JMIR Research Protocols

Impact Factor (2023): 1.4
Volume 7 (2018), Issue 8 ISSN 1929-0748 Editor in Chief: Xiaomeng (Simone) Ma, PhDc, MS, BS

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Original Papers

Protocol

The Use of Aspirin to Reduce the Risk of Thrombotic Events in Patients With End-Stage Renal Disease: Protocol for a Randomized Controlled Trial

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Abstract

Background: End-stage renal disease (ESRD) is the last stage of chronic kidney disease, mainly caused by type 2 diabetes mellitus and characterized by an increased mortality risk related to cardiovascular disease. Low-dose aspirin (acetylsalicylic acid or ASA) seems to effectively prevent cardiovascular events in patients with ESRD. However, the number of interventional studies in this population remains limited and the mechanisms of aspirin-related bleeding remain poorly understood. Aspirin's efficacy and safety may be modified by the presence of type 2 diabetes mellitus or platelet hyperreactivity.

Objective: The overall objective of this protocol is to (1) evaluate aspirin's safety and efficacy in reducing the risk of thrombotic events in patients with ESRD on hemodialysis and (2) examine whether aspirin's efficacy is modified by the presence of type 2 diabetes mellitus or platelet hyperreactivity. Specifically, the primary objective is to compare the 12-month rate of any thrombotic event (cardiac death, nonfatal myocardial infarction, nonfatal stroke, arteriovenous fistula thrombosis) and Thrombolysis in Myocardial Infarction (TIMI) major bleeding in patients treated with aspirin compared to those on placebo. Secondary objectives are to test for effect modification of treatment by the presence of type 2 diabetes mellitus or platelet hyperreactivity and compare the rate of TIMI minor bleeding between treatment groups.

Methods: We developed a protocol for a phase 2 randomized, single-center, placebo-controlled, triple-blind, superiority clinical trial to assess the prophylactic efficacy and safety of aspirin in patients with ESRD and on hemodialysis. It follows the ethical

principles of the Declaration of Helsinki of the World Medical Association. A total of 342 participants would be enrolled over 12 months at a large dialysis center. Patients will be randomized in a 1:1 ratio and stratified by presence of type 2 diabetes mellitus and platelet hyperreactivity to receive either oral aspirin (100 mg/d) or placebo for a treatment period of 12 months. An intention-to-treat statistical analysis will be performed.

Results: The randomized clinical trial will be performed after approval by the ethical committee of the participating center and registration at ClinicalTrials.gov.

Conclusions: We provide a protocol for a randomized controlled trial to evaluate the safety and efficacy of treatment with aspirin to reduce the risk of thrombotic events. In addition, such a study would further our understanding of the mechanism of aspirin-related bleeding and help identify subgroups of best-responders and patients with a higher risk of adverse events.

Registered Report Identifier: RR1-10.2196/10516

(JMIR Res Protoc 2018;7(8):e10516) doi:10.2196/10516

KEYWORDS

randomized controlled trial; end stage renal disease; kidney failure, chronic; aspirin; prophylaxis; thrombosis; drug safety; bleeding; platelet activation; diabetes mellitus, type 2

Protocol

Introduction

Background and Rationale

Chronic kidney disease (CKD) is a pathology defined by a decrease in glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2 or by the presence of kidney damage for at least 3 months [1]. It affects 200 million people worldwide, and the main risk factor for this disease is diabetes mellitus [2-4]. The life expectancy of CKD patients decreases with the severity of kidney impairment [5]. The most severe stage is end-stage renal disease (ESRD) and refers to patients undergoing renal replacement therapy (RRT) or for whom the GFR is lower than 15 mL/min/1.73 m^2 [1]. The high risk of mortality observed in patients with ESRD is mainly due to cardiovascular events, the risks of which are 10- to 20-fold higher in these patients compared to non-CKD subjects and are significantly increased by the presence of diabetes mellitus [4,6,7]. In order to prevent cardiovascular events, patients with ESRD receive anticoagulant or antiplatelet therapy [8,9].

The benefits of low doses (75 to 100 mg/d) of aspirin (acetylsalicylic acid or ASA), an antiplatelet agent, as prophylactic drug for some specific types of cardiovascular events (atherosclerotic and ischemic events) in CKD and patients with ESRD have been reported in several studies. For instance, the impact of low-dose aspirin (75 mg/d) versus placebo on the risk of cardiovascular events was reported in an interventional study of 3619 CKD patients with hypertension (eGFR <60 mL/min/1.73 m^2 at enrollment) [10]. The hazard ratio (HR) of cardiovascular events decreased by 15% (HR 0.85, 95% CI 0.61 to 1.17; *P*=.03) in patients with an eGFR of 45 to 59 mL/min/1.73 m^2 and 66% for patients with eGFR <45 mL/min/1.73 m^2 (HR 0.34, 95% CI 0.17 to 0.67; *P*<.05) [10]. Among secondary end points, a 36% reduction in the rate of myocardial infarction (HR 0.64, 95% CI 0.39 to 1.03; *P*=.08) was observed in patients with an eGFR of 45 to 59 mL/min/1.73 m^2, and subjects with eGFR <45 mL/min/1.73 m^2 had a rate reduction of 69% (HR 0.31, 95% CI 0.11 to 0.85; *P*<.05). Stroke, cardiovascular mortality, and total mortality were also reduced by 50% to 80% in patients with eGFR <45 mL/min/1.73 m^2 receiving aspirin compared to placebo [10]. A systematic review of 2572 randomized controlled trials, meta-analyses, and systematic reviews (27 retained) reported that aspirin was associated with a 6% reduction in the relative risk (RR) for all-cause mortality (RR 0.94, 95% CI 0.88 to 1.00), 10% reduction in major cardiovascular events (RR 0.90, 95% CI 0.85 to 0.96), and 15% reduction in total coronary heart disease (RR 0.85, 95% CI 0.69 to 1.06) [11]. Last, a large case-control observational study performed on stroke patients with ESRD undergoing dialysis between 1998 and 2006 and exposed (n=763) or not (n=666) to aspirin (80 to 325 mg/d) showed significantly lower rates of all-cause mortality (HR 0.671, 95% CI 0.580 to 0.777; *P*<.001) and readmission to hospital for ischemic stroke (HR 0.715, 95% CI 0.580 to 0.882; *P*=.002) in the group receiving aspirin versus placebo, without any significant increase of risk of bleeding (*P*=.29) [12].

However, there is a lack of information about the prophylactic efficacy of aspirin for all types of thrombotic events that patients with ESRD may develop. There is also a gap of knowledge concerning the safety profile of aspirin in patients with ESRD. Concerning the risk of aspirin-related bleeding, there is some discrepancy between the results of observational and interventional studies, as an increased risk of bleeding has been reported in some observational studies [13,14]. However, interventional studies of patients with ESRD have found that low doses of aspirin are not associated with an increased risk of major bleeding in dialysis patients, despite an apparent increased risk of minor bleeding (eg, gastrointestinal bleeding) [10,15]. This discrepancy highlights the fact that the mechanism of aspirin-related bleeding events is not yet fully understood. Some authors have suggested that the prophylactic efficacy of aspirin and risk of bleeding related to this drug may be influenced by a phenomenon of platelet hyperreactivity [16]. However, further research is necessary to establish the real impact of platelet hyperreactivity on aspirin's safety profile in patients with ESRD.

Objectives

The primary and secondary objectives of this study are to evaluate aspirin's prophylactic efficacy and safety in patients

with ESRD. This will include (1) the assessment of aspirin prophylactic efficacy for all types of thrombotic events that patients with ESRD may develop, namely nonfatal stroke, nonfatal myocardial infarction, arteriovenous fistula thrombosis, and cardiac mortality, and (2) the assessment of aspirin-related major bleeding events using Thrombolysis in Myocardial Infarction (TIMI) criteria [17-19]. The study's secondary objectives are to test for effect modification of treatment by the presence of type 2 diabetes mellitus or platelet hyperreactivity and compare the rate of TIMI minor bleeding between treatment groups.

Our hypothesis is that aspirin is superior to placebo as prophylactic therapy for thrombotic events in patients with ESRD on hemodialysis without increasing the risk of major bleeding.

Methods

Participants, Interventions, and Outcomes

Study Design

We will perform a phase 2 randomized, single-center, placebo-controlled, triple-blind, superiority clinical trial with 1:1 allocation to receive either 100 mg of aspirin per day or placebo by mouth for 12 months. Randomization will be stratified based on 2 baseline characteristics: (1) the presence versus absence of type 2 diabetes mellitus and (2) the presence versus absence of platelet hyperreactivity. The study will start following approval of the Institutional Review Board (IRB) and will follow the ethical principles of the Declaration of Helsinki of the World Medical Association. The study design is illustrated in Figure 1.

Study Setting

The trial involves patients on chronic intermittent hemodialysis and will be conducted in a large dialysis center (ie, with ≥2000 patients on RRT).

Eligibility Criteria

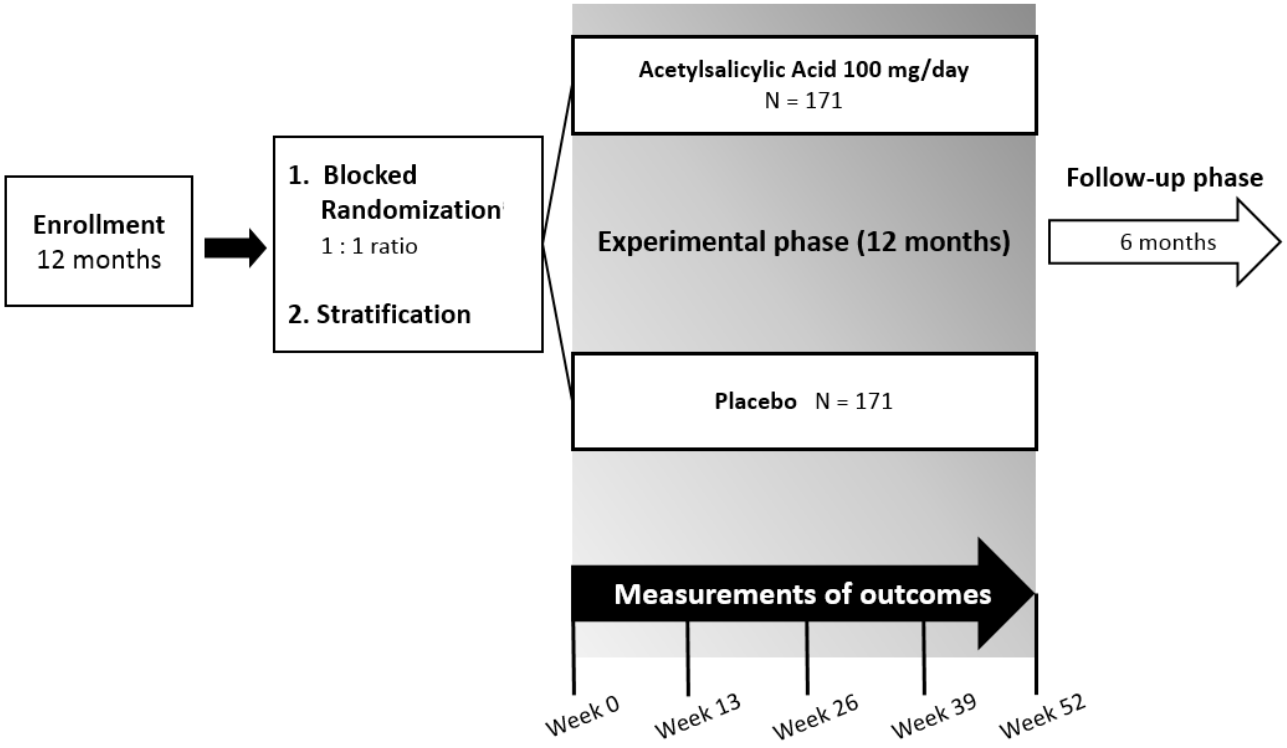
The study population consists of men or women with ESRD who are at least 18 years of age and have started chronic intermittent hemodialysis in the previous 3 months.

Exclusion criteria include any contraindications to ASA, concurrent treatment with anticoagulants or platelet aggregation inhibitors, and pregnancy or lactation. Patients with life-threatening conditions other than renal or vascular disease will also be excluded from the trial: all types of cancer, liver disease, AIDS, or severe lung disease. ESRD due to glomerulopathy has a different pattern of mortality [20], which precludes its inclusion in this trial. Patients on other modalities of RRT will also be excluded.

Interventions

The intervention is an enteric-coated oral pill containing 100 mg of ASA, administered once daily, after lunch, over 12 months. The comparator will be a placebo tablet with the same characteristics as the active pills. Both arms will have the same administration schedule and will start treatment the day after randomization (day 0).

Figure 1. Illustration of the study design. Participants will be randomized in block sizes of 4, 6, and 8. Stratification factors: type 2 diabetes; platelet hyperreactivity.



Adherence

At every hemodialysis session, participants will receive training about the importance of taking the drug as prescribed by viewing a 10-minute educational video about medication compliance on a digital tablet.

Study patients will have monthly visits with the study team to check on treatment adherence and answer any questions. During these visits, patient compliance with treatment will be assessed by direct questioning and by counting returned tablets provided on a monthly basis. Good adherence will be defined as taking at least 80% of the prescribed daily dose and attending 100% of the visits. If a patient withdraws from the trial, the study coordinator will contact the participant to find out the reasons for withdrawal.

Outcomes

The primary outcome is the incidence of a composite event including all of the following: cardiac death, nonfatal myocardial infarction, nonfatal stroke, arteriovenous fistula thrombosis, and TIMI major bleeding [19] by 12 months of treatment. The secondary outcomes are effect modification of treatment efficacy by the presence of type 2 diabetes mellitus or platelet hyperreactivity and the rate of TIMI minor bleeding between treatment groups.

According to the TIMI criteria, major bleeding is defined as the presence of any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo magnetic resonance imaging), fatal bleeding (bleeding that directly results in death within 7 days), or clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in hematocrit [19]. Minor bleeding is defined as clinically overt with a hemoglobin drop of 3 to 5 g/dL [19].

The profile of platelet reactivity will be determined by multiple electrode aggregometry using a Multiplate analyzer (Dynabyte GmBH). This method was chosen because it currently is the most efficient assay used to assess platelet reactivity in humans [21]. The Multiplate will measure platelet activity (defined as aggregation capability after activation with adenosine diphosphate) as the area under the curve reported in area units multiplied by time (AU×min). Platelet hyperreactivity is defined based on the manufacturer's recommendations and published data, with a cutoff of 50 AU×min for adenosine diphosphate–induced aggregation [22].

Outcomes Assessment

A blinded multidisciplinary team composed of a nephrologist, cardiologist, and nurse will follow participants and review medical records and adjudicate outcomes and end points in the study.

A medical appointment will be scheduled for weeks 0, 13, 26, 39, and 52, where the multidisciplinary team will assess the primary and secondary outcomes and report them to the Data Coordinating Center (DCC). At each visit, a venous blood sample (5 mL) will be collected in order to measure hematocrit, hemoglobin, and platelet hyperreactivity.

After the end of the treatment phase of the trial, participants will be followed for an additional 6 months to assess further adverse events. For that purpose, the multidisciplinary team will contact patients monthly during their hemodialysis sessions. The total length of the study will be 30 months.

Study Variables

The outcome variables are the incidence of cardiac death, nonfatal myocardial infarction, nonfatal stroke, and arteriovenous fistula thrombosis, as well as the presence or absence of bleeding and its severity based on TIMI criteria [19]. The treatment variables are the exposure to the intervention (aspirin 100 mg/d or placebo). The stratification variables are the presence versus absence of type 2 diabetes mellitus and the presence versus absence of platelet hyperreactivity.

Participant Timeline

The schedule and procedures during patient visits to the participating center (recruitment, hemodialysis sessions, and monthly assessment of outcomes) are summarized in Table 1.

Sample Size

Sample size was calculated based on estimates for the rate of events in the primary composite outcome over 1 year: TIMI major bleeding (placebo 1% vs aspirin 2.5% [15]), cardiovascular events (placebo 3.0% vs aspirin 2.5% [10]), and fistula thrombosis (placebo 19% vs aspirin 8% [23]), for a total 1-year event rate of 23% in the placebo group and 13% in the aspirin group. A sample size of 318 patients (159 per arm) provides 80% power to detect a difference between groups of this magnitude (corresponding to an HR of 0.53) using a 2-sided log-rank test and alpha=.05 (Power Analysis and Sample Size Software version 14, NCSS LLC). The sample size for the trial was increased to 342 patients (171 per arm) to account for estimated attrition of 10%.

Recruitment

The estimated hemodialysis admission rate at a large dialysis center is 50 patients per month. Therefore, we expect to include 8 to 10 patients every week, completing our recruitment goal in 9 months. We propose a recruitment period of 12 months in case enrollment is slower than expected.

Eligible patients will be identified using medical records, clinician invitation letters, and internal flyers posted in patient areas. The study team will approach eligible patients to invite them to participate in the trial. All aspects of the study will be explained and all participants who agree to participate must provide written informed consent. One venous blood sample will be collected prior to randomization in order to assess platelet reactivity profile, a stratification factor for randomization.

Table 1. Schedule and procedures during patient visits to the participating center.

Procedure	Enrollment phase (12 months)	Experimental phase (12 months)				Follow-up (6 months)
	Preliminary visit (369 to 3 days before the experimental phase)	First medical visit (day 0)	Hemodialysis sessions (approximately every 3 days)	Every 30 days	Weeks 13, 26, 39 and 52	Hemodialysis sessions (every 30 days)
Informed consent form	X[a]					
Physical exam/medical history and medication review	X					
Inclusion/Exclusion	X					
Collection of a blood sample[b]		X			X	
Randomization		X				
Patients' meeting with the study team and oral training about compliance to treatment		X		X		
Provision of the necessary number of pills (on a monthly basis)		X		X		
Patients' training focused on compliance (short educative video)			X			
Counting of returned pills				X		
Blinding assessment (questionnaire)				X		
Measurement of primary and secondary outcomes[c] during consultations with a nephrologist and a cardiologist		X			X	
Assessment of later bleeding adverse events						X

[a]X indicates the time at which each procedure will occur.

[b]Assessment of the hematocrit, hemoglobin concentration, and platelet hyperreactivity profile.

[c]Number of events for cardiac death, nonfatal myocardial infarction, nonfatal stroke, arteriovenous fistula thrombosis, and assessment of major and minor bleeding using the Thrombolysis in Myocardial Infarction scale.

Assignment of Interventions

Sequence Generation

Patients will be allocated to 1 of the 2 study groups based on a computed-generated blocked randomization, with stratification by 2 factors (type 2 diabetes mellitus and platelet hyperreactivity). For that purpose, randomly permuted blocks of sizes 4, 6, and 8 will be used in order to maintain the integrity of the randomization and blinding [24]. The software used to generate the sequence is available at randomization.com, and the study pharmacists will coordinate the randomization, treatment assignment, and delivery of study medication [25].

The research pharmacists will determine the study allocation and randomization and will be the only individuals to know the identity of the drugs delivered.

Blinding

The trial is triple-blinded to the treatment allocation: participants, study clinicians, and staff, as well as data analysts, will not know participant treatment assignments. Blinding will be assured by the use of a placebo comparator, which will be identical in look and taste to the active drug and will last until the data are analyzed.

A questionnaire will be used to assess the effectiveness of the participant's blinding. This will be performed according to the methodology proposed by Rees and collaborators [26]. Every 2 weeks, participants will be asked to complete a survey about the intervention they think have received (active intervention, placebo, or unknown) and their level of certainty on a Likert scale. The accuracy of their answers will be evaluated using the Howard index, and differences in beliefs between 2 successive questionnaires will be assessed using the Fisher exact test.

Participants' beliefs about their treatment assignment are considered consistent if all responses are sequentially identical over time, except one change of opinion that may be explained by a lack of blinding [26].

Emergency Unblinding

In exceptional circumstances, unblinding may happen if knowledge of the actual treatment is essential for further management of the patient. In case of severe adverse events, investigators will discuss unblinding within 24 hours with a medical advisor from the Data and Safety Monitoring Board who is not involved with the trial. Unblinding will take place by the research pharmacy immediately after the decision is made.

Data Collection, Management Analysis, and Monitoring

Data Collection

We intend to minimize missing data by having monthly visits with patients. An adherence check will be done by counting returned tablets as previously stated.

Regarding data collection and storage, the study team will be trained to oversee all key aspects of the protocol: (1) methodology, forms, and tools that must be used for the collection, entry, monitoring, and editing of data; (2) appropriated methods to communicate among investigators and between investigators and participants; and (3) importance of reporting data as close to real time as possible during the course of the study.

