs such as CT and NG may lead to reproductive system damage, while syphilis can cause serious neurological damage [10-12]. Viral STIs such as human papillomavirus, herpes simplex virus, and hepatitis C virus (HCV) can cause cancer, genital blisters, and liver failure, respectively [13-15]. Furthermore, STIs increase the risk of acquiring HIV infection 3-fold to 5-fold [16].

Fortunately, diagnostic tests are available for many STIs. Specifically, rapid diagnostic tests create a new opportunity to screen for and treat STIs in community-based settings previously unequipped to offer testing services [17-19]. As these tests become more readily available, it is important to understand their effectiveness in diagnosing and treating STIs in high-risk adolescent populations. By understanding this, we can better evaluate if rapid STI testing in community-based settings may help improve access to sexual health services, reduce stigma, and prevent confidentiality concerns among key high-risk populations.

Figure 1. *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) infection rates among adolescents from 2007 to 2016.



In this component of the Comprehensive Adolescent Research and Engagement Studies (CARES), part of the Adolescent Medicine Trials Network (ATN) for the HIV/AIDS Interventions Research Program Grant (National Institutes of Health grant U19HD089886), we aim to evaluate the use of rapid STI testing among adolescents at community-based organizations in Los

Angeles, California and New Orleans, Louisiana. Rapid STI testing will be administered to 1500 high-risk HIV-uninfected youth and 220 HIV-infected youth every 4 months over the course of 2 years. We will monitor STI prevalence, acceptability and feasibility of rapid diagnostic STI testing, and STI treatment outcomes.

Methods

Objectives

We are conducting rapid HIV, CT, NG, syphilis, and HCV testing among adolescents aged 15-24 years at community-based organizations in Los Angeles and New Orleans. Our partner community-based organizations cater to GBTY, homeless youth, youth with a history of mental health disorders, and youth with a history of incarceration. Study participants receive STI testing at 4-month intervals for 24 months, totaling 1 baseline visit and 6 follow-up visits. When a participant receives a positive STI test result, they are linked to care at a nearby medical clinic or provided with antibiotic treatment by the interviewing staff. We hypothesize that by providing rapid STI testing among high-risk adolescent populations, we will find STI prevalences higher than the national averages for adolescents. We intend to evaluate the acceptability of testing as the uptake of screening among eligible participants, and we intend to evaluate the feasibility of treatment as the proportion of participants who test positive for an STI and receive treatment. We expect that by providing same-day testing results and treatment, we will be able to provide quicker time to treatment and higher treatment rates than with traditional lab-based testing. We will compare our time to treatment and treatment rates with historical data from AIDS Healthcare Foundation, Los Angeles. We also intend to evaluate other treatment outcomes such as cure rates, reinfection rates, and partner treatment rates. For objectives of other components of the ATN CARES study, refer to other ATN CARES protocol papers [20-24]. For specific power analyses, refer to the ATN CARES paper by Swendeman et al [22].

Research Ethics and Approval

The Institutional Review Board of the University of California, Los Angeles has approved the study protocol (16-001674-AM-00006). We will report any protocol deviations or indications of adverse events to the Institutional Review Board. The study was registered on ClinicalTrials.gov (NCT03134833) on April 28, 2017.

Sexually Transmitted Infection Tests

We selected rapid STI tests according to performance, availability, and cost. Table 1 shows the sensitivity and specificity values of each test.

Table 1. Sensitivities and specificities of sexually transmitted infection rapid diagnostic tests.

Test name	Sensitivity (%)	Specificity (%)
Determine HIV-1/2 Ag/Ab Combo [25]	99.9	99.8
Xpert HIV-1 Qual [26]	98.7	99.9
Syphilis Health Check [27]	71.4	91.5
Hepatitis C Virus Rapid Antibody Test [28]	99.9	99.9
Xpert CT[a]/NG[b] Assay [29]		
Vaginal swabs		
CT	99.5	99.1
NG	99.9	99.9
Urine		
CT	98.5	99.8
NG	98.3	99.9

[a]CT: *Chlamydia trachomatis.*

[b]NG: *Neisseria gonorrhoeae.*

HIV antigen and antibody screening are done using the Determine HIV-1/2 Ag/Ab Combo test (Alere Inc) (Figure 2) [30]. This test is a point-of-care lateral flow strip that detects both HIV-1 and HIV-2 antibodies and the HIV-1 p24 antigen using 50 µL of fingerstick whole blood. The window period is 12-26 days, and results are ready in 20-40 minutes. The test is Clinical Laboratory Improvement Amendments (CLIA) waived and Food and Drug Administration (FDA) approved [25,31].

We will perform HIV RNA and DNA screening with the Xpert HIV-1 Qual test (Cepheid) (Figure 3) [32]. The test is a point-of-care qualitative *in vitro* HIV test, detecting HIV-1 RNA and DNA. The HIV-1 Qual test requires 100 µL of whole blood, and results are available in 90 minutes [26]. The test is approved for use in the European Union and undergoing the approval process with the FDA. Our study is the first in the United States to use the test, and results are available as research use only.

Figure 2. Determine HIV-1/2 Ag/Ab Combo test.