Data Management

For quality control, patient records (source documents) will be stored at the site, and the original data will be shared with the DCC. It is the responsibility of the investigator to keep, maintain, and provide the documents audited by IRB, sponsor, National Institutes of Health, US Food and Drug Administration, or other local regulatory agencies when necessary.

After the collection of study data, patient identification will be encoded, and only the investigator will have access to this information, in accordance with the Good Clinical Practices and the Declaration of Helsinki regarding confidentiality [27].

The collected data will be entered electronically in a Research Electronic Data Capture management system. This database is a cloud-based system, and it will have a backup in a hard disk in the DCC. The dataset will be encrypted in order to guarantee data safety and confidentiality.

Statistical Methods

Statistical analysis will be performed including all randomized patients according to their assigned treatment group (ie, intention-to-treat). The software used will be Stata 14 (StataCorp LLC). All testing will be 2-sided with statistical significance defined as $P<.05$. The primary composite outcome (first time-to-event of thrombotic events and TIMI major bleeding) will be analyzed with Kaplan-Meier curves and a log-rank test to detect difference between the groups. Cox proportional hazards regression may be used to adjust for relevant covariates, if appropriate (eg, for any unbalanced baseline characteristics that may occur by chance). Similarly, secondary outcomes will be analyzed with Kaplan-Meier curves and log-rank tests for all events. For the secondary objectives, interaction terms will be included in the Cox models above to test for interaction between treatment status and (1) the presence of type 2 diabetes and (2) platelet hyperreactivity. The proportion of patients with TIMI minor bleeding in each group will be compared with a chi-square test. If necessary, multiple imputation will be used for missing data.

Data Monitoring

A Data and Safety Monitoring Board consisting of an independent nephrologist and cardiologist (adverse events may happen mainly in those fields) and statistician is planned to oversee the trial. Based on federal regulations, an ethicist may be included. According to our inclusion and exclusion criteria, no vulnerable population is targeted.

Ethics and Dissemination

Institutional Review Board Submission

Prior to recruitment of study subjects, the full study protocol will be submitted to the local research ethics committee and IRB for evaluation and approval.

Registration

The trial will be registered at ClinicalTrials.gov.

Results

This is a protocol for a randomized clinical trial. It must be submitted to an ethical committee and registered at ClinicalTrials.gov before we can specify dates of data collection or the beginning of the study. These practical aspects also depend on the decisions of the center where the trial would be performed.

Discussion

Summary

Finding a safe preventive measure for thrombotic events for patients with ESRD on hemodialysis is of utmost importance, as it would reduce the number of fistula thrombosis and cardiovascular events and have a direct impact on morbidity and mortality rates. This clinical trial will provide data on the safety of antiplatelet blockade with aspirin, which is a possible preventive measure for thrombosis, and assess the impact of the intervention in hemodialysis patients. In addition, it will yield essential information to foster further interventional trials and may help revise international guidelines for the prevention of thrombotic disease in patients with ESRD on hemodialysis.

Strengths and Limitations

The main strength of the trial is its study design, which includes allocation concealment, randomization, and triple-blinding in order to reduce possible bias. In addition, stratification will balance 2 variables that are strongly associated with the outcome, type 2 diabetes mellitus and platelet hyperreactivity, and will allow us to explore whether patients with these

characteristics differentially respond to aspirin therapy. Overall, the study protocol is feasible for both investigators and patients, as study enrollment and subsequent visits will take place during or following the patients' standard hemodialysis sessions.

Potential limitations of the study protocol include the difficulty in interpreting a composite outcome. The use of a composite primary outcome is supported by the fact that major bleeding rates are very rare, requiring a large sample size and lengthy study duration that would render the trial unfeasible. We address this issue by adding efficacy outcomes related to thrombosis to major bleeding outcomes. In order to clarify interpretation of the primary composite outcome, they are individualized in the secondary analysis. Regarding the study population, peritoneal dialysis patients will not be included as most do not have arteriovenous fistula and, hence, are not at risk for fistula thrombosis. Furthermore, glomerular disease patients who developed ESRD will not be included, as they show a different pattern of morbidity and mortality [20]. Another limitation is the possibility that we do not meet the planned recruitment time, as it will affect study power and validity. For that matter, we allow 12 more weeks for recruitment than initially planned. Last, despite the simplicity of drug administration, adherence is always a potential problem, which will be dealt with by identification of nonadherent patients and systematic training.

Conclusion

The study protocol will provide essential evidence to foster further clinical research on preventive measures of thrombotic events in hemodialysis patients. Future research is needed to provide information about the impact of preventive antiplatelet blockage on mortality and thrombotic events in these patients. Moreover, the study of potential biomarkers to identify patients who would benefit the most from the intervention is also required and may have a direct effect on drug prescription and control of adverse events. Therefore, identifying the potential safety and effectiveness of aspirin will improve morbidity and mortality, lowering the burden of such a severe disease for these patients and giving them a chance for a better and longer life.

Acknowledgments

We would like to thank our colleagues who contributed to the early development of this project: Juan Carlos Aldana, Rafael Barreto Silva, Daniella Caputo Dorta, Marcelo Costa, Caio de Assis Moura Tavares, Luís Gustavo de Mil-Homens e Vinagre, Maria Analayi Estudillo, Dayani Galato, Dolores Gonzales Fabra, Eman Hassan Satti Elsayed, Lorna Marisalva Galleguilos, Bruno Silva, Carina Vorisek, Yiling Yang, and Chen Xhi Zian.

We would also like to thank Professor Felipe Fregni (Harvard TH Chan School of Public Health and Harvard Medical School [Laboratory of Neuromodulation and Center for Clinical Research Learning, Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital]) and Professor Ben Min-Woo Illigens (Beth Israel Deaconess Medical Center and Harvard Medical School), Karla Mëtte Waldrich Tauil, Ana Rita Simoes Martins, and Christian Acosta Villegas for their support and valuable suggestions on the study design. This project received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. NMV is a scientific collaborator from the Belgian Scientific Institute of Public Health and is supported by the Belgian National Institute for Health and Disability Insurance (grant W4043.0100.8).

Authors' Contributions

AFG, CKPF, JLB, NMV, and TLC wrote the manuscript. AFG, CKPF, DAS, EEB, JLB, NMV, PGM, RW, TLC, and WEO developed the study protocol. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ASA: acetylsalicylic acid

CKD: chronic kidney disease
DCC: Data Coordinating Center
ESRD: end-stage renal disease
GFR: glomerular filtration rate
HR: hazard ratio
IRB: Institutional Review Board
RR: relative risk
RRT: renal replacement therapy
TIMI: Thrombolysis In Myocardial Infarction

Edited by G Eysenbach; submitted 28.03.18; peer-reviewed by M Nomali; comments to author 11.05.18; revised version received 25.05.18; accepted 28.05.18; published 09.08.18.

Please cite as:
Lemos Cerqueira T, Fartolino Guerrero A, Pérez Fermin CK, Wang R, Balbino EE, Breeze JL, Gonzalez Mego P, Argentina Silva D, Omer WE, Vandevelde NM
The Use of Aspirin to Reduce the Risk of Thrombotic Events in Patients With End-Stage Renal Disease: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2018;7(8):e10516
URL: http://www.researchprotocols.org/2018/8/e10516/
doi:10.2196/10516
PMID:30093367

Protocol

A Liftless Intervention to Prevent Preterm Birth and Low Birthweight Among Pregnant Ghanaian Women: Protocol of a Stepped-Wedge Cluster Randomized Controlled Trial

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Abstract

Background: Preterm birth (PTB) is a leading cause of infant morbidity and mortality worldwide. Every year, 20 million babies are born with low birthweight (LBW), about 96% of which occur in low-income countries. Despite the associated dangers, in about 40%-50% of PTB and LBW cases, the causes remain unexplained. Existing evidence is inconclusive as to whether occupational physical activities such as heavy lifting are implicated. African women bear the transport burden of accessing basic needs for their families. Ghana's PTB rate is 14.5%, whereas the global average is 9.6%. The proposed liftless intervention aims to decrease lifting exposure during pregnancy among Ghanaian women. We hypothesize that a reduction in heavy lifting among pregnant women in Ghana will increase gestational age and birthweight.

Objective: To investigate the effects of the liftless intervention on the incidence of PTB and LBW among pregnant Ghanaian women.

Methods: A cohort stepped-wedge cluster randomized controlled trial in 10 antenatal clinics will be carried out in Ghana. A total of 1000 pregnant participants will be recruited for a 60-week period. To be eligible, the participant should have a singleton pregnancy between 12 and 16 weeks gestation, be attending any of the 10 antenatal clinics, and be exposed to heavy lifting. All participants will receive standard antenatal care within the control phase; by random allocation, two clusters will transit into the intervention phase. The midwife-led 3-component liftless intervention consists of health education, a take-home reminder card mimicking the colors of a traffic light, and a shopping voucher. The primary outcome are gestational ages of <28, 28-32, and 33-37 weeks. The secondary outcomes are LBW (preterm LBW, term but LBW, and postterm), compliance, prevalence of low back and pelvic pain, and premature uterine contractions. Study midwives and participants will not be blinded to the treatment allocation.

Results: Permission to conduct the study at all 10 antenatal clinics has been granted by the Ghana Health Service. Application for funding to begin the trial is ongoing. Findings from the main trial are expected to be published by the end of 2019.

Conclusions: To the best of our knowledge, there has been no randomized trial of this nature in Ghana. Minimizing heavy lifting among pregnant African women can reduce the soaring rates of PTB and LBW. The findings will increase the knowledge of the prevention of PTB and LBW worldwide.

Trial Registration: Pan African Clinical Trial Register (PACTR201602001301205); http://apps.who.int/trialsearch/Trial2.aspx?TrialID=PACTR201602001301205 (Archived by WebCite at http://www.webcitation.org/71TCYkHzu)

Registered Report Identifier: RR1-10.2196/10095

(JMIR Res Protoc 2018;7(8):e10095) doi:10.2196/10095

KEYWORDS

heavy lifting; Ghana; low birthweight; liftless intervention; low-and middle-income countries; physical activity; preterm birth; randomized controlled trial; stepped-wedge

Introduction

Preterm birth (PTB) and low birthweight (LBW) are increasing worldwide, especially within low-and middle-income countries (LMIC). Every year, 15 million babies are born before 37 completed weeks [1,2] and 20 million (15.5%) babies are born with LBW (2500 g) worldwide. Approximately 96% of these births occur in LMIC [1]. It is estimated that LBW infants are at a 20-fold greater risk of neonatal mortality than babies with a birthweight of 3.5-4.0 kg. Approximately 28% of neonatal deaths (first 7 days of life) are a result of PTB [3]. PTB is a major contributing factor to LBW [1]. Millions of preterm and LBW babies die as a result of preventable complications, and some of those who survive will live with lifelong debilitating health conditions [1,4,5]. PTB is a problem even in high-income countries (HIC). The rate of PTB in the United States increased from 9.5% in 1981 to 12.7% in 2005 [6]. The rate of PTB averages 9.6% worldwide and varies between Europe (6.2%) and North America (10.6%) [6]. In LMIC, the incidence of LBW is around 19%, compared with 5%-7% in HIC [7]. Southern Asia and sub-Saharan Africa have recorded 60% of global PTBs in 2010; Ghana was ranked 14th of 184 countries, with a PTB rate of 14.5% in 2010 [2].

There is widespread agreement on the need for immediate action to prevent PTB and LBW. However, this cannot be completed without a critical look at the occupational environment of the ever-increasing global female workforce [8]. A greater number of women in LMIC work in the informal sector [9], and their work entails repetitive lifting and carrying [10] with virtually no ergonomic guidelines to safeguard their welfare. Evidence suggests that most African women perform an average of 328 trunk flexions at angles exceeding 60º in an 8-hour period each day. Of these trunk flexions, 66 are sustained for >4 seconds [11]. In household settings, African women bear most of the transport burden of accessing basic needs such as water, farm produce, and firewood. The average African woman carries a load of about 20 kg over a distance between 2.5 and 6.8 km on a daily basis [11]. The physical stress encountered by these women can result in musculoskeletal disorders and negative reproductive consequences [12-14]. The activities of ordinary Ghanaian women in rural and periurban areas include farming, carrying water and farm produce on their heads, carrying market wares during street hawking, and carrying their younger children on their backs (at home, to the market, and to the farm).

Some observational studies have implicated occupational lifting or heavy physical workload during pregnancy in the causal pathways of PTB and LBW [1,12,15-17], although others did not reach clear conclusions [18]. However, exposure may have been poorly measured, thereby distorting the outcome of such studies. The Occupational Health Clinic for Ontario Workers reported that a 4.5 kg weight carried further away from the back during pregnancy exerts 68 kg of stress on the lower back, compared with 29.5 kg of stress in a nonpregnant woman [19]. A rise in intra-abdominal pressure resulting from lifting can initiate premature uterine contractions [10], and lifting increases the risk of pelvic pain during gestation [20].

There have been many successful health education and advice-oriented interventions that have improved patient outcomes [21]. In their quest to lengthen gestational age, midwives in LMIC such as Ghana advise pregnant women against strenuous physical activity. In certain conditions, the pregnant woman is admitted to a hospital throughout the gestational period to ensure complete bed rest to avert possible PTB [22]. Several occupational guidelines have been formulated by various institutions [19,23] aimed at protecting pregnant employees against physical stress in their respective countries. More recent are the provisional clinical guidelines for occupational lifting in pregnancy by MacDonald et al [24]. However, no such guidelines exist in Ghana and other LMIC. A recent systematic review revealed that no trial has investigated the usefulness of such guidelines aimed at reducing heavy lifting among pregnant women to increase gestational age [22]. The 3-component liftless intervention implemented in this trial is based on the clinical guidelines of occupational lifting in pregnancy by MacDonald et al [24] coupled with a shopping voucher. The rationale for the shopping voucher is to augment the uptake of the intervention components [25,26]. The shopping voucher will be administered during the third trimester with the intention of reducing moderate PTB, which is common in sub-Saharan Africa [2]. As no randomized controlled trial (RCT) has been conducted to ascertain the effectiveness of the proposed liftless intervention, the outcomes will be of public health importance for elucidating the effects of heavy lifting on birth outcomes (PTB and LBW). Through this study, a model for intervention to reduce physical exertion during pregnancy will be developed and its impact on reducing PTB and LBW will be ascertained. The success of the proposed stepped-wedge trial will justify the need for clinical guidelines to modify the occupational and family environment of pregnant women in LMIC. We hypothesize that a reduction in heavy lifting among pregnant women in Ghana will increase gestational age and birthweight.

The objective of this study is to investigate the effects of the liftless intervention on the incidence of PTB and LBW among pregnant Ghanaian women. This study aims (1) to provide guideline-oriented and social support (liftless intervention) to

Ghanaian women to reduce their lifting behavior during pregnancy; (2) to evaluate the effect of the liftless intervention on rates of PTB, LBW, mode of delivery, lower back or pelvic pain, and premature uterine contractions compared to no such intervention; and (3) to examine compliance with the intervention and ascertain factors that influence it.

Methods

Study Design

We propose an open cohort stepped-wedge cluster RCT (PACTR201602001301205). In this design, eligible participants will be recruited until the expected numbers have been achieved. The design is a unidirectional cross-over study wherein all participating antenatal clinics will start with a control phase and eventually end up providing the intervention. The intervention will not be withdrawn once implementation has begun (at least not until the end of the trial). Participants will leave the trial when they deliver. Baseline measurements and information will be collected in all 10 clusters at the beginning of the trial using a 55-item data collection tool. Using random allocation, two clusters will transition into the intervention with each phase lasting 10 weeks. With the exception of clusters 1 and 2 (Figure 1) [27], the rest of the clusters will contribute data to the control more than once. Clusters 9 and 10 will contribute control data at 5 time points before the intervention is implemented. Thus, unlike a traditional cluster RCT where the intervention is administered only to those in the treatment group, every cluster in the stepped-wedge RCT will receive the intervention. The flow of the trial is shown in Figure 2 [28].

During the control phases, participants will receive routine antenatal care including physical and abdominal examination, blood pressure and weight measurement, urine testing, prescription of iron and folic acid supplementation, and tetanus injection. When a clinic enters the intervention phase, in addition to receiving routine antenatal care, participants will attend 5 extra intervention sessions at weekly intervals. During the sessions, study midwives will deliver the 3-component liftless intervention explaining and demonstrating all of the potential harmful task conditions, providing a take-home reminder card, and soliciting for a partner's support. In addition, midwives will make phone calls, do home visits, and provide the shopping vouchers.

The choice of the stepped-wedge design for this trial is based on the anticipation that the intervention will be useful. This design allows the intervention to be offered to all clusters, reduces potential contamination of the control group [29], and provides an opportunity to gradually roll out the intervention to resolve any financial or logistical constraints that may arise at the clinics concurrently. To ensure completeness of the protocol, the Standard Protocol Item: Recommendations for International Trials 2013 recommendation was followed [28].

Study Population and Recruitment

The trial will be conducted at 10 public antenatal clinics in Ghana (the lists of clinics are provided in Multimedia Appendix 1). Eligible clinics will be those that offer antenatal services. The selected clinics are located in 4 cities in Ghana. The clinics will recruit 1000 participants within a period of 60 weeks. Although the facilities vary in size, they are located in areas that have sufficient numbers of pregnant women to make the trial feasible. The socially ascribed activities of most women within the catchment areas of the proposed antenatal clinics include carrying water and farm produce on their heads as well as carrying market wares as street vendors. Most women also carry their younger children on their backs at home, to the market, and to the farm. Additional antenatal clinics will be added to meet the planned target if necessary. The study midwives will recruit participants based on the prespecified participant-level criteria (Textboxes 1 and 2). The nature of the trial and the required commitment on the part of participants will be explained to the participants by the research midwives in a language that they understand. Participation is voluntary and decisions will not affect the routine antenatal care they will receive. Those who agree to participate and are eligible will be provided with a consent form to sign or thumb print (the copy of consent form is available on request from the authors).

Outcomes

Primary outcome

The primary outcome is gestational age based on ultrasound examination in the first trimester (before 16 weeks), or when not available, fundal height and last menstrual period. We expect that only about 10% of the pregnancies will be without ultrasound diagnosis. We will still include these to prevent increasing the workload of the recruiting midwives. We will conduct a sensitivity analysis to see if there is an effect of the ultrasound versus last menstrual period and fundal height diagnosis. We will categorize PTB as extremely preterm (<28 weeks), very preterm (28-32 weeks), or moderate to late preterm (33-37 weeks) based on the World Health Organization classification [30].

Secondary outcomes

The secondary outcomes are as follows:

- Birthweight categorized as preterm LBW, full term but LBW, or postterm LBW babies [7].
- Compliance with the intervention (classified as compliant or noncompliant). We will classify a participant as compliant (1) if the weight and frequency of lifting have decreased to below the provisional guidelines and (2) if lifting below or above the knee or shoulders has decreased, based on the participant's self-reported lifting and observations during home and workplace visits.
- Prevalence of lower back pain or pelvic pain: yes or no; frequency: sometimes or most of the time; stage of pregnancy: first or second or third trimester; severity: mild or moderate (interferes with daily function or severe and needs analgesics to subside).
- Premature uterine contractions: yes or no; frequency: sometimes or most of the time; stage of pregnancy: first or second or third trimester.
- Mode of delivery: normal or forceps or cesarean section, as recorded on birth and postnatal records.

Figure 1. Stepped-wedge design. Shaded boxes: intervention phases; white boxes: control phases. (Adopted from a trial protocol by Hill AM, Waldron N, Etherton-Beer C, et al 2014).

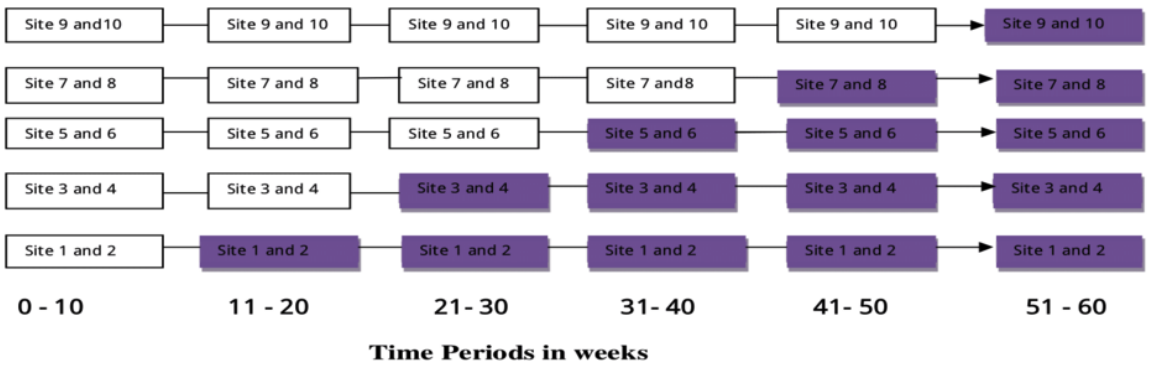
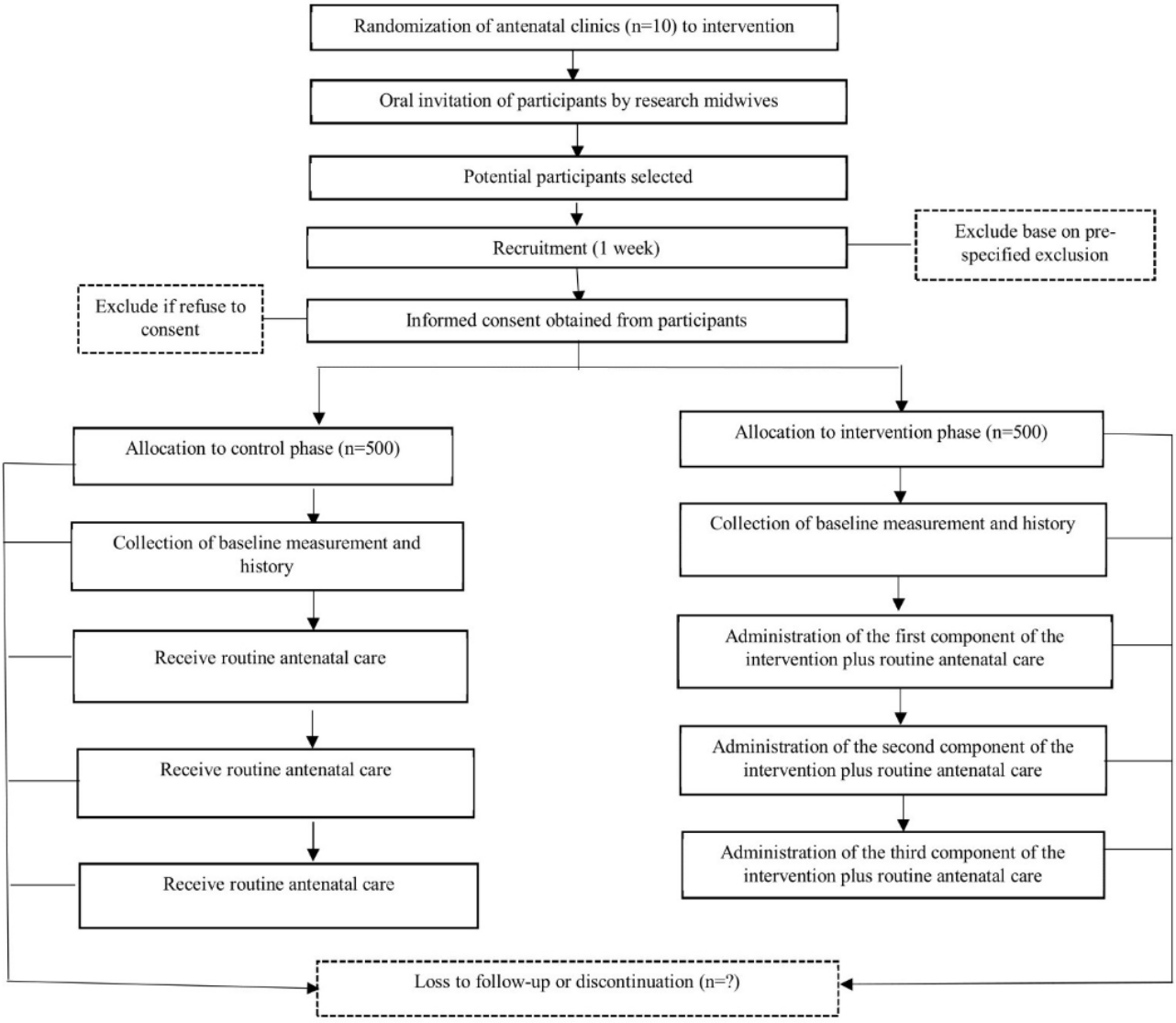


Figure 2. Flow of the trial (adopted from Standard Protocol Item: Recommendations for International Trials 2013).



Textbox 1. Inclusion criteria.

Inclusion criteria
1. Pregnancy has been clinically confirmed.
2. Pregnancy is between 12 and 16 weeks.
3. Pregnancy is singleton.
4. Exposed to lifting of 10 kg at home or work.
5. Attending 1 of 10 antenatal clinics.
6. Participant has consented to participate in the trial.

Textbox 2. Exclusion criteria.

Exclusion criteria
1. Pregnancy has not been confirmed.
2. Gestational age is above 16 weeks.
3. Multiple pregnancies.
4. Not exposed to lifting.
5. Not attending any of the selected clinics.
6. Refusal to participate.

Randomization and Blinding

Using a computer-generated number sequence, the 10 antenatal clinics will be randomized as to when the intervention is implemented. To ensure internal validity of the study, the randomization will be carried out by a professional who is not involved in the delivery of the treatment or its assessment [31]. This will be done before the trial begins. However, due to the nature of the project, neither the research midwives nor participants can be blinded to the treatment allocation. However, a data analyst who will perform the final analysis will be blinded to the treatment allocation.

Intervention

To encourage behavioral changes in heavy lifting tendencies among pregnant women, the study midwives will deliver the proposed 3-component liftless intervention with the assumption that increasing knowledge will promote behavioral changes even in the face of obstacles [32].

Component 1: Health Education

In this component, midwives will deliver health education based on the clinical guidelines for occupational lifting in pregnancy by MacDonald et al [24]. Topics will include possible implications of heavy lifting during pregnancy, avoiding lifting any object that weighs >10 kg, avoiding lifting items over shoulder height, dividing bigger objects into smaller portions before lifting, avoiding one-handed lifting, and avoiding lifting or lowering objects below the knee. Three boosters of this component will be given, and in addition, participants will be asked to invite their spouses or significant others to attend the next session. The aim is to solicit their support throughout gestation to boost compliance with the intervention. The duration for each session will be between 60 and 90 minutes.

At the end of the session, participants will be given a lifting or carrying diary to record their daily lifting exposure. Those who cannot read or write will be provided with an alternative means, such as making ticks on a paper or asking a relative to record the information, depending on the preferred option of the participant. The diary will be checked and the contents recorded at every session. The booklet will also contain the contact information of the midwives for participants to call whenever necessary.

Component 2: Take-home Reminder Card

This component consists of simplified explanations on a reminder card mimicking the colors of a traffic light, Red (SEEK), Yellow (STOP), Green (HOW), based on a similar trial carried out by Lumley and Donohue [33] in Melbourne. This component will be delivered at the second session and will last between 30 and 60 minutes.

SEEK (Red)

- A midwife's assistance when you have questions or problems.
- A midwife's assistance when you have severe lower abdominal pain, lower back pain, severe contractions, or vaginal bleeding or leaking of clear fluid (a more detailed explanation in a local language will be given).

STOP (Yellow)

- Lifting heavy loads that weigh >10 kg, either at home or at work.
- Lifting more than once per 5 minutes after pregnancy has been confirmed until term.
- Lifting or lowering objects below the knee.
- Lifting items over shoulder height.

HOW (Green)

- Divide objects into smaller portions before lifting.

- Attend the antenatal clinic and intervention sessions as scheduled.
- Seek help from close relatives when there is the need to lift an object weighing >10 kg.
- If possible, attend intervention sessions with a significant other.

Component 3: Shopping Voucher

The main focus of the third component will be the third trimester, as moderate preterm births (32 to <37 weeks) accounted for 84% of PTB in 2010, especially in sub-Saharan Africa [2]. This component is aimed to augment the uptake of the other components, as evidence has shown that voucher programs improve the efficiency and health of populations [25,26]. Participants will receive a shopping voucher equivalent to 40 GH (about US $13 or 10€) at 6 different occasions beginning at the third session. The administration of the 6 shopping vouchers will span a period of 6 weeks from 32 to 37 weeks of gestation. The administration of the shopping voucher will begin with prearrangement of shops that sell items such as charcoal, water, and liquefied petroleum gas. Therefore, depending on the particular needs of each participant, they will receive a voucher to access the item from the preselected outlets, and the items will be delivered to participants at home.

Boosters of the first and second components will be delivered during the third and fourth sessions and will last between 30 and 60 minutes.

Follow-up Telephone Call

As part of the intervention, research midwives will make telephone contact with participants after each intervention session to ascertain what measures they are taking to ensure compliance. Participants will be reminded to attend a session with their spouses or any significant family member days before a session.

Home Visits

Research midwives will make 2 home visits (at the beginning and end of the study) with participants' consent. The purpose is for midwives to objectively observe participants in their home environment to ascertain compliance and echo the content of the 3 components using a standardized observational checklist. The visits will also afford participants and their significant others an opportunity to seek clarification on any matters that they do not understand.

Data Collection Tools and Data Management

First, a 55-item questionnaire will be used to collect sociodemographic data, baseline information on gestational age, family support, history of work activities, exposure to heavy lifting or carrying, lifting below the knee or above the shoulders, frequent bending, daily hours of standing, and repetitive movement. Second, the lifting and carrying diary will be used to assess participants' self-reported daily frequency and weight of lifting and carrying and compliance. Third, participants' antenatal and postnatal cards will be used to assess gestational age, birthweight, mode of delivery, and history of premature uterine contractions. The cards are usually filled out by midwives who provide antenatal care and deliver the child. Finally, the intervention session booklet will be used to record session attendance, participants' complaints, and summary of education given. Any text data generated during home visits and telephone calls to or from the participants will also be recorded.

Data and materials obtained during the trial will be transferred and stored electronically, with a back-up on two memory sticks under the supervision of the primary researcher. The digital data will be disposed after dissemination and publication of the results.

Statistical Analysis and Sample Size

We will compare the average proportion of all outcomes in the intervention group clusters to the control group clusters. We will test our hypothesis using a logistic regression model with a random effect for cluster and a fixed effect for each step of implementation of the intervention to adjust for possible effects of calendar time [34,35].

If there are major baseline differences between the intervention and control clusters for potential confounders, such as prolonged standing or squatting, parity, maternal age, infection, occupation, educational level, marital status, and nutritional status, we will include these as covariates in the model. Intention to treat will be the basis for the statistical analysis to ensure that all clusters (with participants) are randomized and included in the final analysis regardless of completion of the study or not [36].

For the sample size calculation, we set alpha at 0.1 and beta at 0.8. We assumed that the intervention will decrease PTB rate by 30% (ie, from 14.5% to 10.5%, with 14.5% being the current official PTB rate in Ghana). With 10 antenatal clinics, we estimated that we need 1000 participants to provide the power to detect a 30% difference in the rate of PTB between the control and intervention clusters. The individual performing the analysis will be blinded to the treatment allocation.

Planning and Training

Prior to the start of the trial, the administrative heads of the selected antenatal clinics and midwives will be consulted. The rationale of the trial, contents of the intervention, periods of the trial, ability to perform the trial without disrupting the routine work of the participating midwives, and the recruitment process will be discussed. In consultation with the heads of the antenatal clinics, 30 research midwives will be selected. All participating midwives will receive trial-specific training using appropriate training methods by the first author. The training will be group-based to ensure consistency in the delivery of the intervention and will include how to recruit participants using the inclusion criteria listed and how best to ask sensitive questions to allay the fears and apprehension of participants. The research midwives will receive a monthly per diem.

Results

Permission to conduct the study has been obtained from the University of Eastern Finland Committee on Research Ethics (Statement No. 13/2015) and the Ghana Health Service Ethics Review Committee (ID No: GHS-ERC:20/11/15), covering all the 10 proposed antenatal clinics. Application for funding to

begin the trial is ongoing. Findings from the main trial are expected to be published by the end of 2019.

Discussion

We propose an interventional study to fill the research gap on whether heavy lifting in pregnancy has negative effects on gestational age and birthweight, particularly among women in LMIC. There is no intervention study on the effects of lifting in pregnancy on birthweight and gestational age. Similar to many other health indicators, PTB and LBW prevalence rates underscore the overwhelming health disparities and inequalities between high-income and low-income countries. Strenuous physical activity, LBW, and PTB are common occurrences in low-income countries, which lack guidelines to protect against hazardous work conditions [11]. There are inconsistencies in the existing etiological studies on the subject, thereby creating an evidence gap [22]. As a result of the inconsistencies, recommendations and all other clinical guidelines lack the necessary evidential backing for practice. This clinic-level intervention using a stepped-wedge design will thus provide a vital contribution to the existing knowledge for the prevention of PTB and LBW, especially within LMIC.

Problems anticipated in the course of this intervention may arise from participant attrition, especially among controls, due to the longer duration of the trial. We intend to reduce attrition by explaining the potential benefits of the trial in detail and providing shopping vouchers, which is the third component of the intervention, to all control participants during postnatal periods. The strengths of the trial include the prospective data collection method, the study design, and the size of the study population. The results of this trial have the potential to justify the need for policy to modify the occupational and family environment of pregnant women within Ghana and other LMIC with similar socioeconomic conditions.

Authors' Contributions

EKA conceived the idea about the study and finished the study protocol with supervision and collaboration from KR and JV. JV provided the statistical expertise for the study. LA and JDS contributed to formulate the study plan to meet local acceptance. EKA, KR, JV, LA, and JDS read and provided feedback on drafts. All authors have read and approved the final manuscript for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Proposed antenatal clinics and total number of antenatal attendance in 2017.

[PDF File (Adobe PDF File), 24KB - resprot_v7i8e10095_app1.pdf]

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Abbreviations

HIC: high income countries
LBW: low birthweight
LMIC: low- and middle-income countries
PTB: preterm birth
RCT: randomized controlled trial

Edited by G Eysenbach; submitted 12.02.18; peer-reviewed by TM Luu, B Singh; comments to author 11.05.18; revised version received 22.05.18; accepted 19.06.18; published 23.08.18.

Please cite as:
Kwegyir-Afful E, Verbeek J, Aziato L, Seffah JD, Räsänen K
A Liftless Intervention to Prevent Preterm Birth and Low Birthweight Among Pregnant Ghanaian Women: Protocol of a Stepped-Wedge Cluster Randomized Controlled Trial
JMIR Res Protoc 2018;7(8):e10095
URL: http://www.researchprotocols.org/2018/8/e10095/
doi:10.2196/10095
PMID:30139723

Protocol

Evaluation of Biological and Functional Changes in Healthy Smokers Switching to the Tobacco Heating System 2.2 Versus Continued Tobacco Smoking: Protocol for a Randomized, Controlled, Multicenter Study

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Abstract

Background: Tobacco harm reduction, substituting less harmful tobacco products for combustible cigarettes, is a complementary approach for smokers who would otherwise continue to smoke. The Philip Morris International (PMI) Tobacco Heating System (THS) 2.2 is a novel tobacco product with the potential to reduce the risk of harm in smokers compared to continued smoking of combustible cigarettes. It heats tobacco electrically in a controlled manner, never allowing the temperature to exceed 350°C, thereby preventing the combustion process from taking place and producing substantially lower levels of toxicants while providing nicotine, taste, ritual, and a sensory experience that closely parallels combustible cigarettes. Previous clinical studies have demonstrated reduced exposure to the toxicants (approaching the levels observed after quitting) for smokers who switched to THS 2.2, for three months. For adult smokers who would otherwise continue smoking combustible cigarettes, switching to THS 2.2 may represent an alternative way to reduce the risk of tobacco-related diseases.

Objective: This study aimed to further substantiate the harm reduction potential of THS 2.2 by demonstrating favorable changes in a set of 8 coprimary endpoints, representative of pathomechanistic pathways (ie, inflammation, oxidative stress, lipid metabolism, respiratory function, and genotoxicity), linked to smoking-related diseases, in smokers switching from combustible cigarettes to THS 2.2.

Methods: This study was a randomized, controlled, two-arm parallel group, multicenter ambulatory US study conducted in healthy adult smokers switching from combustible cigarettes to THS 2.2 compared with smokers continuing to smoke combustible cigarettes for six months. Subjects had a smoking history of at least ten years and did not intend to quit within the next six months.

Results: Enrollment started in March 2015 and the trial was completed in September 2016. In total, 984 subjects were randomized (combustible cigarettes, n=483; THS 2.2, n=477), and 803 completed the study. The results are expected to be available in a subsequent publication in 2019.

Conclusions: In this paper, we describe the rationale and design for this clinical study that focused on the evaluation of THS 2.2's potential to reduce the risk of smoking-related diseases compared with that of combustible cigarettes. This study will provide insights regarding favorable changes in biological and functional endpoints informed by effects known to be seen upon smoking cessation.

Trial Registration: ClinicalTrials.gov NCT02396381; http://clinicaltrials.gov/ct2/show/NCT02396381 (Archived by WebCite at http://www.webcitation.org/71PCRdagP)

Registered Report Identifier: RR1-10.2196/11294

(JMIR Res Protoc 2018;7(8):e11294) doi:10.2196/11294

KEYWORDS

smoking; tobacco; harm reduction; tobacco products; risk; heated tobacco; smoking cessation; biomarkers; metabolic networks; pathways

Introduction

Cigarette smoking is the leading cause of preventable disease in the US, accounting for more than 480,000 smoking-related deaths every year. More than 16 million Americans live with a smoking-related disease [1]. Although the smoking prevalence in the US has declined from 21% to 17% over the last decade, an estimated 40 million people currently smoke cigarettes in the US [2], and one billion people worldwide continue to smoke [3]. Smoking is addictive, and smoking cessation is difficult for many smokers, even though it is the best way to reduce the risk of developing smoking-related diseases.

In addition to the prevention of smoking initiation and the promotion of smoking cessation, tobacco harm reduction is being recognized as a valuable and promising approach to further accelerate the decline in smoking prevalence and smoking-related population harm [4]. Tobacco harm reduction is based on switching smokers to markedly less harmful alternative products, referred to by the Food and Drug Administration as modified risk tobacco products (MRTP). The US Family Smoking Prevention and Tobacco Control Act defines an MRTP as "any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products" [5].

Importantly, to improve health at the population level, these substitutes for cigarettes must be acceptable for smokers, providing adequate nicotine delivery and satisfaction to prevent relapse to cigarette smoking. In this context, Philip Morris International (PMI) has developed Tobacco Heating System (THS) 2.2, as a candidate MRTP that has been designed to provide nicotine to smokers, who otherwise would have continued to smoke, offering sensory and ritual aspects like cigarettes while reducing the exposure to harmful and potentially harmful constituents (HPHC) found in cigarette smoke [6-8]. Additional studies have been conducted on alternatives to cigarettes. A carbon heated tobacco product developed by PMI has demonstrated markedly reduced biomarkers of exposure to HPHCs (NCT02503254) [9]. British American Tobacco has developed a product that heats rather than burns tobacco, significantly reducing exposure to smoke toxicants to levels comparable to quitting tobacco [10]. Japan Tobacco has also introduced a smokeless tobacco product with data reflecting substantially lower exposure to smoke toxicants [11]. Electronic cigarettes have also demonstrated reduced exposure to smoke toxicants compared to cigarettes [12].

THS 2.2 uses a precisely controlled heating device into which a specially designed tobacco product, the Tobacco Stick, is inserted and heated to generate an aerosol. The THS 2.2 heater starts heating the Tobacco Stick in a controlled and gradual manner, with the temperature set between 320°C and 350°C. Heating the Tobacco Stick in a controlled manner and not allowing the temperature to exceed 350°C prevents the combustion process from taking place. The elimination of combustion results in a significant reduction in the production and exposure to HPHCs [13] while the nicotine is delivered to the THS 2.2 user in a way that is like cigarettes. The holder must be recharged after each use, and the charger must be recharged after approximately 20 uses.

PMI has designed a multilayered scientific program to assess whether THS 2.2 can significantly reduce the risk of harm and smoking-related diseases in adult smokers who otherwise would have continued to smoke cigarettes. Preclinical and clinical studies have been conducted on THS 2.2 and its predecessors. Aerosol from THS 2.2 contains, on average, approximately 90% less HPHCs found in smoke from a standard reference cigarette, which translates to a reduced toxicity of approximately 90% [13]. Chronic exposure to THS 2.2 aerosols in animal models, even at high concentrations, resulted in lower systemic toxicity, with reduced lung inflammation and histopathological changes in the nasal epithelium and lung tissue [14]. Furthermore, in the $ApoE^{-/-}$ mouse model, which is commonly used to study atherosclerosis and emphysema, exposure to THS 2.2 aerosol did not induce a change in the lipid profile or enlargements of aortic plaque area, nor lung inflammation or emphysema, unlike cigarette smoke. Additionally, switching from cigarette smoke to THS 2.2 aerosol exposure reversed inflammation, and halted aortic plaque growth and the progression of emphysema in a manner that mimics smoking cessation [15].