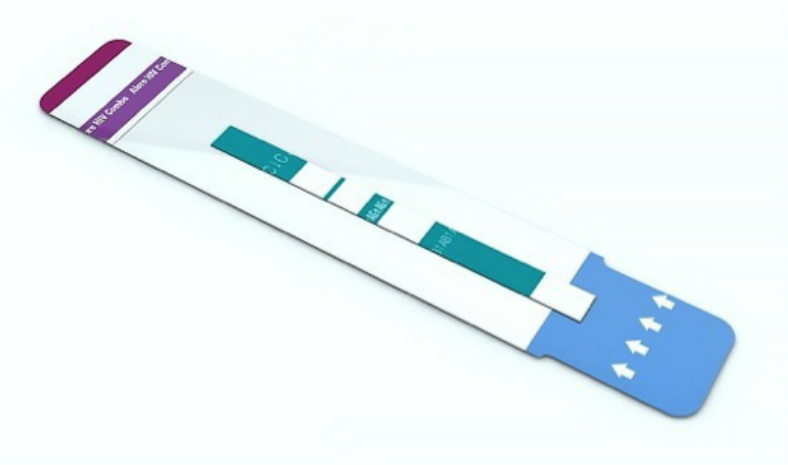


Figure 3. GeneXpert machine used for HIV-1 Qual and CT/NG tests.

The HIV-1 Qual test can detect HIV infection an average of 5 days earlier than a p24 antigen test. Therefore, this test is done to detect acute HIV infections that we may not be able to detect with the Alere HIV test.

Syphilis screening is done using the Syphilis Health Check, a rapid point-of-care treponemal antibody test (Diagnostics Direct) (Figure 4) [33]. The test uses 50 µL of whole blood, and results are available in 10 minutes. The Syphilis Health Check is the only FDA-approved rapid syphilis test [27].

We will perform HCV screening with the HCV Rapid Antibody Test (OraSure Technologies), a rapid point-of-care assay used for the detection of HCV antibodies (Figure 5) [34]. The test uses whole blood and gives results in 20-40 minutes. The test has a waiver from the CLIA and is approved by the FDA [28].

Finally, we will perform CT and NG screening using the Xpert CT/NG Assay (Cepheid) (Figure 3). The test is a qualitative *in vitro* real-time polymerase chain reaction test for the detection of CT and NG. Results are available in 90 minutes [29]. The test is FDA approved for urine samples and vaginal swabs. However, it is also verified in accordance with CLIA for pharyngeal and rectal swabs [35]. Male participants self-collect pharyngeal and rectal swabs as well as a urine sample, while female participants self-collect pharyngeal, rectal, and vaginal swabs.

Training

Interviewing staff conducts all STI and HIV rapid testing at community-based recruitment sites. Interviewers are typically Bachelor of Arts-level paraprofessionals with little prior experience related to rapid diagnostic testing. Some have previously received phlebotomy training, but most receive phlebotomy training upon hiring. Interviewers receive training and certification in state-specific HIV counselor training. HIV counselor training includes training on fingerpricking, conducting different types of rapid HIV tests, interpreting results, and providing counseling regarding safe sex practices. We also coordinate specific training in Los Angeles and New Orleans for each diagnostic test. The respective diagnostic test companies (Alere, Cepheid, Diagnostics Direct, and OraSure) conduct the training. We evaluate interviewers on their ability to properly collect fingerprick blood and on their ability to correctly interpret test results. We conduct repeat diagnostic test training every 6 months to ensure interviewers continue to correctly perform tests. A binder with step-by-step test instructions is at every site in case any questions arise.

Figure 4. Syphilis Health Check test.

Figure 5. HCV Rapid Antibody Test.

We also train interviewers on how to instruct participants to self-collect rectal swabs, pharyngeal swabs, vaginal swabs, and urine samples. For rectal swabs, we provide an image to show the acceptable level of fecal contamination on the swab (Figure 6).

Interviewers use Fleshlite (Austin) models to demonstrate how to self-collect vaginal and rectal swabs (Figures 7 and 8) [36], while they use a mirror to locate the tonsils and demonstrate how to self-collect a pharyngeal swab.

Finally, we train interviewers on how to administer treatment for CT and NG infections. A physician prescribes the antibiotics, and interviewers are trained by the physician on how to properly deliver antibiotic therapy. Training includes information about antibiotic mechanisms, pharmacokinetics, potential adverse effects, partner therapy, retesting, and STI counseling. Interviewers practice providing treatment using sample scenarios to demonstrate competence.

Testing Flow

While we perform HIV, CT, NG, and syphilis testing at every recruitment site, we only perform HCV testing at sites with populations at higher risk of HCV (history of incarceration or drug use). Every study participant receives every STI test unless they specifically choose to opt out. Opting out does not affect eligibility or reimbursement.

Figure 6. Instructions for self-collected rectal swabs. CT: *Chlamydia trachomatis*; NG: *Neisseria gonorrhoeae*.

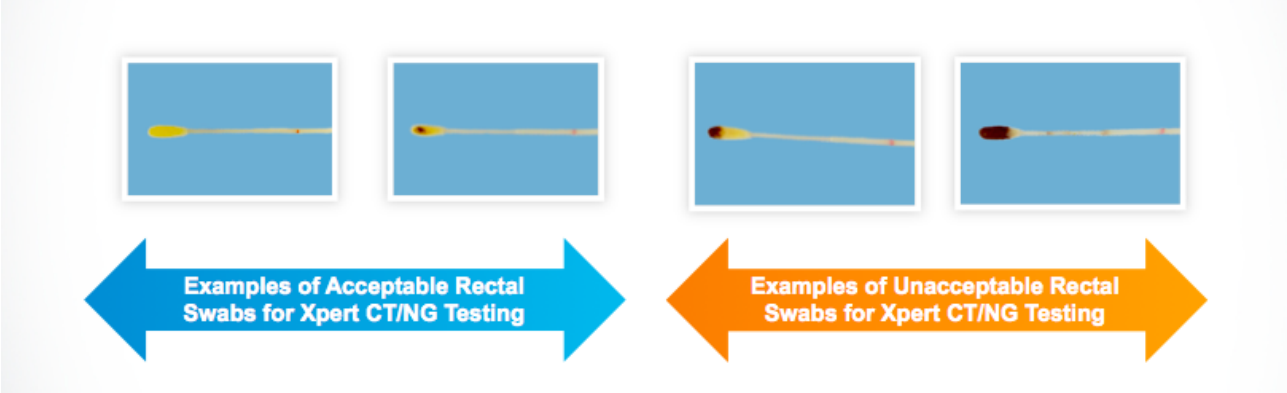


Figure 7. Vaginal Fleshlite used to demonstrate how to self-collect vaginal swabs.

Figure 8. Anal Fleshlite used to demonstrate how to self-collect rectal swabs.

At baseline, the rapid HIV test is done as part of the eligibility screening to determine if the participant is HIV-infected or -uninfected. We determine eligibility based on a risk assessment, with a minimum risk score necessary for enrollment. Inclusion criteria and risk scoring are explained in detail in the ATN CARES protocol papers by Rotheram-Borus et al and Comulada et al [21,24]. If a participant is eligible for the study, they are enrolled and receive the additional STI testing. An interviewer with phlebotomy certification draws blood for use in the HIV RNA/DNA test, the syphilis test, and the HCV test at certain sites. The participant self-collects their urine sample or pharyngeal, rectal, and vaginal swabs. Clients are encouraged to stay until their test results are available.

Routine follow-up appointments occur at 4-month intervals for 2 years. However, if a patient reports potential STI exposure or STI symptoms to the interviewer, they will be invited for testing at any point during the study.

Linkage to Care, Treatment, and Partner Management

Participants receive their test results on the same day as the testing. Whenever possible, they are told the results in person. If the participant needs to leave their appointment before results are available, the interviewer asks the participant how they

would like to receive the results and then communicates the results with them through a phone call, text, or email. When a patient receives a positive test result, they are either referred to a partner medical clinic or to their primary care provider to receive treatment, or they are provided with treatment by the interviewing staff. All partner medical clinics agreed to and signed an STI treatment protocol that is in accordance with Centers for Disease Control and Prevention recommendations.

If the participant elects to seek treatment at a clinic, the interviewer works with the participant to find a clinic that is geographically convenient, and the study organizes free transport to the clinic via the Uber app. Interviewers counsel participants on the importance of partner treatment and safe sex practices. They also follow up with study participants to ensure they were able to receive treatment, and study staff obtains records of the treatment from the clinic.

For syphilis infections, we will always refer the participant to a clinical provider since follow-up blood work and a penicillin injection may be required. For CT and NG infections, it is up to the participant if they prefer to be referred to a clinic or receive same-day antibiotic treatment from the interviewing staff. The interviewers treat vaginal, urethral, and pharyngeal CT infections with 1 g oral azithromycin [1]. They treat rectal CT infections with 100 mg oral doxycycline twice daily for 7 days, as evidence shows doxycycline is more effective than azithromycin in treating rectal CT [37-40]. NG infection, while often clinically treated with 1 g oral azithromycin and an injection of 250 mg ceftriaxone, is instead treated with 1 g oral azithromycin and 400 mg oral cefixime [1]. The treatment of concurrent CT and NG infections are according to the type of CT infection. If there is a vaginal, urethral, or pharyngeal CT infection in addition to an NG infection, treatment is 1 g oral azithromycin and 400 mg oral cefixime. If there is a rectal CT infection in addition to an NG infection, treatment is 100 mg oral doxycycline twice daily for 7 days and 400 mg oral cefixime. All treatment regimens follow Centers for Disease Control and Prevention guidelines and are effective treatment methods.

We prepackage treatment packs that include antibiotic instructions, antibiotics, physician contact information, water, and a snack. Every recruitment site has these treatment packs available. We also offer participants with a positive CT or NG result up to 10 expedited partner therapy packets according to the number of partners reported in the past 90 days [41]. We provide the expedited partner therapy packs according to the type of infection participants test positive for as well as the type of sex they report having with their partner. For example, if a participant tests positive for urethral CT and reports insertive anal sex, we will provide doxycycline in the expedited partner therapy pack.

Quality Control

The study team monitors STI prevalence to ensure that it falls within the expected range. A research assistant performs monthly quality control testing at every testing site to confirm that all tests are functioning properly. Monthly quality control testing involves running a positive and negative control sample for each rapid STI test at each site. This ensures that the tests correctly identify both positive and negative results. In addition to every month, we perform quality control testing whenever a new interviewer is conducting the tests, a new test lot number is received, or if the storage temperature falls outside the recommended range.