In humans, previous clinical studies showed a similar nicotine absorption profile in smokers using a single Tobacco Stick or smoking a cigarette [16] and demonstrated reductions in the levels of 15 biomarkers of exposure to HPHCs in healthy adult smokers who switched exclusively to THS 2.2 for five days in confinement or for three months in ambulatory setting relative to cigarettes. The magnitude of reductions was comparable to what was observed in adult smokers who abstained from smoking [16-18].

In summary, the available clinical evidence demonstrates that humans who switch from cigarettes to THS 2.2, are exposed to significantly lower levels of selected HPHCs. This observed reduction is of a similar magnitude as that observed in smokers who abstain from smoking, which has been referred to as the "gold standard" for the assessment of candidate MRTPs [19,20]. Considering the preclinical and clinical data on exposure reduction, it is reasonable to assume that the reduction in exposure to toxicants leads to favorable changes in biological and functional endpoints involved in smoking-related disease development and progression.

Smoking-related diseases have a complex etiology and involve several mechanisms that affect multiple organ systems [20]. Chronic exposure causes alterations at the cellular and tissue level that result in physiological changes and disrupt multiple biological processes, contributing to disease manifestation. Oxidative stress and inflammation play a critical role in the development and progression of the major smoking-related

diseases: cardiovascular disease, chronic obstructive pulmonary disease, and cancer. There is no single clinical risk endpoint (CRE) or biomarker that is an adequate surrogate measure for the multiple adverse health effects associated with smoking, and that can fully demonstrate a reduction in risk.

Because smoking-related diseases often take decades to manifest, conducting long-term epidemiological studies would require decades to demonstrate the reduced risk of THS 2.2.

Thus, the demonstration of favorable changes in a set of CREs that are representative of multiple biological processes, physiological systems, and mechanistic pathways in smokers who switch to THS 2.2 is a reasonable approach to provide scientific evidence in a pre-market setting that THS 2.2 can reduce the risk of harm and smoking-related diseases.

This study will assess the risk profile of THS 2.2 in a pre-market setting and support risk assessment of this novel tobacco product together with all available evidence as one set of logical, empirically coherent, and consistent data.

Methods

Study Design

This study was a randomized, controlled, two-arm parallel group, multicenter study comparing multiple CREs in smokers switching from cigarettes to THS 2.2 and smokers continuing to smoke cigarettes for six months (NCT02396381). This open-label study was conducted at 20 clinical research centers in the US. The study design is illustrated in Figure 1. The first subject was screened on March 12, 2015, and the last subject completed the study on September 13, 2016.

After visit 1 (V1), the screening visit, during which eligibility criteria were checked, participants received study supplies, such as a container for urine collection and an electronic diary. Participants were trained by the site staff on how to collect 24-hour urine and how to fill the diary daily. Urine collection started in the morning of the day preceding a study visit and ended 24 hours later on the morning of a visit. Starting from V2, subjects recorded all nicotine and tobacco-containing products used in their daily diary. At V3, after a recheck of selected eligibility criteria, participants were enrolled in the study, and baseline assessments were performed, including blood and 24-hour urine sample collection for biomarker analysis. After enrollment, at the end of V3, THS 2.2 units were distributed to all participants to be used during an eight-day run-in period to get familiar with the use of THS 2.2. The use of other tobacco and nicotine products was also permitted.

At the end of the run-in period (V4), all enrolled participants willing to use THS 2.2 for the next six months were randomized in a 1:1 ratio to either the THS 2.2 or the combustible cigarette (CC) arms. The sponsor provided THS 2.2, and participants were instructed to use it ad libitum. Participants randomized to the CC arm were asked to purchase and smoke their own brand of cigarettes ad libitum. Randomization was performed using an interactive voice and web response system using gender and study site as stratification criteria. Use of tobacco or nicotine products other than the allocated product during the randomized exposure period did not lead to the removal of the participant from the study. For participants randomized to the CC arm, the use of THS 2.2 was not allowed. Therefore, the THS 2.2 device and remaining Tobacco Sticks were collected from subjects randomized to the CC arm after the run-in period.

Subjects returned to the clinic each month for safety checks and resupply of THS 2.2 Tobacco Sticks when needed. Major study visits occurred every three months (V7, V10) for lung function assessment and collection of blood and 24-hour urine for biomarker analysis. After V10 (six months postrandomization), subjects who completed the study were invited to participate in an extension study for an additional six months (NCT02649556). Subjects participating in the extension study continued to use the same product to which they had been assigned and continued to visit the same clinical sites monthly. The purpose of the extension study was to follow the study participants for a more extended period and to further describe changes in CREs, lung function, as well as biomarkers of exposure. For that purpose, blood and 24-hour urine samples were collected, and lung function was assessed at V16 (month 12).

Subjects choosing not to enroll in the extension study entered into a 28-day safety follow-up period. Adverse events were recorded from the signature of informed consent onwards until the end of the safety follow-up period.

Objectives and Endpoints of the Study

The smokers' health profile (Table 1) is a collection of 8 co-primary CREs that together cover various mechanistic and pathological pathways (ie, inflammation, oxidative stress, lipid metabolism, changes in respiratory function, and genotoxicity), that are known to contribute to smoking-related diseases, such as cardiovascular and respiratory disease as well as cancer [20]. These CREs, selected for the smokers' health profile, are also known to be reversible upon smoking cessation within a few days to one year. The individual CREs were chosen for (1) their link to smoking-related diseases, (2) evidence that the smoking status influences the CREs, and (3) their favorable change upon smoking cessation within a timeframe feasible for the study duration (Table 1). Many of these CREs are mentioned in the 2010 Surgeon General's Report entitled *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease* [20].

Biomarkers of exposure to carbon monoxide (CO) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (nicotine-derived nitrosamine ketone; NNK) were included in the list of CREs, as they contribute to exacerbate acute ischemic effects (ie, CO), and are known tobacco-specific carcinogenic compounds (ie, NNK).

The primary objective of the study was to indicate favorable changes in the 8 CREs in the smokers' health profile. The evaluation criteria for the study was that at least five out of the eight CREs would show statistically significant favorable changes.

The secondary objectives and their related CREs included additional biological and functional CREs supportive of the smokers' health profile, biomarkers of exposure to HPHCs, assessments of subjective effects, and safety CREs (Table 2).

Figure 1. Design of the study. Eligible subjects were provided with the Tobacco Heating System 2.2 (THS 2.2) at visit 3 (V3) and were allowed to use the product freely during the 6- to 10-day run-in period until V4. Those willing to use THS 2.2 exclusively during the study were randomized to the THS 2.2 or cigarette arms.

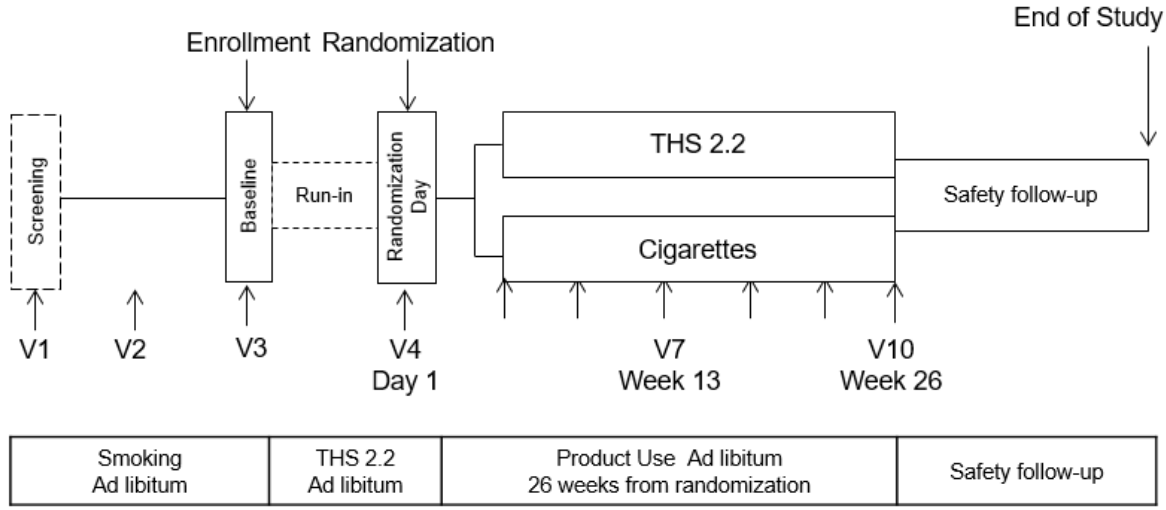


Table 1. Components of the smokers' health profile.

Component	Related physiological process	Sample	Expected change in THS 2.2[a] arm	Expected timeframe of reversibility
High-density lipoprotein cholesterol	Lipid metabolism	Serum	Increase	3 months [21]
White blood cell count	Inflammation	Blood	Decrease	6-12 months [21]
Soluble intercellular adhesion molecule-1	Endothelial dysfunction	Serum	Decrease	4 weeks [22,23]
11-dehydrothromboxane B2	Platelet activation	Urine	Decrease	2-4 weeks [24,25]
8-epi-prostaglandin F2alpha	Oxidative stress	Urine	Decrease	1-2 weeks [26,27]
Carboxyhemoglobin	Transport of oxygen by hemoglobin	Blood	Decrease	1-7 days [28]
Forced expiratory volume in one second	Lung function	None	Increase	6-12 months [29-31]
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	Exposure to carcinogenic potentially harmful constituents	Urine	Decrease	3 months [32]

[a]THS 2.2: Tobacco Heating System 2.2.

The selection criteria for the biomarkers of exposure included: (1) detectability, reproducibility, and precision of the analytical methods, (2) specificity for the toxic exposure or reliable surrogate of exposure to HPHCs, (3) presence in the gas or particulate phases, (4) formation at different temperatures, and (5) relation to different chemical and organ toxicity classes. Additionally, the relationship between levels of urinary biomarkers of exposure and nicotine equivalents were assessed at six months, to evaluate the effect of combined product use (cigarettes and THS 2.2 Tobacco Sticks) on the smokers' health profile, the intention to use THS 2.2, and the change in tobacco dependence in smokers switching from cigarettes to THS 2.2.

Study Measurements

The details of the assessments performed during the study are provided in the schedule of events (Multimedia Appendix 1) [33]. Subjects' reported smoking intensity (cigarettes per day during the previous year) and duration, as well as subjects' lifestyle characteristics (diet, alcohol intake, exercise, sleep deficit, living in a household with other smokers), were collected using questionnaires at baseline. Standard spirometry was conducted pre- and postbronchodilator (salbutamol), and lung volumes were assessed using the Helium Dilution Technique. Both CREs were assessed following the respective guidelines of the European Respiratory Society [34,35]. Full lung function assessment was read centrally. Blood collection and urine sampling from the 24-hour urine were conducted for CREs and biomarkers of exposure analyses at baseline (V3), at month 3 (V7), and at month 6 (V10). One central laboratory was responsible for storage and shipment of urine and blood samples, and multiple laboratories performed the analyses using validated methods to assess all laboratory safety parameters, biomarkers of exposure, and CREs (Multimedia Appendix 2) [36].

Table 2. Secondary objectives and endpoints of the study.

Objective	Endpoint
To evaluate self-reported product use over the duration of the study	• Number of cigarettes or THS 2.2[a] Tobacco Sticks used daily, as reported in the product use electronic diary
To determine short-term changes of the smokers' health profile at month 3	• All components of the smokers' health profile
To indicate the reduction of exposure to HPHC[b] at month 3 and month 6	• Biomarkers of exposure to carbon monoxide (CO): CO in exhaled breath • Biomarker of exposure to 1,3-butadiene: monohydroxybutenylmercapturic acid in urine • Biomarker of exposure to acrolein: 3-hydroxypropylmercapturic acid in urine • Biomarker of exposure to N-nitrosonornicotine: total N-nitrosonornicotine in urine • Biomarker of exposure to acrylonitrile: 2-cyanoethylmercapturic acid in urine • Biomarker of exposure to benzo[a]pyrene: 3-hydroxybenzo[a]pyrene in urine • Biomarker of exposure to crotonaldehyde: 3-hydroxy-1-methylpropylmercapturic acid in urine • Biomarker of exposure to pyrene: total 1-hydroxypyrene in urine
To describe the levels of nicotine exposure at month 3 and month 6	• Nicotine equivalent: molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3′-hydroxycotinine, trans-3′-hydroxycotinine-glucuronide in urine • Nicotine and cotinine in plasma
To describe the changes of clinical risk endpoints associated with respiratory diseases, cardiovascular diseases, and xenobiotics	• Lung function (spirometry postbronchodilator): FEV_1[c], FVC[d], FEV_1/FVC, FEF[e] 25-75 • Lung volumes (lung volume prebronchodilator): functional residual capacity, vital capacity, total lung capacity, inspiratory capacity, and residual volume at month 3 and month 6 • Cough symptoms (intensity and frequency), amount of sputum production, and bothersomeness of cough symptoms, from the cough questionnaire at month 3 and month 6 • Lung function (spirometry prebronchodilator): FEV_1, FVC, FEV_1/FVC, FEF 25-75 at month 6 • Lung function (spirometry, pre- and postbronchodilator): bronchodilator reversibility in FEV_1 at month 6 • Myeloperoxidase, apolipoprotein A1 and B, low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein in serum at month 3 and month 6 • Fibrinogen and homocysteine in plasma at month 3 and month 6 • Platelet count and hemoglobin glycosylated in whole blood at month 3 and month 6 • Albumin in urine at month 3 and month 6 • Blood pressure, weight, and waist circumference at month 3 and month 6 • Cytochrome P450 2A6 activity in plasma at month 3 and month 6
To describe the changes in subjective effects of smoking at month 3 and month 6	• Product evaluation (Modified Cigarette Evaluation Questionnaire) [37]
To evaluate the safety profiles associated with THS 2.2 and cigarettes over the course of the study	• Adverse Events, Serious Adverse Events, and device events, including THS 2.2 malfunction or misuse • Vital signs, body weight, and body mass index • Respiratory symptoms • Spirometry • Electrocardiogram • Clinical chemistry, hematology, and urine analysis safety panel • Physical examination • Concomitant medications

[a]THS 2.2: Tobacco Heating System 2.2.

[b]HPHC: harmful and potentially harmful constituents.

[c]FEV_1: forced expiratory volume in one second.

[d]FVC: forced vital capacity.

[e]FEF: forced expiratory flow.

Collection of 24-hour urine started at the subject's home on the morning of the day before the scheduled visit and ended the morning of the day of the study visit. Blood was collected after at least 10 hours of fasting except for carboxyhemoglobin measurement. Exhaled breath was measured for CO using a Smokerlyzer device (Bedfont Scientific Ltd, UK) as another biomarker of exposure to CO. Cough assessment by visual analog scale and Likert scales (intensity of a cough, frequency of a cough, and the amount of sputum collection) were conducted at baseline (V3), at month three, and at month six.

Enrollment

This study enrolled current adult smokers of nonmenthol cigarettes who did not intend to quit smoking within the next six months. At least 950 participants were to be randomized.

Once 950 subjects had been randomized, no additional subjects were enrolled; however, all subjects who were already enrolled and started the run-in period were still randomized.

The main inclusion and exclusion criteria are listed in Textbox 1. Participants had at least ten years of smoking history and smoked at least ten cigarettes per day over the last 12 months based on self-reporting. There were no limitations on race or ethnicity other than a quota on Caucasian subjects to ensure that they did not represent more than 75% of randomized subjects. Participants of each gender were limited to no more than 60% of the study population.

Approval for the study was granted by one central Institutional Review Board for each of the participating sites. All participants provided written informed consent before the start of the study. The study was conducted following Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki [38-40]. Study participants were remunerated for the time they devoted to the study in line with the local market practice and approved by the Institutional Review Board.

Statistical Considerations

A sample size of 950 subjects (randomized 1:1) was calculated to be enough to attain a statistical power of >99% to show statistically significant favorable changes in at least five out of eight CREs of the smokers' health profile at six months. The Hailperin-Rüger approach will be used to adjust for test multiplicity [41,42].

Although this was an open-label study, and the subjects and the investigators or their designees were unblinded to the subject's study arm after randomization, a limited degree of blinding was implemented during the conduct of the study, including the data review and data analysis process. The study statisticians and clinical scientists involved with the definition of the analyses were blinded to the actual values of primary CREs from the time of randomization until database lock.

The primary analysis will be run on the full analysis set (FAS) of subjects based on their actual product exposure [43] according to predefined product use pattern categories (Table 3). Subjects switching to THS 2.2 and those smoking cigarettes will be identified by THS-use and CC-use product use categories, respectively. Results of the Dual-use versus CC-use comparison will also be evaluated in secondary and exploratory analysis tables. Only subjects with at least one record of reported product use postrandomization will be included in the primary analysis. Missing data will be considered as missing at random, and each CRE will be analyzed using a mixed-effect model repeated measure adjusting for value of the CRE at baseline and its interaction with visit, gender, Caucasian origin, product use pattern category, and other lifestyle covariates relevant for each CRE following examination of baseline comparability between THS-use and CC-use (see Table 4). Site will be included as a random effect. Sensitivity analyses will be conducted for the FAS considering alternative missing imputation approaches for primary endpoints and product use. Sensitivity analysis will also be conducted on the FAS by randomization arm.

Textbox 1. Main criteria for inclusion and exclusion of subjects.

Inclusion criteria

- Healthy smoker
- At least 30 years old
- Smoking history of at least 10 years
- Smoking history of at least 10 nonmenthol cigarettes per day on average in the 12 months preceding the screening
- No intention to quit smoking within the next six months

Exclusion criteria

- Clinically relevant gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, pulmonary, immunological, psychiatric, or cardiovascular disorders or any other conditions that would jeopardize the safety of the participant or affect the validity of the study results
- Abnormal findings on physical examination, in the medical history, or in clinical laboratory results deemed clinically relevant by investigators (as per the common terminology criteria for adverse events)
- Acute illness (eg, upper respiratory tract infection, viral infection) requiring treatment within 30 days before enrollment in the study
- Use of any prescribed or over-the-counter systemic medications with an impact on the clinical risk endpoints of the smokers' health profile within five half-lives of the medication before study enrollment, except over-the-counter vitamin supplements, hormonal contraceptives, and hormone replacement therapy
- FEV_1/FVC below 0.7 and FEV_1 below 80% predicted value at postbronchodilator spirometry (FEV_1 refers to the forced expiratory volume in 1 second while FVC refers to forced vital capacity)
- Pregnancy or breastfeeding
- Unwilling to use an acceptable method of effective contraception (females only)

Table 3. Principal categories of actual product use pattern.

Category label	Definition
THS[a]-use	• ≥1 THS 2.2 Tobacco Sticks or cigarettes and • ≥70% THS 2.2 Tobacco Stick use over the entire analysis period and • ≥70% THS 2.2 Tobacco Stick use on ≥50% of the days in the analysis period
Dual-use	• ≥1 THS 2.2 Tobacco Sticks or cigarettes and • 1%≤ THS 2.2 Tobacco Sticks <70% over the entire analysis period or • THS 2.2-use and CC[b]-use do not apply to <50% of these days
CC-use	• ≥1 THS 2.2 Tobacco Sticks or cigarettes and • <1% THS 2.2 Tobacco Sticks over the entire analysis period, and • <1% THS 2.2 Tobacco Sticks on ≥50% of the days in the analysis period
Other use	• General category encompassing subjects with missing product use, subjects using e-cigarettes or other tobacco products, subjects who quit, or subjects who switched across different use patterns between consecutive analysis periods

[a]THS: Tobacco Heating System.

[b]CC: combustible cigarette.

Table 4. Baseline covariates for the analysis of primary endpoints.

Endpoint	Defined covariates[a]	Evaluated covariates[a]
High-density lipoprotein cholesterol	Age, smoking intensity	Smoking duration, diet, alcohol intake, exercise, body mass index
Total white blood cell	Age, smoking intensity	Smoking duration, race/ethnicity, sleep deficit
sICAM-1[b]	Age, smoking intensity	Smoking duration
11-DTX-B2[c]	Age, smoking intensity	Living in household with smokers
8-epi-PGF2α[d]	Age, smoking intensity	Smoking duration, body mass index, weight
Carboxyhemoglobin	Age, smoking intensity	Living in household with smokers
FEV_1[e]	Smoking intensity	Sex, age[f], race and ethnicity, height, diet, exercise, body mass index, weight, smoking duration
Total NNAL[g]	Age, smoking intensity	Living in household with smokers

[a]The model will include terms for the "Defined Covariates" and for the subset of "Evaluated Covariates" selected if found to be significant at 10% level (between THS-use and CC-use) at baseline.