Data Collection and Analysis

Interviewing staff record STI lab results on a paper lab form as well as through CommCare, a mobile data collection platform created by Dimagi (Cambridge). We then obtain the documentation of STI treatment from the medical clinics.

Using these data, we will evaluate STI prevalence, risk factors, and HIV seroconversion rates throughout the study period. We will also evaluate successful linkage to care and treatment of positive STI cases.

Moving Forward

At the time of manuscript submission, we are in the process of making one change to our study protocol. Due to the high prevalence of a history of syphilis in our study population and the low specificity of the Syphilis Health Check, a participant with a positive Syphilis Health Check result requires additional laboratory testing. Therefore, we will obtain rapid plasma reagin titers and *Treponema pallidum* particle agglutination testing when a participant has a reactive Syphilis Health Check result. Quest Diagnostics will perform the rapid plasma reagin and *Treponema pallidum* particle agglutination tests. We anticipate that this change will significantly improve our ability to properly diagnose syphilis infections.

Results

The project was funded in 2016, and enrollment will be completed in 2019. Preliminary data analysis is currently under way.

Discussion

As STI prevalence in the United States continues to rise, it is critical to improve access to STI screening and treatment. This means improving the availability of acceptable and feasible screening methods, particularly for our country's highest risk populations. In this study, we use point-of-care rapid diagnostic STI tests to screen adolescents for HIV, CT/NG, syphilis, and HCV. We are recruiting and enrolling participants at local community-based organizations in Los Angeles and New Orleans that cater to homeless youth and GBTY as well as youth with histories of drug use, mental health disorders, and incarceration. By targeting that traditionally tough-to-reach, high-risk group, we hope to determine the prevalence of STIs in the population and demonstrate the acceptability and feasibility of rapid STI testing and treatment programs in community-based settings.

A limitation of our study is that we are not evaluating cost-effectiveness. The GeneXpert machines used in our study were provided by the manufacturer as part of the Xpert CT/NG and Xpert HIV-1 Qual cartridge purchase agreement. While the machines themselves are expensive, they are cheaper than commercial laboratories. Moving forward, it would be

advantageous to evaluate the cost-effectiveness of rapid STI testing in community-based settings.

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Conflicts of Interest

None declared.

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Abbreviations

ATN: Adolescent Medicine Trials Network
CARES: Comprehensive Adolescent Research and Engagement Studies
CLIA: Clinical Laboratory Improvement Amendments
CT: *Chlamydia trachomatis*
FDA: Food and Drug Administration
GBTY: gay, bisexual, and transgender youth
HCV: Hepatitis C virus
NG: *Neisseria gonorrhoeae*
STI: sexually transmitted infection

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Editorial

Improving the Youth HIV Prevention and Care Continuums: The Adolescent Medicine Trials Network for HIV/AIDS Interventions

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Abstract

Background: Epidemiologic and clinical information in the United States indicate that HIV transmission and acquisition among adolescents and young adults (youth) remain unchanged, without improvement. Interventions to prevent HIV transmission among youth are critically needed, as are interventions to improve adherence to all components of the continuum of care for youth living with HIV.

Objective: The primary mission of the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) is to conduct both independent and collaborative research that explores promising behavioral, microbicidal, prophylactic, therapeutic, and vaccine modalities in HIV-infected and at-risk youth aged between 12 and 24.

Methods: Through the ATN, the National Institutes of Health is supporting HIV interventional research for youth in the United States.

Results: The ATN comprises 3 cooperative multiproject research programs and a coordinating center. Each program is led by a network hub and has well-defined research themes to assist, guide, and coordinate HIV research project activities.

Conclusions: ATN activities encompass the full spectrum of research needs for youth, from HIV primary prevention for at-risk youth in the community to secondary and tertiary prevention with clinical management of HIV infection among youth living with HIV experiencing adherence challenges.

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KEYWORDS

HIV; youth; adolescent; treatment; care continuum

Introduction

Background

Epidemiologic and clinical information in the United States indicate that HIV transmission and acquisition among adolescents and young adults (youth) remain unchanged, without improvement. The Centers for Disease Control and Prevention (CDC) estimates that in the United States, youth aged 13 to 24 years accounted for 21% of all new HIV diagnoses in 2016 [1]. In 2016 alone, among the approximately 8450 youth diagnosed with HIV in the United States, 80.99% (6844/8450) were gay or bisexual males. The CDC also estimates that at the end of 2015, an estimated 60,300 youth were living with HIV in the United States [2]. Of these, 51.00% (30,753/60,300) were living with undiagnosed HIV—the highest rate of undiagnosed HIV in any age group. Increased efforts for routine HIV testing have not substantially increased the numbers of diagnoses among youth who are unaware that they are living with HIV infection. To obtain a better understanding of the transmission risks and needs of youth to improve HIV testing and diagnosis rates, systematized and widespread monitoring and surveillance of outcomes along the entire HIV prevention continuum of care, including linkage to prevention services and engagement in risk-reduction interventions, are needed [3-6]. Furthermore, interventions to prevent HIV transmission among youth are critically needed, including behavioral interventions and studies

of HIV vaccines, microbicides, and pre-exposure prophylaxis (PrEP) uptake and adherence.

Not only do youth and young adults have the highest rates of undiagnosed HIV [1] but they also have some of the poorest outcomes across the HIV treatment and care cascade [7-9]. They have the lowest rate of linkage to care (among youth who were diagnosed with HIV in 2014, 68% were linked to care within 1 month) and the lowest rate of viral suppression for any age group (among youth who were diagnosed with HIV in 2012 or earlier, 55% were retained in HIV care and 44% had a suppressed viral load) [1]. Linkage to care is a critical step for youth who test HIV-positive that is hampered by barriers on many levels, including structural, individual, and developmental [10]. Numerous studies have documented the challenges that youth experience maintaining adherence to their antiretroviral regimens, including side effects, medication dosing schedules, unstable living situations, disclosure of HIV status, co-occurring illnesses, and lack of health insurance [11-13]. Recent data, however, suggest that youth can be successfully treated at health care sites that have expertise in treating youth [14], whereby 59% of youth achieved sustained viral load suppression over the course of a year. Health care delivery and other interventions tailored to the unique needs of youth and their effects on HIV continuum of care outcomes need to be investigated further [15]. Studies are urgently needed to better understand the factors leading to poor outcomes for youth across the care continuum and to identify strategies that can substantially improve the achievement of essential milestones along the care continuum, ultimately helping infected youth achieve durable viral suppression. Given the adherence challenges that many youth experience, trials are needed to study newer drug schedules and formulations that allow simpler regimens, evaluation of programs to promote antiretroviral treatment adherence in youth, and clinical trials to evaluate therapies that may exploit the immunologic resilience of recently infected youth.

Objectives

Through the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN), the National Institutes of Health (NIH) is supporting HIV interventional research for youth in the United States. The primary mission of the ATN is to conduct both independent and collaborative research that explores promising behavioral, microbicidal, prophylactic, therapeutic, and vaccine modalities in HIV-infected and at-risk youth aged between 12 and 24. ATN activities encompass the full spectrum of research needs for youth, from HIV primary prevention for at-risk youth in the community to secondary and tertiary prevention with clinical management of HIV infection among youth living with HIV experiencing adherence challenges. Primary prevention research addresses motivational readiness for and subsequent uptake of biomedical prevention strategies, including innovative, technology-based interventions tailored for youth at greatest risk for HIV infection or transmission. Secondary and tertiary prevention research investigates novel treatment strategies and regimens, antiretroviral therapy (ART) adherence, risk reduction interventions, and linkage to and long-term engagement in care strategies that can lead to optimal ART initiation and sustained virologic suppression. Innovative strategies to engage youth are especially important in vulnerable populations such as youth, who may encounter more obstacles and challenges when attempting to access care [10,15]. Furthermore, as reflective of the US epidemic, a significant portion of the current ATN portfolio of studies seeks to enroll traditionally difficult-to-reach populations of medically disenfranchised, low socioeconomic status, sexual and gender minority, and/or racial or ethnic minority young men and women.

Methods

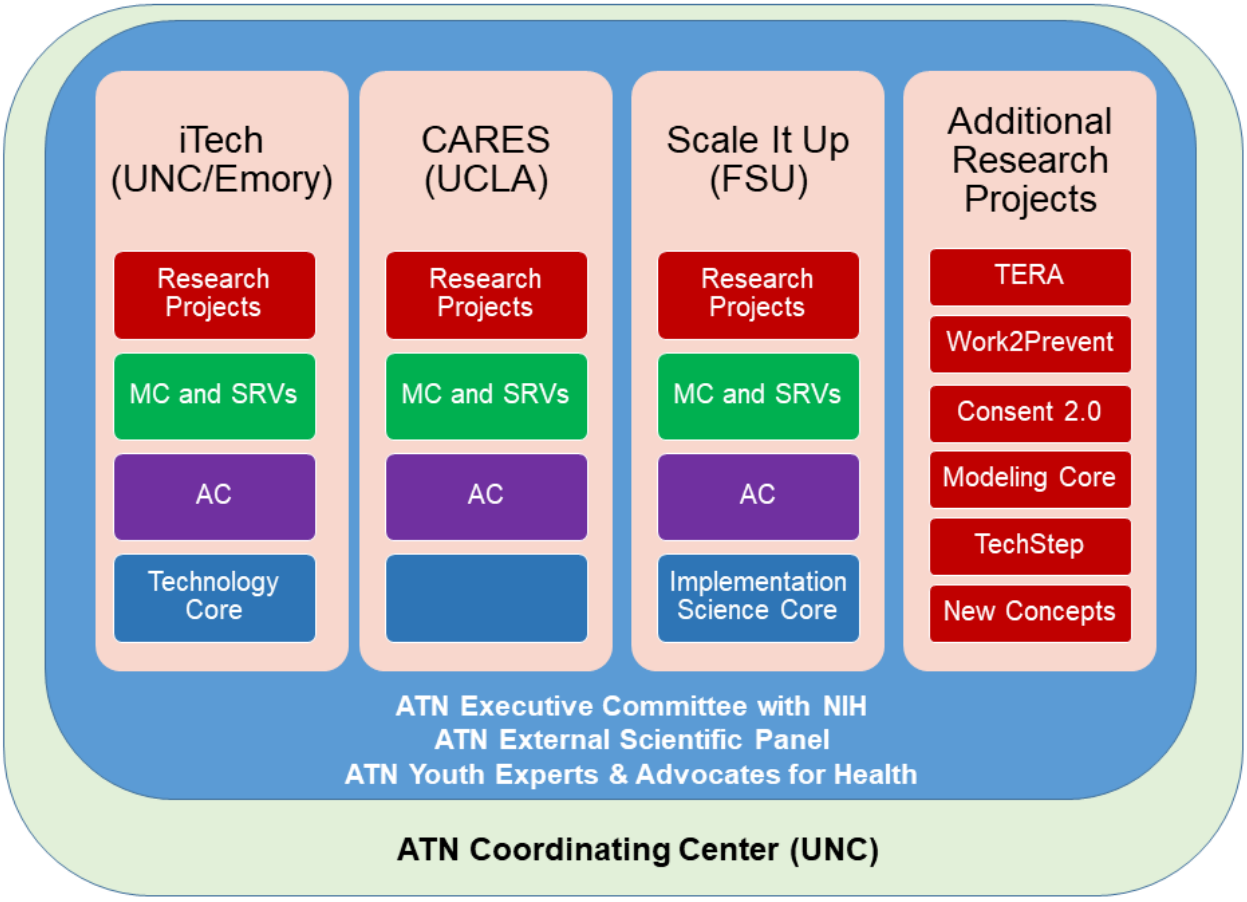
Adolescent Medicine Trials Network for HIV/AIDS Interventions 2001-2013