[b]sICAM-1: soluble intercellular adhesion molecule 1.

[c]11-DTX-B2: 11-dehydrothromboxane B2.

[d]8-epi-PGF2α: 8-epi-prostaglandin F2alpha.

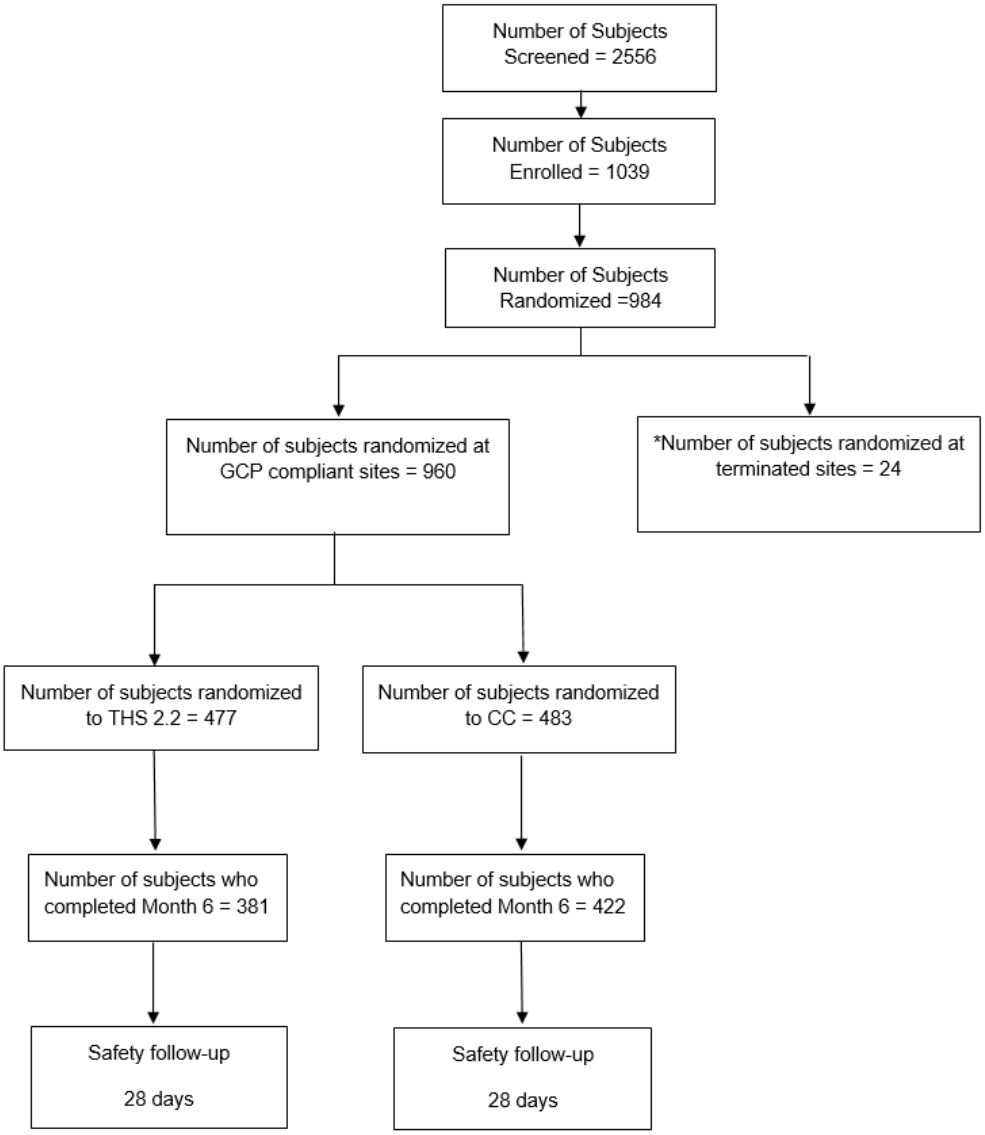
[e]FEV_1: forced expiratory volume in 1 second and measured as percent of predicted value.

[f]Age is not included in the defined covariates because it is accounted for in the percent predicted assessment.

[g]NNAL: 4-(methylnitrosamino)-1-(3 pyridyl)-1-butanol.

For the primary analysis, substantiation that switching to THS 2.2 from cigarettes modifies the risk of smoking-related diseases will rely on the following criteria. First, all CREs in the smokers' health profile must shift in the same direction as they would upon smoking cessation. Second, switching to THS 2.2 must show a statistically significant improvement in at least five of the 8 components of the smokers' health profile, with each CRE evaluated using a one-sided alpha of 1.5625%, corresponding to half of the Hailperin-Rüger adjusted type I error (.031). The Hailperin-Rüger approach calculates the statistical significance that is required for each test when at least five of the 8 primary CREs in the smokers' health profiles are required to be significant to maintain the overall study-wise alpha-level of 5%. Effect estimates will be presented accompanied by 2-sided 96.875% (100-alpha %) confidence intervals. It will be finally evaluated if most of the effect of smoking cessation is preserved in subjects switching to THS 2.2, based on the results of an integrated analysis pooling data from a separate smoking cessation study (NCT02432729) designed to benchmark the clinical, biological, and functional changes in smokers who are continuously abstinent from smoking for 1 year. The methods and results will be reported in a separate manuscript. There were no interim analyses planned.

Figure 2. Flow chart of study participants. Asterisk indicates sites terminated due to noncompliance with Good Clinical Practice (GCP). CC: combustible cigarette; THS 2.2: Tobacco Heating System 2.2.



Participants

For the study, 2,556 subjects were screened, 1,039 were enrolled, 984 were randomized (483 to CC arm and 477 to THS 2.2 arm), and 803 completed the study (Figure 2). The database lock of the study is completed.

Results

Enrollment started in March 2015 and the trial was completed in September 2016. The results of this paper are expected in 2019.

Discussion

Preliminary Insights

The diseases attributed to smoking are complex. Continuous exposure to HPHCs affects multiple organ systems, disease pathways, and mechanisms, such as inflammation, oxidative stress, platelet activation, and lipid metabolism, which coincide, leading gradually to the development of smoking-related diseases over the course of years. This study examined changes in biological and functional CREs in adult smokers switching to THS 2.2 in an ambulatory, near real-life setting. Because no single CRE is validated as a surrogate measure for any smoking-related disease, the primary endpoint of this study was a selection of equally important, nonhierarchical, co-primary CREs defined as the smokers' health profile.

The analysis of this study uses a robust approach in the field of tobacco harm reduction. All co-primary CREs of the smokers' health profile must shift in the same direction as they would upon smoking cessation, and at least five of the 8 components of the smokers' health profile must be significantly improved statistically in THS 2.2 users compared with those who continued smoking cigarettes. Significance will be evaluated using a one-sided test with the Hailperin-Rüger adjusted alpha-level.

Furthermore, the planned analysis approach considers baseline comparability of confounding factors that can potentially

influence study results, such as exercise, diet, alcohol intake, and potential exposure to passive smoking. Additional CREs that are representative of various mechanistic or pathological pathways will be evaluated in the secondary objectives to support the analysis of the primary objective. Because smoking alters multiple pathways, tissues, and organs, which together contribute to disease risk, this approach will provide coherent and multifaceted scientific evidence of the reduced-risk potential of THS 2.2.

The ambulatory setting will provide information not only on product consumption and combined or dual-use (smoking of cigarettes in addition to using THS 2.2) but also on user satisfaction and acceptance of the product, as assessed by the proportion of product used, the "intent to use" questionnaire, and the modified cigarette evaluation questionnaire.

In summary, results from this study will be a noteworthy addition to the growing body of data from the assessment program to scientifically substantiate that THS 2.2 can potentially reduce the risk of smoking-related diseases [6]. The design and approach used in the present study should be considered in light of its limitations. One potential limitation is that the study population might not match the general population of potential THS 2.2 consumers. The study enrolled only smokers who smoked at least 10 cigarettes a day. Also, the study may provide only limited insight on the effect of THS 2.2 in various races and ethnicities.

Conclusions

This study is part of a multilayered assessment program designed to evaluate whether THS 2.2 can potentially reduce the risk of smoking-related diseases relative to continued smoking. The results of this study will confirm whether the reduction in exposure to HPHCs when switching from cigarettes to THS 2.2 leads to statistically significant favorable changes in CREs linked to smoking disease and following the direction expected upon smoking cessation. Detailed information on product use, product satisfaction, and acceptance will also emerge from this study. This study will provide evidence to substantiate the reduced-risk potential of THS 2.2. Longer term duration of exposure is needed to evaluate these changes in biological and functional biomarkers further.

Acknowledgments

The authors sincerely appreciate the contributions of all the investigators and other clinical and research staff involved in the present study. We thank Susan E Cottrell, PhD, of Edanz Medical Writing, for providing medical writing support.

Conflicts of Interest

The work reported in this publication involved a candidate MRTP developed by PMI Research & Development. All authors are (or were) employees of PMI or worked for PMI under contractual agreements. PMI is the sole source of funding and sponsor of this project.

Multimedia Appendix 1

Schedule of events.

[PDF File (Adobe PDF File), 70KB - resprot_v7i8e11294_app1.pdf]

Multimedia Appendix 2

Methods and measurements.

[PDF File (Adobe PDF File), 31KB - resprot_v7i8e11294_app2.pdf]

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Abbreviations

8-epi-PGF2α: 8-epi-prostaglandin F2alpha
11-DTX-B2: 11-dehydrothromboxane B2
CC: combustible cigarette
CO: carbon monoxide
CRE: clinical risk endpoint
FAS: full analysis set
FEF: forced expiratory force
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
HPHC: harmful and potentially harmful constituents
PMI: Philip Morris International
MCEQ: Modified Cigarette Evaluation Questionnaire
MRTP: modified risk tobacco product

NNAL: 4-(methylnitrosamino)-1-(3 pyridyl)-1-butanol
NNK: nicotine-derived nitrosamine ketone
sICAM-1: soluble intercellular adhesion molecule 1
THS 2.2: Tobacco Heating System 2.2
V: visit

Edited by G Eysenbach, N Kuter; submitted 14.06.18; peer-reviewed by R Mermelstein, J Prochaska; comments to author 09.07.18; revised version received 25.07.18; accepted 25.07.18; published 24.08.18.

Please cite as:
Ansari SM, Lama N, Blanc N, Bosilkovska M, Donelli A, Picavet P, Baker G, Haziza C, Lüdicke F
Evaluation of Biological and Functional Changes in Healthy Smokers Switching to the Tobacco Heating System 2.2 Versus Continued Tobacco Smoking: Protocol for a Randomized, Controlled, Multicenter Study
JMIR Res Protoc 2018;7(8):e11294
URL: http://www.researchprotocols.org/2018/8/e11294/
doi:10.2196/11294
PMID:30143474

Protocol

Technologies for Innovative Monitoring to Reduce Blood Pressure and Change Lifestyle Using Mobile Phones in Adult and Elderly Populations (TIM Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: Hypertension is a growing problem worldwide, markedly in low- and middle-income countries, where the rate of control slightly decreased. The overall prevalence of hypertension in Brazil is 28.7% among adult individuals and 68.9% in the population aged 60 years and older, and less than a third of patients have controlled blood pressure (BP). The use of technologies—mobile phones and the internet—to implement interventions to reduce blood pressure can minimize costs and diminish cardiovascular risk. Interventions through text messaging and electronic BP monitoring present divergent results.

Objective: This trial evaluates the effectiveness of interventions—personalized messages and telemonitoring of BP—to reduce systolic BP and improve lifestyle compared to the usual care of patients with hypertension (control group).

Methods: This factorial randomized controlled trial enrolls individuals aged 30 to 75 years who have a mobile phone and internet access with the diagnosis of hypertension under drug treatment with up to 2 medications and uncontrolled BP. Eligible participants should have both increased office BP and 24-hour BP with ambulatory BP monitoring. Participants with severe hypertension (systolic BP ≥180 or diastolic BP ≥110 mm Hg), life threatening conditions, low life expectancy, recent major cardiovascular event (last 6 months), other indications for the use of antihypertensive medication, diagnosis of secondary hypertension, pregnant or lactating women, or those unable to understand the interventions are excluded. Participants are randomly allocate to 1 of 4 experimental arms: (1) Telemonitoring of blood pressure (TELEM) group: receives an automatic oscillometric device to measure BP, (2) telemonitoring by text message (TELEMEV) group: receives personalized, standardized text messages to stimulate lifestyle changes and adhere with BP-lowering medication, (3) TELEM-TELEMEV group: receives both interventions, and (4) control group: receives usual clinical treatment (UCT). Data collection is performed in a clinical research center located in a referent hospital. The primary outcomes are reduction of systolic BP assessed by 24-hour ambulatory BP monitoring (primary

outcome) and change of lifestyle (based on dietary approaches to stop hypertension (DASH)-type diet, sodium restriction, weight loss or control, increase of physical activity).

Results: This study was funded by two Brazilian agencies: the National Council for Scientific and Technological Development and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul. Enrollment was completed at the end of 2017 (N=231), the follow-up is ongoing, and data analysis is expected to begin in early 2019. A reduction of 24-hour systolic BP of approximately 8.8 [SD 13.1] mm Hg for participants in the BP monitoring group versus 3.4 [SD 11.6] mm Hg in the UCT group is expected. A similar reduction in the text messaging group is expected.

Conclusions: The use of mobile technologies connected to the internet through mobile phones promotes time optimization, cost reduction, and better use of public health resources. However, it has not been established whether simple interventions such as text messaging are superior to electronic BP monitoring and whether both outperform conventional counseling.

Trial Registration: ClinicalTrials.gov NCT03005470; https://clinicaltrials.gov/ct2/show/NCT03005470 (Archived by WebCite at http://www.webcitation.org/70AoANESu). Plataforma Brasil CAAE 31423214.0.0000.5327.

Registered Report Identifier: RR1-10.2196/9619

(JMIR Res Protoc 2018;7(8):e169) doi:10.2196/resprot.9619

KEYWORDS

blood pressure; blood pressure monitoring; hypertension; weight; diet; sodium; physical activity; randomized controlled trial; text messages

Introduction

Hypertension is a growing problem worldwide, markedly in low- and middle-income countries where increased prevalence was not followed up by higher awareness and control rates [1]. The overall prevalence of hypertension in Brazil is 28.7% (95% CI 26.2% to 31.4%) among adults [2] and 68.9% (95% CI 64.1% to 73.3%) in the population aged 60 years and older [3], and less than a third of patients have controlled blood pressure (BP). Low- and middle-income countries may even be facing a persistent increase of individuals with high BP in the next decade [1,4]. Successful attempts have been shown to increase BP control [5,6] but have not been implemented in clinical practice.

In recent years, the spectrum of interventions to increase hypertension control and reduce cardiovascular risk factors has widened as researchers seek alternatives that do not overburden the public health system [7]. The use of technologies using mobile phones and the internet to implement interventions can improve BP control, minimize health care resource use and costs [8], and reduce cardiovascular risk [7,9]. However, the effectiveness of these approaches depends on patient adherence to both types of interventions—behavioral and pharmacological [10]. Several randomized controlled trials (RCTs) have evaluated nonpharmacological interventions to reduce BP [5,6,11] and, in some studies, stimuli for lifestyle changes [12-14]. Text messaging interventions implemented in individuals with hypertension showed a small impact on BP compared to usual care [15]. In addition, similar levels of BP control have been observed with electronic monitoring and usual care [16]. Meaningful reductions in BP were observed with interventions involving frequent visits to a family doctor and adjustments of the therapeutic regimen [17], home BP monitoring [5], and home BP monitoring combined with medication titration, education, or lifestyle counseling [11]. Individuals with coronary heart disease undergoing an intervention based only on text messaging to improve lifestyle had a significant reduction of cardiovascular risk factors [18]; no clear-cut results were observed with an intervention based on text messages to improve medication adherence [19].

Innovative technologies can be used to achieve BP reduction, but it remains unknown if interventions should be focused only on hypertension control or should address lifestyle as well. Therefore, the purpose of this study is to compare the effectiveness of 3 strategies to reduce systolic BP assessed by ambulatory BP monitoring and improve lifestyle in comparison to the usual care of patients with hypertension (usual clinical treatment [UCT], control group). Our hypothesis is that participants assigned to active interventions will achieve greater BP reduction than those in the control group. The intervention by text messaging (TELEMEV) is a stimulus for adoption of a healthy lifestyle that may reduces BP, while telemonitoring of BP (TELEM) can enhance adherence to antihypertensive medication and stimulate healthy lifestyle. In addition, we hypothesized that participants who receive the combined intervention (TELEM+TELEMEV) will obtain greater reduction in BP than those submitted to individual interventions.

Methods

Study Design

This is a factorial RCT (Figure 1) of effectiveness of the use of technologies—mobile phones and BP monitoring—to reduce systolic BP and change lifestyle. Figure 2 shows that participants are randomly allocated to 1 of 4 groups: telemonitoring BP (TELEM), telemonitoring messages (TELEMEV), telemonitoring BP plus telemonitoring messages (TELEM+TELEMEV), or UCT, with an allocation ratio of 1:1:2:1.

Figure 1. Factorial design of the trial showing the groups. TELEM: telemonitoring of blood pressure; TELEMEV: telemonitoring by text message; UCT: usual clinical treatment.

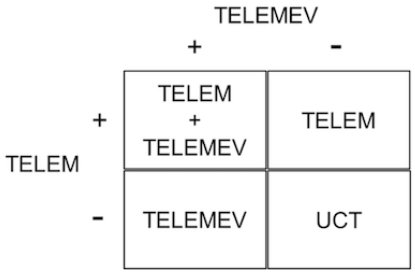


Figure 2. Overall design of the trial. ABPM: Ambulatory Blood Pressure Monitoring; BP: blood pressure; TELEM: telemonitoring of blood pressure; TELEM: telemonitoring by text message.

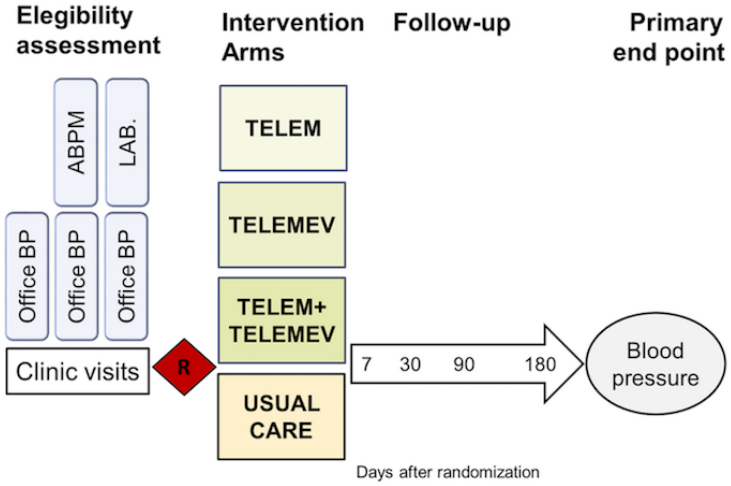
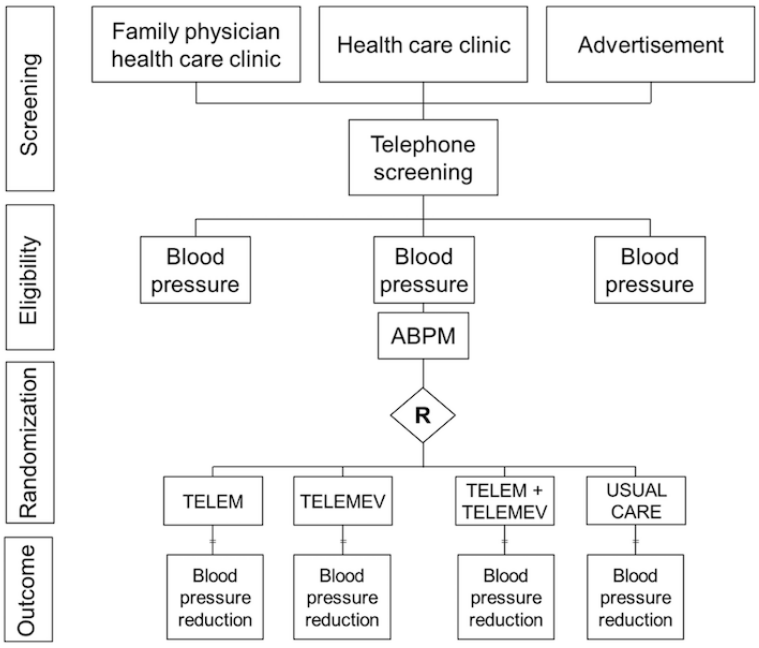


Figure 3. Study flowchart. usual clinical treatment. TELEM: telemonitoring of blood pressure; TELEMEV: telemonitoring by text message.



Study Participants

Participants are recruited from primary care clinics face to face or by phone call to screen for eligibility or online advertisement. Figure 3 shows the screening of potential participants performed in 2 clinics, a Family Health Strategy and a Basic Health Care Unit. Eligible participants must be aged 30 to 75 years, have hypertension, be undergoing treatment with up to 2 medications for lowering BP, and possess a mobile phone with internet access.

The choice of antihypertensive medications is made prior to the trial at the discretion of the attending physician, and no titration of medications is made during the trial. Office standardized BP

measurement is evaluated 4 times at the screening visit and 3 times in each eligibility visit. The first BP measurements are discarded, and an average systolic BP of ≥135 or diastolic BP of ≥85 mm Hg is required to be eligible, as well as systolic BP of ≥130 or diastolic BP ≥80 mm Hg in 24-hour ambulatory BP monitoring.

Participants with severe hypertension (systolic BP of ≥180 or diastolic BP of ≥110 mm Hg), life-threatening conditions, low life expectancy, other indications for antihypertensive medication, major cardiovascular event (acute myocardial infarction, stroke) in the last 6 months, diagnosis of secondary hypertension, participants from another RCT in the last 6 months, pregnant or lactating women, or those unable to understand the interventions are excluded. Data collection is performed at a clinical research center, Hospital de Clinicas de Porto Alegre, in southern Brazil. Automated office BP is also performed 6 times at each eligibility visit [20].

Interventions

Participants in the 4 groups receive an illustrated booklet with recommendations for a healthy lifestyle and are required to adhere to the BP-lowering medications. In addition, participants who receive the active interventions are scheduled for an individual personalized session in which the booklet information is explained and specific recommendations are highlighted. The 4 arms are as follows:

- TELEM group: participants receive an automatic oscillometric device to measure BP 5 days a week and at least 1 day on the weekend. Participants are trained to use the monitor and instructed to perform 4 measurements per day (2 in the morning and 2 in the evening) using a standardized technique. Measurements are captured from the BP monitor by software developed for the study that also sends the BP measurements to the study coordination center. The software is adapted according to the participant's mobile phone brand and iOS or Android version. After BP measurements are sent to the data center, participants receive a prompt on the mobile phone with information about the value. At the end of the trial, participants will return the BP monitor.
- TELEMEV group: participants receive personalized, standardized text messages to stimulate lifestyle changes and adhere to BP-lowering medication. Messages focus on the adoption of dietary approaches to stop hypertension (DASH)-type diet, sodium restriction, reduction of alcohol intake, increase of physical activity, weight loss or control, and daily intake of BP-lowering medications. These messages are sent to mobile phones on 4 random business days at random business hours using software developed for the study. There is no contact other than the messages on the mobile phone. At the end of the trial, participants have no further access to the messages.
- TELEM-TELEMEV group: participants receive both interventions, telemonitoring of BP plus telemonitoring messages, as previously described.
- UCT: participants of the control group start the trial already on antihypertensive treatment, chosen at the discretion of the attending physician. At randomization, they receive a brief counseling about healthy lifestyle choices using the information in the booklet. Participants will not receive any technological tools to stimulate BP control or lifestyle modification.

Outcomes and Their Assessment

Primary outcome is 24-hour systolic BP measured using ambulatory BP monitoring with the Ambulo ABP 2400 (Mortara Instrument) or Spacelabs 90207 (Spacelabs Healthcare) programmed to take measurements every 15 minutes from 0700 to 2300 hours and every 20 min from 2300 to 0700 hours. Office BP is assessed using an automatic oscillometric device (Omron HBP-1100 or HEM-705 CPN, Omron Healthcare Inc), and the average of 4 out of 6 measurements is used. Table 1 shows primary and secondary outcomes and their operational definitions.

Randomization and Allocation Concealment

A computer-generated sequence was created in the random allocation software [22], which is used to randomly assign participants to 1 of 4 groups using permuted random block sizes of 4 and 8. The randomization sequence was generated prior to the trial initiation and is kept in the Research Electronic Data Capture software, which releases the allocated group only after completion of the enrollment. Just after completion of the enrollment of a participant, the randomized group is released, preventing the research team from anticipating to which arm the next participant will be allocated. Follow-up visits are scheduled for 7, 30, 90, and 180 days from randomization. At the 7-day visit, participants in the intervention groups can address any problems with image capture or text messages. The protocol was registered in the Plataforma Brasil (CAAE: 31423214000005327), a condition to be submitted to the Ethics Committee. It was approved by the Ethics Committee of the Hospital de Clinicas de Porto Alegre (GPPG number 16-0187), which is accredited by the Office of Human Research Protections as an institutional review board. After the institutional approval, the protocol was registered with ClinicalTrials.gov [NCT03005470]. A written informed consent is obtained from all participants according to the principles expressed in the Declaration of Helsinki. Potentially eligible participants will be evaluated in 3 consecutive clinical visits, held in the morning, in order to confirm eligibility criteria.

Table 1. Description of clinical and laboratory outcomes and their definitions.

Outcomes and definitions[a]	Primary outcome	Secondary outcomes
Blood pressure		
Reduction in 24-hour systolic blood pressure in ambulatory blood pressure monitoring	X	
Reduction in 24-hour diastolic blood pressure in ambulatory blood pressure monitoring		X
Reduction in daytime systolic blood pressure		X
Reduction in nighttime systolic blood pressure		X
Office BP control (<130/80 mm Hg) [21]		X
Sodium restriction		
Reduction in sodium urinary excretion (urinary spot)		X
Healthy diet		
Increase in reported dietary intake (24-hour recall of food groups)		X
Alcohol intake		
Reduction of reported intake (grams of ethanol per day)		X
Physical activity		
Increase in average steps taken during 7 days (pedometer counting)		X
Weight loss		
Reduction of at least 3 kg and average reduction		X

[a]Reduction or increase is calculated based on baseline and end of trial assessments.

Table 2. Sample size calculations based on a previous trial [5] and additional simulations maintaining constant 80% power and 95% confidence interval.

Intervention-to-control ratio	Average reduction in the intervention group, mm Hg (SD)	Average reduction in the control group, mm Hg (SD)	Calculated sample size per group	Total sample size
1:1:1:1	8.8 (13.1)	3.4 (11.6)	31	124
1:1:1:1	7.8 (13.1)	3.4 (11.6)	39	156
1:1:1:1	6.8 (13.1)	3.4 (11.6)	51	204
1:1:1:2	8.8 (13.1)	3.4 (11.6)	44/22	132
1:1:1:2	7.8 (13.1)	3.4 (11.6)	56/28	168
1:1:1:2	6.8 (13.1)	3.4 (11.6)	74/37	222

Assessments During the Trial

The presence of risk factors associated with raised BP and cardiovascular risk are determined using standardized questionnaires in face-to-face interviews performed by staff members with undergraduate degrees in nutrition, biomedicine, or biology. Evaluations are performed at the beginning and end of the study using standardized interviews on prior morbidity, drug use, eating habits, and lifestyle. At the clinic, measurements are taken of weight; height; waist, hip, and neck circumferences; estimated body composition (bioelectrical impedance analysis); electrocardiography; retinography; and laboratory evaluation of cholesterol and fractions, triglycerides, fasting glucose, glycated hemoglobin A_{1c}, creatinine, potassium, C-reactive protein, and urinary sodium. At home, measurements are taken of capillary glucose (before breakfast and dinner for 3 days; Accu-Chek glucose meter, Roche Diabetes Care Inc) and step count (Omron HJ-112 digital pocket pedometer, Omron Healthcare Inc) during the waking hours for 7 days. Participants have BP recorded in the office using an automatic oscillometric device and at home using a Spacelabs 90207 monitor (Spacelabs Healthcare).

In addition, participants are instructed not to change doses or type of antihypertensive medication during the trial.

Sample Size Calculation and Statistical Analysis

The sample size calculation is based on results from a prior RCT with a factorial design [5]. Table 2 shows simulations for sample size calculations maintaining constant 80% power and 95% confidence interval. The largest sample size was obtained for a BP reduction of 6.8 [SD 13.1] mm Hg on 24-hour systolic BP in the intervention group compared to 3.4 [SD 11.6] mm Hg in the usual care treatment. Therefore, a sample of at least 222 participants is necessary to test our hypothesis.

Trial results will be analyzed using the intention-to-treat approach. The effectiveness of the active interventions will be tested in comparison to the control group. A pooled analysis of the differences between the active interventions versus control will be performed if there is no interaction. For continuous

variables, the assumptions to use *t* tests will be verified using the Shapiro-Wilks test (for normal distribution) and the Levene test (for homogeneity of variance), and equal variances are assumed. Therefore, baseline characteristics will be analyzed using the *t* test for independent samples and chi-square test for categorical variables. Generalized estimating equations models will used to analyze the group, time, and time × group differences. The relative risk will be used to determine the corresponding relative risk reduction. $P<.05$ will be considered statistically significant, and $.05<P<.15$ will be considered a trend toward association.

Results

This RCT was funded by two Brazilian agencies, and the results can be used to redefine public health policies. Data collection is ongoing and results are expected in early 2019. A 24-hour reduction in systolic BP of approximately 8.8 mm Hg is anticipated for participants in the electronic BP monitoring group with a similar effect in the text messaging group, against 3.4 mm Hg reduction in the usual care group. This reduction is clinically relevant and capable of impacting cardiovascular mortality. The two active interventions (TELEM and TELEMEV) are likely to provide equivalent benefits and, in this scenario, would be favorable to usual care in the public health system. Text messages seems to be more easily implemented at a lower cost.

Discussion

Lowering Blood Pressure

Hypertension is an inexorable and progressive condition that has deleterious effects on the heart, brain, and vascular system. Reducing BP and increasing control of hypertension are the main targets of interventions. However, if possible, the best intervention should be that which doesn't require additional BP-lowering medications. Thus, any intervention capable of lowering BP or increasing BP control and, at the same time, attenuating other cardiovascular risk factors could represent an advantageous step in treatment.

This trial is the first to comprehensively compare two strategies for reducing BP and risk factors in cardiovascular disease. Results from previous trials have indicated the potential beneficial impact of self-monitoring programs [23], home blood pressure monitoring [5], and text messages [24], but these interventions have not been compared or assessed regarding other cardiovascular risk factors. The sample size, although larger than other trials, might be a limitation to test the secondary hypothesis.

Conclusions

The evaluation of different health interventions allows us to select the most effective and lowest cost treatment to implement in clinical practice.

Acknowledgments

This work is supported by grants from the National Council for Scientific and Technological Development (CNPq; Ref: 457469/2013-7), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (Ref: 2274-2551/14-9), Funding of Incentive to Research, Hospital de Clinicas de Porto Alegre, and fellowships from the Coordination for the Improvement of Higher Education Personnel (CNdD, GPS) and CNPq (SCF, FDF). We would like to thank Igor Guazzelli Costa da Costa and Thales Alcantara Rocha, computer science undergraduate students, for their assistance.

Authors' Contributions

SCF, EH, CNdD, LBM, MRG, and FDF conceived and designed the experiment. CNdD, GPS, CMC, FDF, and SCF performed the experiment. SCF, EH, CNdD, LBM, and FDF analyzed the data. SCF, GPS, MRG, CMC, LBM, and FDF wrote the paper.

Conflicts of Interest

None declared.

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Abbreviations

BP: blood pressure
CNPq: National Council for Scientific and Technological Development
RCT: randomized controlled trial
TELEM: telemonitoring of blood pressure
TELEMEV: telemonitoring by text message
UCT: usual clinical treatment

Edited by G Eysenbach; submitted 11.12.17; peer-reviewed by S Omboni, B McKinstry; comments to author 25.01.18; revised version received 12.04.18; accepted 22.04.18; published 07.08.18.

Please cite as:
Fuchs SC, Harzheim E, Iochpe C, David CND, Gonçalves MR, Sesin GP, Costa CM, Moreira LB, Fuchs FD
Technologies for Innovative Monitoring to Reduce Blood Pressure and Change Lifestyle Using Mobile Phones in Adult and Elderly Populations (TIM Study): Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2018;7(8):e169
URL: http://www.researchprotocols.org/2018/8/e169/
doi:10.2196/resprot.9619
PMID:30087093

Protocol

Internet-Based Universal Prevention for Students and Parents to Prevent Alcohol and Cannabis Use Among Adolescents: Protocol for the Randomized Controlled Trial of Climate Schools Plus

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Abstract

Background: Early initiation of alcohol and cannabis use markedly increases the risk of harms associated with use, including the development of substance use and mental health disorders. To interrupt this trajectory, effective prevention during the adolescent period is critical. Despite evidence showing that parents can play a critical role in delaying substance use initiation, the majority of prevention programs focus on adolescents only. Accordingly, the *Climate Schools Plus* (CSP) program was developed to address this gap.

Objective: This paper outlines the protocol for a cluster randomized controlled trial (RCT) of the CSP program, a novel internet-based program for parents and students to prevent adolescent substance use and related harms. The CSP program builds on the success of the *Climate Schools* student programs, with the addition of a newly developed parenting component, which allows parents to access the internet-based content to equip them with knowledge and skills to help prevent substance use in their adolescents.

Methods: A cluster RCT is being conducted with year 8 students (aged 12-14 years) and their parents from 12 Australian secondary schools between 2018 and 2020. Using blocked randomization, schools are assigned to one of the two groups to receive either the CSP program (intervention) or health education as usual (control). The primary outcomes of the trial will be any student alcohol use (≥1 standard alcoholic drink/s) and any student drinking to excess (≥5 standard alcoholic drinks). Secondary outcomes will include alcohol- and cannabis-related knowledge, alcohol use-related harms, frequency of alcohol consumption, frequency of drinking to excess, student cannabis use, parents' self-efficacy to stop their children using alcohol, parental supply of alcohol, and parent-adolescent communication. All students and their parents will complete assessments on three occasions—baseline and 12 and 24 months postbaseline. In addition, students and parents in the intervention group will be asked to complete program evaluations on two occasions—immediately following the year 8 program and immediately following the year 9 program.

Results: Analyses will be conducted using multilevel, mixed-effects models within an intention-to-treat framework. It is expected that students in the intervention group will have less uptake and excessive use of alcohol compared with the students in the control group.

Conclusions: This study will provide the first evaluation of a combined internet-based program for students and their parents to prevent alcohol and cannabis use.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12618000153213; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374178 (Archived by WebCite at http://www.webcitation.org/71E0prqfQ)

Registered Report Identifier: RR1-10.2196/10849

(JMIR Res Protoc 2018;7(8):e10849) doi:10.2196/10849

KEYWORDS

alcohol; Australia; cannabis; parents; prevention; school; internet-based intervention

Introduction

Alcohol and cannabis are the most commonly used licit and illicit drugs in Australia and are associated with substantial socioeconomic costs [1-4]. The initiation of substance use begins during adolescence, and early initiation markedly increases the risk of harms from use and subsequently developing substance use disorders [5]. To interrupt this trajectory, effective prevention during the adolescent period is critical. Traditional approaches to substance use prevention have focused on adolescents only; however, recent evidence suggests that expanding student interventions to include parenting components could markedly increase prevention effects [6-8]. This is because parents are key agents of adolescent socialization, especially in the initiation and development of substance use [9-13], and parenting interventions have been identified as critical components of effective substance use prevention programs [6,9,13,14]. Moreover, adolescent substance use is an area of substantial concern for parents, who generally want to be engaged in substance use harm prevention [15]. Parents also report that they actively seek information about parenting and adolescent substance use; however, most parents are not confident in their ability to stop their child from becoming drunk [16].

Despite the importance of including parents in prevention efforts, relatively few substance use prevention programs have involved both students and parents, and the programs developed have faced numerous challenges during their implementation (eg, high attrition rates, lack of engagement, and lack of sustainability [6,17]). Moreover, no substance use prevention programs that adopt an internet-based delivery approach have involved both parents and students, despite the potential for internet-based delivery to overcome some of the challenges encountered in the implementation and sustainability of prevention programs [6,17]. Therefore, the *Climate Schools Plus* (CSP) program was developed to address this gap and meet the need for a sustainable, evidenced-based student and parent prevention program. Building on the effective internet-based *Climate Schools* drug prevention programs for students [18-21], the CSP program combines the effective *Climate Schools: Alcohol and Cannabis* course for students aged 12-14 years [21-24] with a newly developed parent component [16].

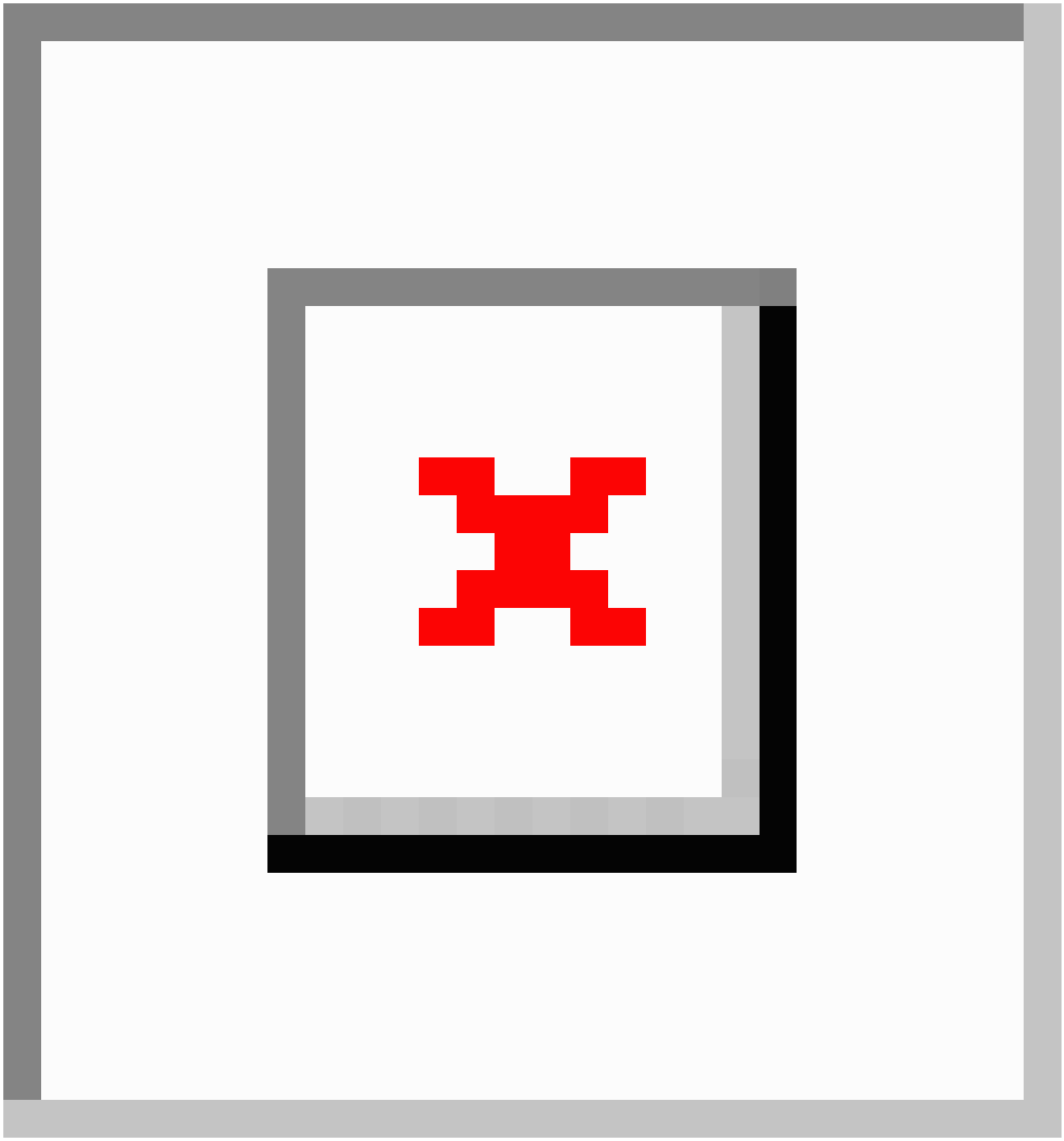
The course is an internet-based universal prevention program delivered to all students regardless of their level of risk and is based on a social influence approach to prevention [22]. The social influence approach has been found to be the most effective approach for school-based prevention programs in decreasing alcohol and cannabis use [22,25]; this approach involves delivering accurate information about substance use, placing substance use within a normative context (ie, most students their age are not using alcohol or cannabis), and developing students' resistance skills (ie, their ability to identify sources of pressure to use substances and their ability to resist these pressures). The course covers these three components, using cartoon storylines to engage students and is delivered online to ensure high-implementation fidelity. The course consists of 12 internet-based lessons, which align with stage 5 of the Australian Health and Physical Education curriculum; it is designed to be implemented in early adolescence when youth are aged 12-14 years, before marked exposure to alcohol and cannabis occurs. The program has been trialed in two independent cluster randomized controlled trials (RCTs), which have demonstrated the effectiveness of the program in improving alcohol- and cannabis-related knowledge, reducing the uptake and harmful use of alcohol and the frequency of cannabis use up to 2 years following the intervention [18-21]. In addition, the program has been found to reduce psychological distress, moral disengagement (ie, the tendency to disengage from moral self-control and responsibility that ordinarily governs behavior, which has been associated with a range of antisocial behaviors, including heavy drug use and alcohol consumption in young people [26-30]), and truancy [22]. In light of recent evidence, which suggests that expanding universal interventions to include parenting components could markedly increase prevention effects [6], we developed the CSP program [16].