The ATN is the only domestic, multicenter research network devoted to the health and well-being of HIV-positive and at-risk youth. The NIH initiated the ATN in 2001 after the Adolescent Medicine HIV/AIDS Research Network external scientific advisory panel stated that interventional studies in adolescents were needed. The first, second, and third funding cycles ended in February 2006, 2011, and 2016, respectively; the ATN was re-competed in 2016 and was funded for a fourth, 5-year period. The ATN has demonstrated extensive experience in recruiting and retaining understudied at-risk and HIV-infected youth populations in the United States. During the 10-year period (2003-2013), more than 26,000 youth have been enrolled among 88 ATN studies, with >90% enrollment and retention rates among completed studies. The ATN published descriptive findings of 1712 youth living with HIV/AIDS, recruited from December 2009 to January 2011 from 15 ATN sites to participate in a cross-sectional survey of demographic, psychosocial, and health factors [16]. From 1 of the largest national samples of adolescents and young adults living with HIV, distinct patterns of risk behaviors were identified, pointing to the importance of tailoring clinical and preventive interventions. A more recent longitudinal cohort study at 14 ATN sites across the United States also reported demographic and psychosocial characteristics of 467 youth living with HIV and assessed how the later steps of the HIV continuum of care were achieved over a 1-year period [14]. Among 32 studies with completed analyses, the ATN has published over 214 manuscripts and presented over 156 abstracts at various domestic and international scientific conferences. In addition, the ATN has successfully forged collaborations with other federal agencies and NIH-funded HIV research networks, as evidenced by 12 coendorsed collaborating protocols.

Adolescent Medicine Trials Network for HIV/AIDS Interventions 2016-2021

In 2016, the ATN was newly structured to better align network resources with scientific priorities and further increase collaborations both within the ATN and with other HIV research networks through 3 adolescent-focused HIV/AIDS clinical trial network hubs (Figure 1).

Figure 1. Adolescent Medicine Trials Network for HIV/AIDS Interventions structure. AC: Analytic Core; CARES: Comprehensive Adolescent Research & Engagement Studies; FSU: Florida State University; iTech: University of North Carolina/Emory Center for Innovative Technology; MC: Management Core; NIH: National Institutes of Health; SRVs: Subject Recruitment Venues; TERA: Triggered Escalating Real-time Adherence; UCLA: University of California Los Angeles; UNC: University of North Carolina.



Led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the ATN is cofunded by the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute on Minority Health and Health Disparities, through 3 cooperative multiproject research programs. Each program is coordinated and led by a network hub and has well-defined research themes, with substantial NIH scientific involvement to assist, guide, and coordinate research project activities. The research projects are resourced with a Management Core for the overall management, coordination, and scientific oversight of the program. Projects are also resourced with an Analytic Core to ensure that shared scientific and analytic resources are available alongside the methodologic and analytic expertise necessary to evaluate their scientific progress. An optional resource for each program is a Scientific Core with unique resources and expertise to support the success of the research. The new structure is designed to create transparent mechanisms for network investigative leaders to solicit and support ideas from the research community and allow for external researchers as well as other networks to benefit from the networks' infrastructure and capacity, and support coordinated efforts with community partners.