The parent component for the CSP program is based on the successful Dutch Prevention of Alcohol Use in Students (PAS) program [31-33] and was adapted for Australia in consultation with Australian parents and education and health experts [16]. The parent component of the CSP program is designed to be delivered entirely online, across the same school terms as the student *Climate Schools* program. The parent component targets modifiable parenting factors associated with adolescents' alcohol and cannabis initiation and misuse [10,34], including rule-setting, parental supply, modeling, and monitoring. The parent component comprises introductory webinars, a rule-ranking component, internet-based modules, and internet-based parent summaries of the material covered in the student program. A complete description of the parent component can be found in a development paper published by the members of the research team [16].

Currently, we are seeking to evaluate the effectiveness of the CSP program in preventing alcohol and cannabis use and increasing parents' self-efficacy to prevent their child from using these substances. Incorporating an internet-based parent component into an effective school-based student program has the potential to remarkably enhance prevention outcomes and reduce alcohol- and cannabis-related harms among adolescents.

We will determine the effectiveness of the CSP intervention by running a cluster RCT in Australian Independent and Catholic secondary schools (ACTRN12618000153213). Cluster randomization will be used to avoid contamination of the control group with the intervention groups through student and staff communication. Schools will be randomly allocated to the CSP condition or the "control" condition. Students and parents in the CSP condition will be provided access to the *Climate Schools*: *Student* component and the *Climate Schools Parenting Program*, respectively, whereas students in the control condition will receive their health education classes as usual, which covers alcohol and other drug education topics. Students and parents in both groups will complete self-report surveys at baseline and 12 and 24 months postbaseline. Figure 1 depicts the study design.

Figure 1. The *Climate Schools Plus* (CSP) intervention trial flow based on the Consolidated Standards of Reporting Trials (CONSORT) guidelines.



Methods

Participants, Interventions, and Outcomes

Participants

Study Setting and Recruitment

This study is set in Independent and Catholic secondary schools in Australia. We obtained Human Research Ethics Committee (HREC) approval to approach Independent schools (HREC 17852) and Catholic schools in two dioceses in the Greater Sydney area (reference: 201731 and 060318) and invite them to participate. In October 2017, 156 schools were approached using a variety of methods, including advertisement during the Personal Development Health and Physical Education (PDHPE) Teachers' Association Annual Conference, emails sent directly to schools or school principals, newsletter entries (ie, the Independent Secondary Schools Association and *Climate Schools* newsletters), posts on social media, and through follow-up phone calls. Parents will first be recruited to participate in the CSP study when their students bring home the parent permission form, along with a postcard containing information about the study and instructions on how to register. Then, they will also be recruited through an email sent from their school with information about the study, a link to a short, 45-second video introducing the aims of the study and instructions on how to register; this involves parents consenting for their adolescent's and their own participation. Next, to access the content of the program, parents will need to register for an account through the CSP website. Students who have received parental permission to participate in the study will be approached to register and consent during their regular PDHPE classes and will be given the opportunity to send an email to their parents, reminding them to register for the program through an "Invite Your Parent" icon on the CSP website.

Sample Size

For cluster randomization, sample size calculations were based on sample size requirements developed by Heo and Leon [35] to detect the intervention by time interactions in longitudinal cluster randomized clinical trials. This trial is powered to detect differences in the overall student sample across three time-points. Five schools, with an average of 70 students per school, are required per intervention group; this would achieve an 80% power to detect a standardized, between-group mean difference of 0.2 (P=.05) in primary outcomes at the end of the trial, with 3 measurement occasions. An effect size of 0.2 is comparable with previous trials of combined student and parent programs (effect size range: 0.2-0.3) [36]. To account for school dropouts during the trial, which we expect to be approximately 15%, we aim to recruit at least 12 schools in total. Assuming that the majority (if not all) students in the year group participate in this study (approximately 70 on average; based on participation rates found in previous school-based trials of a similar nature [18-21,23,24,37]), it will give us a total of 700 students from 10 schools at the baseline to test the effect of the intervention.

Eligibility Criteria

Eligible participants are students attending participating schools and are enrolled in year 8 in 2018 and these students' parents. These students will be 12-14 years of age at baseline and 14-16 years of age at the final assessment point. Furthermore, to be eligible to participate, students and parents must have at least intermittent internet access and basic proficiency in English.

Consent or Assent

After school principals agree to participate in the study, active consent will be sought individually from parents, students, and teachers. Parents will be asked to provide active consent for (1) their child's participation in the study and (2) their own participation. Eligible students with parental consent will be directed to the participant information statement and consent form when registering on the CSP website, and all parents will similarly be directed to their participant information statements and consent forms when registering for the first time. Conversely, students and parents in the CSP group who do not consent to participate in the research trial will still be offered access to the content of the program; however, they will not be prompted to complete assessment surveys, and no data will be collected from those individuals.

Interventions

Active Intervention (Climate Schools Plus Group)

Climate Schools Plus: Student Component

The student component of the intervention consists of the effective and validated *Climate Schools: Alcohol* and modules [18-21,23,24,37], which involve 12, 40-minute lessons aimed at reducing alcohol and cannabis use and related harms. The first 6 lessons focus specifically on alcohol and are delivered in year 8, the remaining 6 lessons focus on alcohol and cannabis and are delivered 12 months later when the students are in year 9, prior to the development of harmful patterns of alcohol and cannabis use [38]. Therefore, the *Climate Schools* lessons are designed to avoid the development of harmful use by intervening when students are aged 12-14 years. The program will be completed at school, during regularly scheduled PDHPE classes, and to access the material, teachers, parents, and students are asked to create unique confidential log-in details on the CSP study website. The first part of each *Climate Schools* lesson is in the form of an internet-based cartoon storyline completed individually by students, which imparts information about alcohol (in years 8 and 9) and cannabis (in year 9; see Figure 2 for an example of the cartoon content). The second part of each lesson consists of optional class activities delivered by the teacher, such as role-plays and group discussions, which reinforce the information in the cartoons and allow communication among students. Teachers are provided access to an internet-based teacher's manual, which contains lesson activities, implementation guidelines, links to the syllabus, and teacher summaries for each lesson.

Figure 2. Screenshot of example student cartoon. Source: Netfront Pty Ltd.

Climate Schools Plus: Parent Component

The parent component was developed in consultation with parents of Australian secondary school students and relevant experts through a large scoping survey, beta-testing, and pilot-testing of the developed program [16]. At the beginning of the study, parents will be sent an email from their school with information about the CSP program and instructions on how to register. Once parents have registered with their username, password, and unique school code, they will have access to 2 webinars (approximately 5 minutes each, at the beginning of years 8 and 9). These webinars are hosted by CC, who is a senior research fellow at the National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Mental Health and Substance Use and also a member of the research team. The webinars provide overviews of alcohol and cannabis use in adolescents and related harms and highlight the role parents can play in preventing substance use in their child. During the webinar, parents will also be encouraged to engage in the "rule-ranking" component of the program, which allows parents from the same school to rank a series of rules related to alcohol use (eg, "Any alcohol in the family home is strictly off-limits to adolescents and their friends"); this component aims to facilitate a collective understanding of alcohol prevention and the role parental rule-setting plays in prevention by facilitating agreement among parents on a shared set of rules, which they can implement on their adolescents as a group. The top 3 rules will be published after 6 weeks, and parents will be encouraged to view and implement these rules with their adolescents over the school year (see Figures 3 and 4 for example screenshots of these components).

Figure 3. Screenshot of the year 8 webinar. Source: Netfront Pty Ltd.

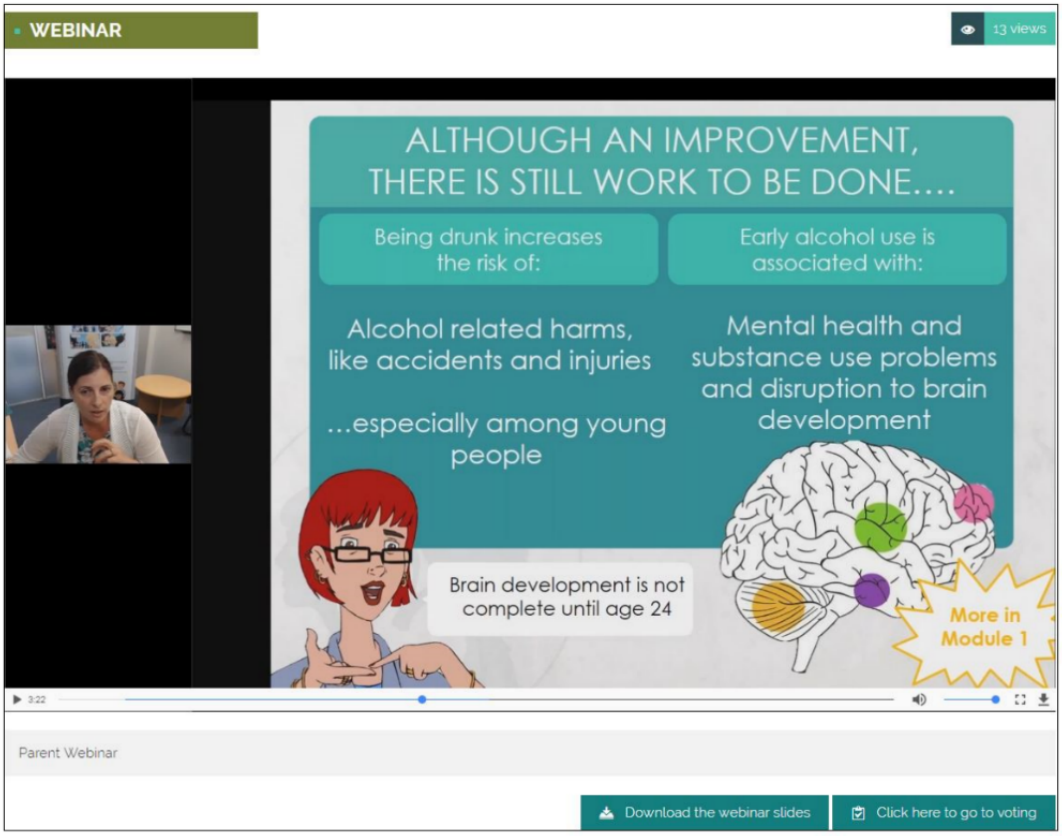
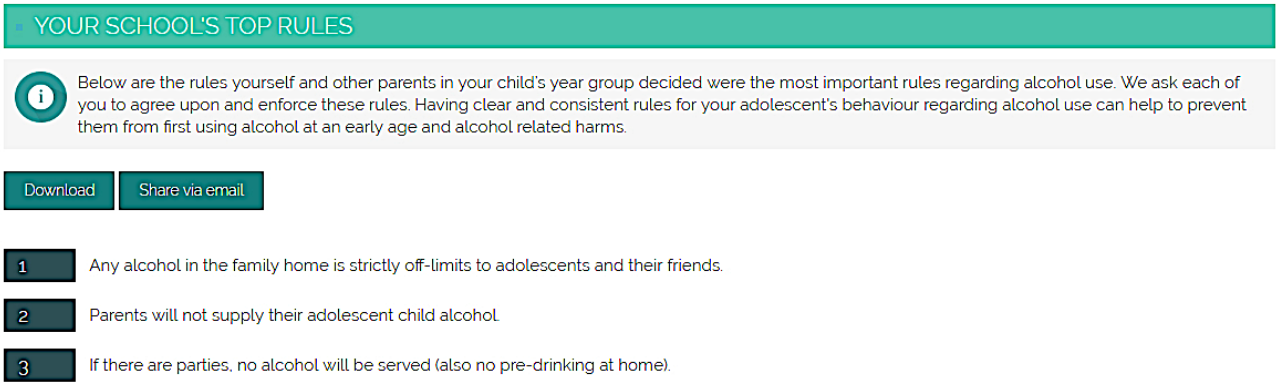


Figure 4. Screenshot of the rule-ranking component (when top 3 rules have been finalized). Source: Netfront Pty Ltd.



Parents will also have access to 6 brief internet-based modules (under 10 minutes each, 4 in year 8 and 2 in year 9) covering a range of topics about alcohol and cannabis use, as well as parenting strategies and communication tips (Textbox 1; Figure 5). Parents can access the year 8 content anytime over the course of the study, whereas the year 9 content will be locked until the beginning of 2019. Parents will be sent occasional reminders through their school and the CSP website informing them when new content is available. Parents will also be emailed weekly summaries of the content covered in each of the *Climate Schools* student lessons. Figure 6 provides further information regarding the parent intervention and how it relates to the outcomes of the study.

Control Group

Students and their parents will follow the same registration and consent process in both the control group and the CSP group and will be asked to complete the baseline questionnaire. Then, students will receive their regular drug and alcohol education during their PDHPE classes (ie, they will cover topics such as drug use, health and well-being, sources of support, personal safety, exploring risk, etc, in accordance with the student outcomes defined by the Australian National Health and Physical Education syllabus) during the study. These students will be asked to complete the 12-month follow-up questionnaire in 2019 and the final follow-up questionnaire in 2020. Similarly, parents in the control group will be asked to complete the baseline questionnaire and 12- and 24-month follow-up questionnaires over the same period.

Participant Timeline

Students and parents in the CSP group will be invited to register for the CSP program online during the first year of the study (for the majority of schools, this will be during term 1 of 2018; however, for some, it will be term 2 or 3 of 2018). Students will complete their registration and baseline survey during their regularly scheduled PDHPE classes, and their teachers will facilitate their progression through the *Climate Schools: Alcohol* lessons. During the first week of the intervention, parents register for the program and are invited to view the webinar, participate in the interactive rule-ranking component, and explore the available modules. Approximately 8 weeks after registering for the program, parents and students will be prompted to complete an evaluation of the program content online, through the CSP website. Similarly, in 2019, students will complete the 12-month follow-up questionnaire, and their teacher will facilitate their progression through the lessons. Simultaneously, parents of these students will be invited to view the second webinar, the second round of rule-ranking, and invited to explore year 9 parent modules. Students and parents will also be asked to complete an evaluation of the year 9 program through the CSP website, as they did in the previous year. Finally, in 2020, parents and students will be asked to complete the 24-month follow-up questionnaire; a reminder email will be sent to nonresponding parents and students 1 week after they are invited to complete it and another reminder 1 week later. Table 1 summarizes the student and parent involvement in the study.

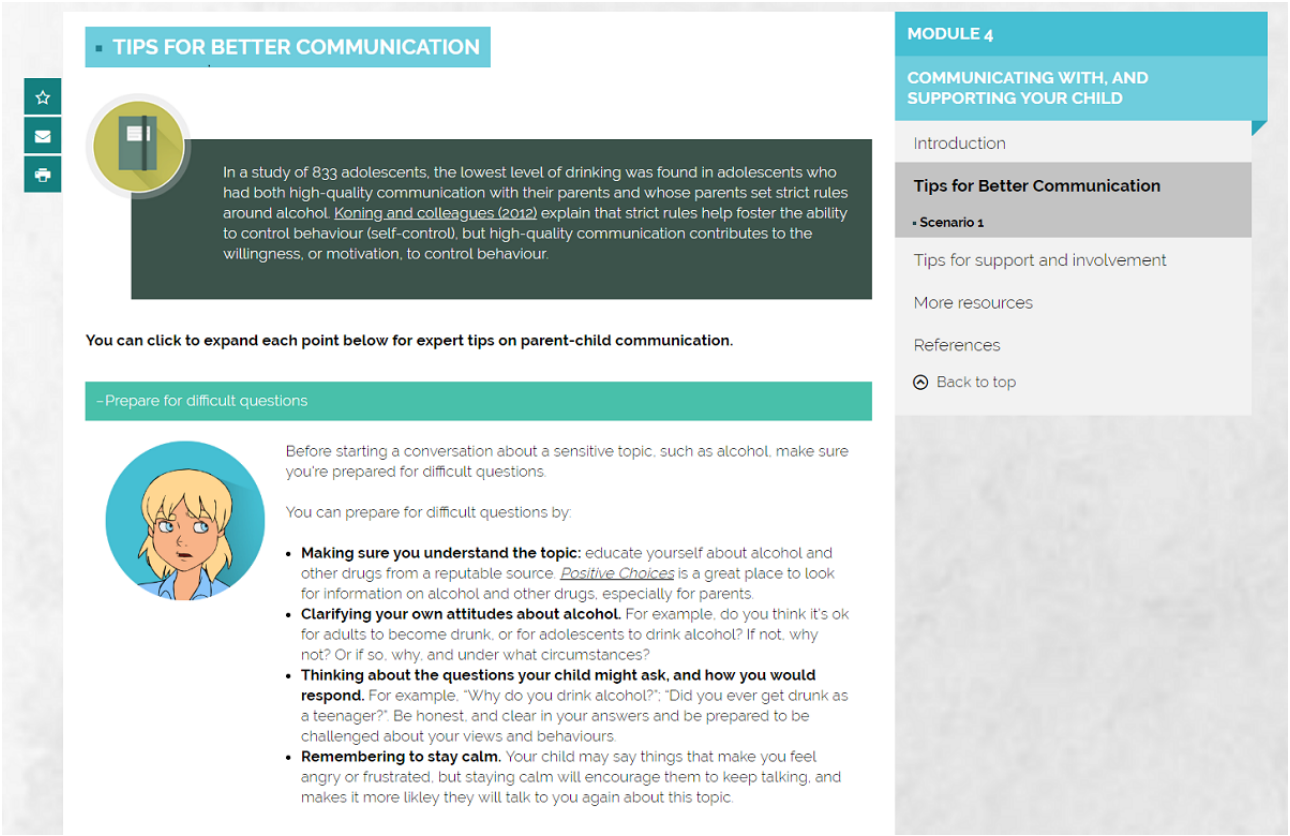
Ancillary or Posttrial Care

Upon conclusion of the trial, all schools in the control group will receive access to the same materials offered to the CSP group, free of charge.

Textbox 1. Overview of content in Climate Schools Plus parent modules.

Module 1: Prevalence, patterns, and harms of adolescent alcohol use
Module 2: Parental attitudes and rule-setting
Module 3: Parental supply and use
Module 4: Communication and involvement
Module 5: Prevalence, patterns, and harms of adolescent cannabis use
Module 6: What parents can do to prevent adolescent cannabis use

Figure 5. Screenshot of one of the parent modules (Parent Module 4, in the year 8 program). Source: Netfront Pty Ltd.



Outcomes

We selected the following primary outcomes to reflect the overall target of the intervention (ie, to prevent alcohol use and related harms in adolescents). All primary outcomes will be measured at baseline and 12- (prior to the delivery of the year 9 intervention) and 24-month follow-up, with the primary endpoint being 24 months.

Primary Outcomes

Any Alcohol Use

Any alcohol use is defined as the consumption of at least 1 full serve or standard drink of alcohol (ie, any drink containing 10 grams of alcohol). To measure this outcome, students would be provided with a chart used to illustrate a standard drink (as used in the NHMRC Australian Guidelines [39]) and asked *"Have you ever had at least one standard alcoholic drink?"* and *"Have you had at least one standard alcoholic drink in the past 12 months?"* Responses to both questions are in the form of "Yes" versus "No."

Any Drinking to Excess

Any drinking to excess is defined as the consumption of ≥5 standard drinks on a single occasion, in line with the NHMRC Australian Guidelines for risky drinking on a single occasion [39]. These alcohol use measures were used in the National Drug Strategy Household Survey [4], the Australian Secondary Students Alcohol and Drug Survey [38], and previous *Climate Schools* trials [18-21,23,24,37] and allows for comparisons between this sample and a large-scale representative group of Australians. Specifically, students would be asked *"Have you ever had 5 or more standard alcoholic drinks on one occasion?"* and *"Have you had 5 or more standard alcoholic drinks on one occasion in the past 12 months?"* Responses to both questions are in the form of "Yes" versus "No."