Results

Adolescent Medicine Trials Network for HIV/AIDS Interventions Multiproject Research Programs

The principal investigators and the programs they lead are summarized in Table 1, with research project titles provided in Table 2. Detailed protocol information regarding each of the ongoing research projects have been published separately [17], with results from the projects expected at the end of the ATN 5-year cycle in 2021. The ATN Comprehensive Adolescent Research & Engagement Studies (CARES) Program will evaluate community-based strategies to leverage gateways and settings where high-risk and youth living with HIV can be engaged in HIV prevention and treatment in 2 HIV epicenters (Los Angeles, CA, and New Orleans, LA). The ATN University of North Carolina/Emory Center for Innovative Technology (iTech) Program aims to lower the burden of HIV infection by developing and evaluating innovative, interdisciplinary research on technology-based interventions across the HIV prevention and care continuum for at-risk or youth living with HIV. The ATN Scale It Up Program specifically focuses on developing, testing, and bringing to practice self-management interventions that positively impact the youth HIV prevention and care cascades. Furthermore, efforts to refine the ATN research agenda

will be augmented by an External Scientific Panel, a group of members with a wide range of expertise, who will review the scientific progress and activities of and provide input to the ATN, with the goal of maintaining the highest level of scientific productivity, quality, and relevance of proposed and ongoing research projects.

Adolescent Medicine Trials Network for HIV/AIDS Interventions Governance

Overall, the integration of efforts across the programs is overseen by an ATN Executive Committee (EC) through leadership, efficient communication, coordination, and scientific collaboration. The ATN EC also facilitates collaborations with other HIV research networks and investigators, maintaining the overall responsibility for developing, implementing, and adapting the clinical research agenda of the ATN to include the following:

1. Primary prevention interventions
   - Biomedical prevention interventions
   - Novel approaches to identifying undiagnosed infection
   - Behavioral and social interventions (eg, multilevel, combination prevention, mental health, substance use studies) to address uptake of HIV prevention strategies
2. HIV continuum of care
   - Interventions and programs, both independent and collaborative, to improve outcomes
   - Community- and structural-level interventions to improve outcomes
   - Strategies to address evolving health care financing challenges
   - Evaluation of long-acting antiretroviral therapy for treatment
   - Risk-reduction interventions
   - Interventions to promote care engagement and adherence to antiretroviral medications
   - Integrated treatment approaches (psychological, medical, and ancillary services studies).

Furthermore, the EC oversees the coordination and scientific collaboration of the ATN's National Community Advisory Board, self-titled Youth Experts and Advocates for Health (ATN-YEAH). The ATN-YEAH comprises 12 youth representatives from the programs' local CABs and provides expertise, consultation, and perspective to ensure that the research agenda and work of the ATN reflects and addresses the current needs and issues of youth. Members also provide feedback on recruitment materials, ATN Network policies, research study protocols and procedures, and potential collaborations. They also serve as liaisons to local ATN-related Community Advisory Boards. Logistically, the members meet via virtual meetings on a quarterly basis and via an annual face-to-face meeting to collaborate on community HIV prevention and care activities, learn from each other's experiences regarding how HIV affects their lives, and provide input on different research project updates. The annual meeting occurs in conjunction with 1 of the biannual ATN meetings where an ATN-YEAH panel session is highlighted to foster open dialogue between the ATN-YEAH members and ATN research investigators regarding HIV research topics and issues. Youth perspectives and input to the ATN research agenda are further augmented by the direct participation of 3 youth representatives on the EC itself, with voting rights.

The vital importance of stimulating the engagement of junior investigators with fresh perspectives, additional bandwidth, and innovative ideas to the success of the ATN's research has spurred the ATN to prioritize the mentorship of junior-level investigators through a mentorship/scholars initiative, also monitored by the EC. This initiative includes a comprehensive, research career development program for scholars who come from communities most affected by HIV/AIDS in the United States and who are underrepresented in the scientific field. The program aims to help scholars acquire the skills and expertise to develop and sustain productive, rewarding youth-focused HIV research careers; successfully compete for independent research grants; and develop collaborative working relationships within the context of the ATN's research efforts.

Table 1. Adolescent Medicine Trials Network for HIV/AIDS Interventions multiproject research programs.

Adolescent Medicine Trials Network for HIV/AIDS Interventions multiproject research program	Principal investigators	Principal investigator's institution	Research theme	Number of research projects
Comprehensive Adolescent Research & Engagement Studies	MJ Rotheram-Borus, PhD	University of California, Los Angeles	Comprehensive, community-based strategies for youth recruitment and engagement	3
iTech	L Hightow-Weidman, MD, MPH, and P Sullivan, PhD, DVM	University of North Carolina, Chapel Hill, and Emory University	Innovative, interdisciplinary, technology-based interventions	10
Scale It Up	S Naar, PhD	Florida State University	Effectiveness-implementation research to enhance youth self-management	4

Table 2. Adolescent Medicine Trials Network for HIV/AIDS Interventions research projects.

ATN[a] protocol number	ATN research program	ATN project title
ATN 138	iTech	YouThrive: Connecting Youth and Young Adults to Optimize ART[b] Adherence Through the Interactive YouTHrive WebApp
ATN 139	iTech	Get Connected: Linking YMSM[c] to Adequate Care through a Multilevel, Tailored WebApp Intervention
ATN 140	iTech	LYNX: A Novel Mobile App to Support Linkage to HIV/STI[d] Testing and PrEP[e] for YMSM
ATN 141	iTech	MyChoices: Mobile-Based Application to Increase Uptake of HIV Testing, Detection of New HIV Infections, and Linkage to Care and Prevention Services by Young Men who have Sex with Men
ATN 142	iTech	P3: Prepared, Protected, emPowered: Promoting PrEP Adherence through a Social Networking, Gamification, and Adherence Support App for Men and Transgender Women Who Have Sex With Men
ATN 143	iTech	Compare: Comparing Efficacy of LYNX (ATN 140) and MyChoices (ATN 141) Mobile Applications for HIV Testing and PrEP Uptake
ATN 144	Scale It Up	SMART: Adaptive Antiretroviral Therapy Adherence Interventions for Youth Living with HIV through Text Messaging and Cell Phone Support Embedded within the Sequential Multiple Assignment Randomized Trial (SMART) Design
ATN 145	Scale It Up	Young Men's Health Project: Comparative Effectiveness Trial of Clinic-Based Delivery of an HIV Risk Reduction Intervention for YMSM
ATN 146	Scale It Up	TMI: Tailored Motivational Interviewing Implementation Intervention Effectiveness Trial in Multidisciplinary Adolescent HIV Care Settings
ATN 147	CARES[f]	Acute, Recent and Established Youth Living with HIV
ATN 148	CARES	Stepped Care for Youth Living with HIV: Optimizing the HIV Treatment Continuum with a Stepped Care Model for Youth Living with HIV
ATN 149	CARES	Cost-efficient Interventions for Youth at Risk for HIV: Engaging Seronegative Youth to Optimize the HIV Prevention Continuum
ATN 150	ATN Coordinating Center	Consent 2.0: Innovative Approaches for Minor Consent to Biomedical HIV Prevention Research
ATN 151	ATN Coordinating Center	Work2Prevent: Employment as HIV prevention for Young Men who have Sex with Men (YMSM) and Young Transgender Women (YTW)
ATN 152	ATN Coordinating Center	TERA: A Triggered, Escalating, Real-Time Adherence Intervention
ATN 155	ATN Coordinating Center	Planning4PrEP: Integrating PrEP into Family Planning Services at Title X Clinics in the Southeast
ATN 156	Scale It Up	WeTest: Enhancing sexual safety: Couples' communication and HIV testing among YMSM
ATN 157	iTech	We Prevent: A Relationships Skills Intervention to Improve HIV Prevention Uptake Among Young Gay, Bisexual and other Men who have Sex with Men and their Primary Partners
ATN 158	iTech	Life Steps for PrEP for Youth (LSPY) An Evidence-based Cognitive Behavioral Adherence Intervention to Enhance PrEP Uptake and Adherence in High Risk YMSM
ATN 159	iTech	ePrEP: A Randomized, Controlled Trial of an Electronic HIV Pre-exposure Prophylaxis Care System Among Young Men who have Sex with Men in Rural and Small Town Areas
ATN 160	iTech	TechStep: Technology - based Stepped Care to Stem Transgender Adolescent Risk Transmission
ATN 161	ATN Coordinating Center	ATN Modeling Core: Investing in the HIV care continuum: Model - based methods to translate ATN findings into policy recommendations

[a]ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions.

[b]ART: antiretroviral therapy.

[c]YMSM: young men who have sex with men.

[d]STI: sexually transmitted infection.

[e]PrEP: pre-exposure prophylaxis.

[f]CARES: Comprehensive Adolescent Research & Engagement Studies.

The ATN also encompasses a coordinating center (CC at the University of North Carolina, Chapel Hill, with PIs L LaVange, PhD, M Carpenter, PhD, and M Hudgens, PhD) to provide overall infrastructure and logistical and organizational support for the ATN and to facilitate emerging studies and collaborative activities across the ATN and with external networks and investigators. Support for these newly emerging activities includes statistical, data management, study management, study quality assurance, and operational services and infrastructure. The CC also administratively manages a suite of high-priority research protocols (see Table 2) addressing issues such as adolescent consent for research, employment for transgender youth, ART adherence, integration of HIV prevention with family planning, and a modeling core that uses innovative, model-based methods to translate findings from ATN studies into policy recommendations.

Discussion

The ATN aims to change the sobering trends among youth affected by HIV in the United States through innovative approaches and a suite of research projects that address many high-priority scientific questions. Overall, the objectives and overarching goals of the ATN are to increase the number of at-risk youth who are aware of their HIV status and bend the infection rate curve downward toward zero, and for those who are diagnosed with HIV, to increase the numbers in each segment of the care continuum to 95%. The ATN with its highly experienced, multidisciplinary investigators has a renewed focus to address the HIV epidemic by addressing both individual and structural issues particularly salient to adolescents. These include stigma, substance use, mental health difficulties, developmental challenges and transitions to adulthood, and availability of and access to youth-friendly health services. Important additional priorities include facilitating mentorship of junior-level investigators as well as including the voices of diverse youth input throughout all activities of the ATN. The ATN remains committed to performing the highest priority research and disseminating findings in a timely and transparent manner with the primary goal of ending the youth HIV epidemic in the United States.

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Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions
CC: coordinating center
CDC: Centers for Disease Control and Prevention
EC: Executive Committee
iTech: University of North Carolina/Emory Center for Innovative Technology
NIH: National Institutes of Health
PrEP: Pre-Exposure Prophylaxis
YEAH: Youth Experts and Advocates for Health
YMSM: young men who have sex with men

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