Secondary Outcomes

All secondary outcomes will be assessed at baseline and 12- (prior to the delivery of the year 9 intervention) and 24-month follow-up, except for cannabis-related knowledge and patterns of cannabis use, which will only be measured at 12- and 24-month follow-up.

Alcohol-Related Harms

This outcome will be assessed using the 23-item Rutgers Alcohol Problem Index, which measures the consequences of alcohol use. Students would be asked to report the consequences of their alcohol use over the past 12 months, in which higher scores indicate greater harms [40].

Parental Self-Efficacy

Data regarding parental self-efficacy will be collected by a 3-item scale measuring parents' confidence in their ability to prevent their adolescent from drinking alcohol, in which higher scores indicate a greater sense of self-efficacy [41]; this has been used and validated in the past PAS studies [42,43].

Parental Supply of Alcohol

This will be measured by a 2-question scale from the Australian Parental Supply of Alcohol Longitudinal Study (APSALS) [44] to examine the frequency and quantity of alcohol supplied by parents; higher scores indicate a higher frequency and quantity of alcohol supplied.

Figure 6. Theory of Change Logic Model for *Climate Schools Plus*.

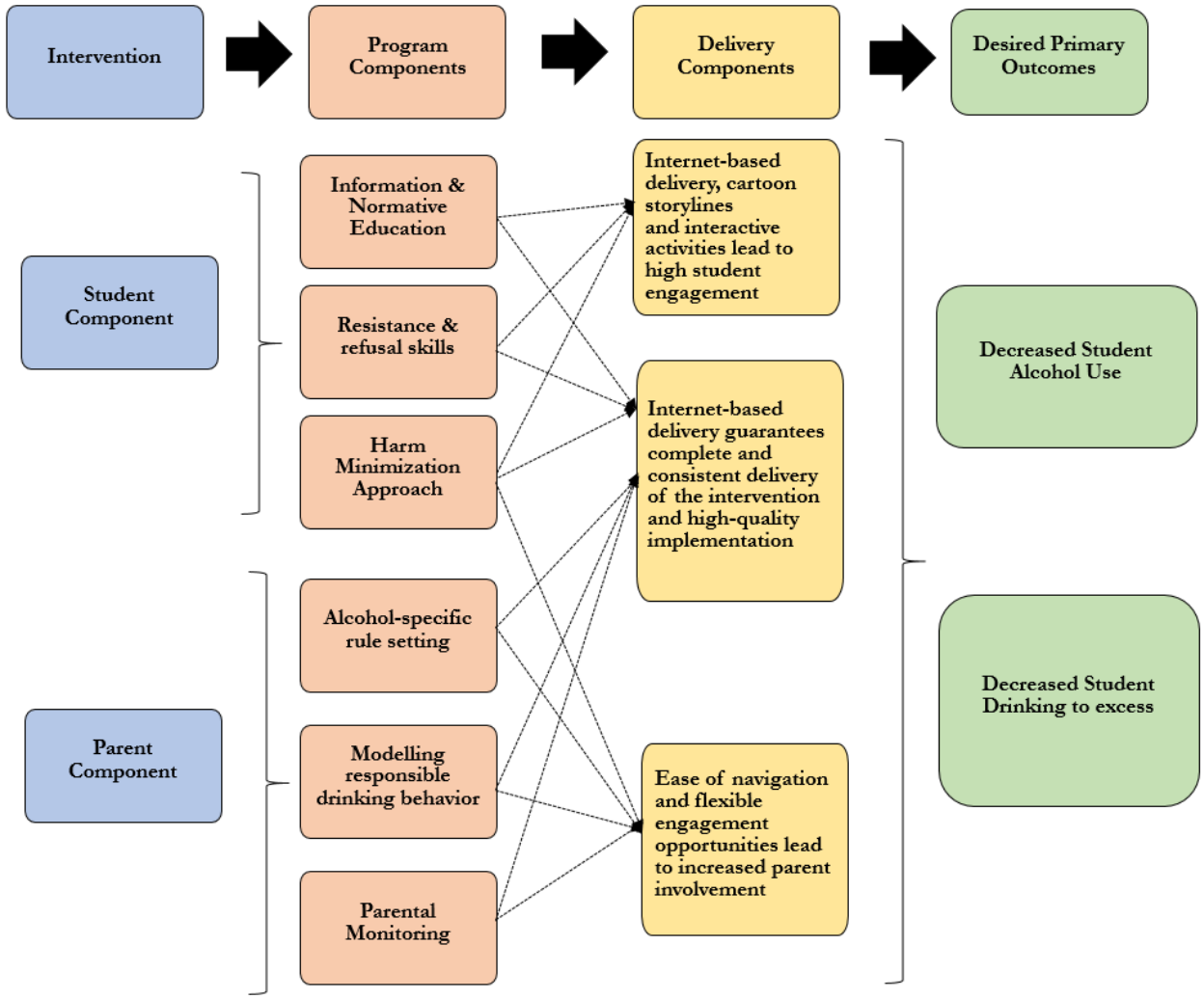


Table 1. The timeline of student and parent or guardian participation in the study.

Timeline	*Climate Schools Plus*		Control	
	Parent	Student	Parent	Student
Term 1, 2018				
Assessment	Parent survey 1: baseline	Student survey 1: baseline	Parent survey 1: baseline	Student survey 1: baseline
Intervention	Parent modules: alcohol	Year 8 student lessons: alcohol	—	—
Evaluation	Evaluation of alcohol modules	Evaluation of alcohol lessons	—	—
Term 1, 2019				
Assessment	Parent survey 2 (12-month follow-up)	Student survey 2 (12-month follow-up)	Parent survey 2 (12-month follow-up)	Student survey 2 (12-month follow-up)
Intervention	Parent modules: alcohol and cannabis	Year 9 student lessons: alcohol and cannabis	—	—
Evaluation	Evaluation of alcohol and cannabis modules	Evaluation of alcohol and cannabis lessons	—	—
Term 1, 2020				
Assessment	Parent survey 3 (24-month follow-up)	Student survey 3 (24-month follow-up)	Parent survey 3 (24-month follow-up)	Student survey 3 (24-month follow-up)

Use of Cannabis and Other Drugs

Cannabis and other drug use (tobacco or cigarettes, amphetamines, ecstasy, hallucinogens, sedatives, inhalants, or "other") will be measured by 5 questions adapted from the National Drug Strategy Household Survey [4] and the Australian Secondary Students Alcohol and Drug Survey (2014) [38], which have been used in previous *Climate Schools* trials to measure cannabis and other drug use [18-21,23,24,37]. For example, students would be asked *"Have you used cannabis in the past 12 months?,"* in which response options are "Yes" versus "No," and *"How often have you used cannabis in the past 12 months?,"* in which response options range from "Never" to "More than once a day," and higher scores indicate more frequent cannabis use. This allows for comparisons between this sample and a large-scale representative group of Australians.

Parent-Adolescent Communication

This outcome will be measured by a 6-question scale from the APSALS, examining parental knowledge and child disclosure of activities, friends, and whereabouts (eg, *"I usually know what my child is doing after school,"* with response options ranging from "Never" to "Always"; higher scores indicate a higher quality of communication). This outcome will also be measured by the 20-item Parent-Adolescent Communication Scale [45], which measures how cohesive and adaptable communication is between parents and children (eg, *"I can discuss my beliefs with my child without feeling restrained or embarrassed"* with response options ranging from "Strongly Disagree" to "Strongly Agree").

Alcohol-Related Knowledge

Alcohol-related knowledge will be assessed using a 16-item "Knowledge of Alcohol" scale originally adapted from the School Health and Alcohol Harm Reduction Project (SHAHRP) questionnaire and used in previous trials of the *Climate Schools* programs [18-21,23,24,37,46]. Students and parents would be required to answer "True" or "False" to each item (eg, *"The recommended guidelines say that it is OK for adults to have up to 2 drinks on any one day"*), and a greater proportion of correct answers indicates greater alcohol knowledge.

Cannabis-Related Knowledge

Parents' and students' knowledge about cannabis will be assessed by 16 items of the "Knowledge about Cannabis" scale adapted from the SHAHRP questionnaire, as used in previous trials of the *Climate Schools* programs [18-21,23,24,37]. Students and parents would be required to answer "True" or "False" for each item, for example, *"Using cannabis can cause people to feel anxious, depressed (sad), paranoid (suspicious) and panicky,"* and a greater proportion of correct answers indicates greater cannabis knowledge.

Frequency of Alcohol Consumption

Students will be asked to report how frequently they consumed alcohol, in terms of standard drinks; this outcome will be measured by questions that were originally adapted from the SHAHRP "Patterns of Alcohol" index and have been used in previous *Climate Schools* trials [18-21,23,24,37,46]. Students would be asked questions such as*"How often did you have a standard alcoholic drink of any kind in the past 12 months?,"* with response options ranging from "Less than monthly" to "Daily or almost daily," and higher scores indicating a higher frequency of alcohol consumption.

Frequency of Drinking to Excess

Students will be asked to report the frequency of drinking to excess (defined as having ≥5 standard drinks on a single occasion). These questions were originally adapted from the SHAHRP "Patterns of Alcohol" index and reflect those used in previous *Climate Schools* trials [18-21,23,24,37,46]. Students would be asked to report *"How often did you have 5 or more standard alcoholic drinks on one occasion in the past 12 months?"* with response options ranging from "Less than monthly" to "Daily or almost daily" and higher scores indicating a higher frequency of drinking to excess.

Additional measures include demographic information, such as gender, age, country of birth, truancy rates, and academic performance (to determine the baseline equivalence of groups), which will be assessed using questions that have been included in previous *Climate Schools* trials [18-21,23,24,37]. Students will also be asked to complete the Kessler 6 scale [47] to assess psychological distress in the past 30 days, and their quality of life will be measured by the Child Health Utility 9D scale [48]. Finally, students' self-control will be measured using a 13-item scale developed by Tangney et al [49], which was used in the PAS program [32,33,42] and which includes questions such as *"I am good at resisting temptation,"* in which students would be asked to indicate how they typically are on a 5-point scale from "Not at all" to "Very Much." These additional measures will be assessed at baseline and 12- and 24-month follow-up.

Assignment of Interventions

Allocation

Following school consent, schools have been randomly allocated to the CSP or control group by an external researcher; this process involved stratified random allocation, in which schools were divided into three mutually exclusive strata: (1) coeducational (mixed males and females) school, (2) single-sex or predominantly girls school, and (3) single-sex or predominantly boys school. The allocation was random within strata to achieve balance across intervention and control groups with respect to the number of males and females participating in the trial. Randomization was achieved using a randomization table created in StataSE, version 14, using the Stratarand procedure. The randomization sequence was computer-generated by an external biostatistician, who then informed the research team of which group each school had been allocated to.

Blinding (Masking)

It is not possible for the research team to remain blinded to the group allocation of schools during the study, given the nature of the intervention and the need to manage schools (particularly teachers as they progress through the program). However, the research team were not involved in the *allocation* of schools to the control or intervention groups, as this allocation was conducted externally, thereby removing the possibility of bias in the group allocation. Furthermore, the research team will not be in direct contact with the students or parents during the study

(with the exception of students who are absent from school on the day of assessment; a list of absent students will be provided by the school teachers and these students will be contacted through email and invited to complete subsequent follow-up assessments by the research team). As such, no bias is likely to result from the research team's knowledge of each school's group allocation.

Data Collection, Management, and Analysis

Data Collection

Students and parents will complete a self-assessment questionnaire online through the CSP website at baseline and 12- and 24-months postbaseline. The questionnaires contain scales used in previous *Climate Schools* trials, as well as specific parenting scales from the APSALS survey [44] and scales used to evaluate the effectiveness of the PAS program [42].

All measures are self-reported, as it has been found to be the most favored method of assessment for young people and has excellent discriminant [50] and predictive [51] validity [46,52]. Self-report has also previously been found to be a reliable method for assessing the frequency and quantity of adolescent alcohol use [53]. Furthermore, currently, no viable alternatives exist for data collection on alcohol use in an adolescent sample, as biological measures would not be appropriate in a sample at the early stages of alcohol use initiation [54].

Intervention Fidelity

Internet-based tracking will be used to monitor the extent to which students and parents engage with the intervention (ie, tracking the number of webinar views, the number of parents who ranked the rules, the number of parents who completed each module, the number of students who completed each lesson, etc). While teachers in the intervention group will be asked to complete a logbook as a record of how they delivered the intervention, teachers in the control group will complete a logbook detailing the type of drug and alcohol education they offered to their students over the same period.

Program Evaluation

Students, parents, and teachers in the CSP group will also be asked to complete two additional questionnaires, asking them to evaluate the intervention content that they received (ie, they will be asked how acceptable, appropriate, and enjoyable they found the program content). Teachers will be asked to indicate the likelihood that they would recommend the program to others, whereas students and parents will be asked to rate the likelihood that they would use the information and skills they learned in their own lives. Students and parents will be invited to complete these evaluation questionnaires once in 2018 after completing the *Alcohol* program and again in 2019 after completing the *Alcohol and Cannabis* program.

Retention

To facilitate the retention of students and parents in the trial, frequent communication will be maintained through email prompts generated from the CSP website, which reiterates the requirements of the study. Participants will also be offered reimbursement after completing each study questionnaire; specifically, students will be entered into a draw to win one of three Aus $500 JB Hi-Fi or Apple store vouchers at each assessment occasion, and parents will enter the draw to win one of three Aus $500 Westfield or Coles gift cards. Moreover, teachers will receive a one-off reimbursement of Aus $50 for the extra administration involved during the trial. When completing the baseline questionnaire at the beginning of the study, students and parents will be asked to enter their contact details (ie, name, address, home number, mobile number, and secondary email), which will be used solely for contacting students who are absent from school on the day of a questionnaire (absent students will be identified by their teacher, who will inform the research team of the absent students) and inviting them to complete subsequent follow-up assessments. Any data collected from students and parents who have consented but discontinue the study will be used in the analysis, in accordance with the intention-to-treat principle. The chosen statistical analysis techniques consider missing data resulting from participant discontinuation.

Statistical Analysis

In this study, primary and secondary outcomes will be analyzed in longitudinal analyses using multilevel mixed-effects regression models. The effects of highest interest are intervention × time interactions that reflect differences between intervention groups in the growth of each outcome over time. The multilevel modeling can account for the expected correlations between different observations of the same individual and between individuals in the same school [55], which would otherwise violate assumptions of independence in traditional regression models. Therefore, models used in these analyses will incorporate both random intercepts and slopes for time at the individual level and random intercepts at the school level. Mixed-effects regression approaches accommodate missing data through the maximum likelihood estimation, an approach that is superior to alternative missing data strategies such as pairwise deletion [56]. Maximum likelihood methods produce unbiased estimates when missing data are assumed to be either missing completely at random or missing at random [57].

Mixed-effects logistic regression with a logit link function will be applied when analyzing binary outcomes. A range of potential fixed effects and random effects structures will be compared using likelihood ratio tests and model fit statistics, such as the Akaike information criterion, to determine the best fitting model for each outcome. For all outcomes, between-condition effect sizes (eg, Cohen *d*) and odds ratios will be calculated along with their corresponding 95% CIs, to provide interpretable estimates of the intervention effects. All analyses will be conducted on an intention-to-treat basis, retaining and analyzing all students and parents in the groups they were originally allocated.

Planned Comparisons

The primary aim of this study is to evaluate the efficacy of the CSP program in comparison with the standard health education received by the control group. Therefore, planned comparisons for each outcome will compare students and parents in the CSP condition with students and parents in the control condition at baseline and 12- and 24-month follow-up.

Monitoring

This study will be overseen by an external biostatistician, and any adverse events will be reported to the University of New South Wales Sydney HREC to maintain the integrity of the study including the data collected, trial progress, and ethical compliance. However, given that the intervention reflects normative alcohol and cannabis education provided as part of the PDHPE curriculum, no serious adverse events are anticipated to occur during the study; therefore, a formal steering committee is not required.

Ethics and Dissemination

Research Ethics Approval

Ethics approval was obtained by the University of New South Wales Sydney HREC (HC17852), the Sydney Catholic Education Office (Ref: 201731), and Catholic Education Parramatta (Ref: 060318).

Confidentiality

Confidentiality of the collected information will be strictly maintained, and participants' data will remain anonymous. To access internet-based questionnaires and materials, students and parents will be required to register on the CSP website and once logged in, all data collected will be automatically deidentified, and the database will generate a unique ID code for each participant and the individual's data files across sessions will be linked with this unique ID code. All data collected will be in a computerized format and stored in password-protected files on university servers, accessible only to the research staff and stored separately to questionnaire data. These procedures mirror those used in previous and existing school-based prevention trials conducted by the research team (eg, The CAP Study, HREC 11274 [50]).

Dissemination Policy

The results of this study will be presented to academic peers at conferences and published in health and education peer-reviewed journals. The feedback will be provided to participating schools in the form of a deidentified report of the study's findings. This report will also be available to students and their parents at the end of the study. When publishing results of this study, no information will be published on the basis of individual cases, and all published data will reflect group data.

Trial Funding

This study is supported by funding from the Australian Government Department of Health and a Society for Mental Health Research Early Career Research Award to NCN. This study was also funded by the NHMRC through the NHMRC Centre of Research Excellence (APP1041129).

Results

This study is funded by the Australian Government Department of Health from 2016 to 2020 and by Society for Mental Health Research Early Career Research from 2015 to 2017. Enrollment of schools began in January 2018, with 8 out of 12 schools enrolled at the time of submission (enrollment is expected to be complete by October 2018). Baseline assessments are currently underway, and the first results are expected to be submitted for publication in 2019.

Discussion

Trialing Climate Schools Plus

This paper describes the design and protocol of the CSP study, the first international trial of an integrated internet-based intervention for students and parents to prevent alcohol and cannabis use. The effectiveness of the CSP program will be assessed through a cluster RCT, relative to health education as usual at 12- and 24-months postbaseline. Contamination will be avoided by the use of a cluster RCT design, in which each school forms its own cluster and is allocated to either the intervention or control group, preventing individuals at the same school being allocated to separate conditions and thus preventing contamination between staff and students at each school. We aim to ascertain whether a combined internet-based approach to drug prevention can be effective in preventing alcohol use among adolescents and improving parents' self-efficacy to prevent their children from using substances.

Strengths and Limitations

To date, approaches to substance use prevention have traditionally focused on adolescents themselves, despite evidence suggesting that parents play a critical role in substance use initiation [10-13]. The CSP study addresses the need for an integrated program for both students and their parents that is potentially sustainable through internet-based facilitation. The CSP program is built on a decade of sound research, which has shown that the internet-based *Climate Schools* programs for students are effective in preventing substance use. The expansion of this model to involve parents has the potential to improve prevention effects and provides a sustainable and scalable model for both students and parents.

The CSP program utilizes cartoon storylines to engage students and maintain their interest and internet-based technology to engage parents and improve ease of access to substance use prevention information, based on a successful evidence-based intervention [32,33]. Importantly, the internet-based nature of the CSP parent program (namely the on-demand webinars, modules, and parent summaries), provides parents with the flexibility to access the program material remotely at a time and location of their choice, which has the potential to improve the uptake of the program. Nonetheless, engagement and adherence are common challenges faced in trials of internet-based interventions [58,59]; therefore, this study uses a number of strategies to increase parent engagement (including frequent email communication, an "Invite Your Parent" icon displayed on students' homepage, facilitation of a parent-generated "shared" set of school-specific rules among parents, etc). All of these engagement strategies are sustainable if the program were to be delivered outside of a trial setting. Importantly, the detailed measurement of internet-based engagement and interaction with the program will provide important information about the feasibility of engaging parents in internet-based substance use prevention trials in the future.

A potential limitation of this study is the use of self-report, which could be subject to the social desirability bias. However, previous research has demonstrated that self-report measures of substance use among adolescents have yielded excellent discriminant [50] and predictive [51] validity [46,52] and have been found to be a reliable method of assessing the frequency and quantity of adolescent alcohol use [53]. In addition, researchers will use strategies to maximize the accuracy of self-report, which have been successful in previous school-based trials [18-21,23,24,37,46]; these strategies include blind administration of any assessments within schools and a strong emphasis on anonymity and confidentiality.

Attrition is another potential limitation to this study, which could result from students not being present on the day of assessments or not providing correct or complete contact details to allow the research team to link their responses over time. However, missing data are likely to be at random, and the chosen data analytic techniques (mixed-effects regression modeling) use all available data, thus reducing the bias brought about by participant attrition.

The school sample used in this study (ie, Independent and Catholic school types) may limit the generalizability of the findings to the broader population. However, we do not expect this factor to markedly impact the outcomes of the trial, as previous research has found that the consumption and frequency of cannabis use within independent (nongovernment) schools was comparable to the larger population of young people of the same age [18,60], suggesting that the consumption and frequency of substance use is comparable between government and nongovernment school types. Furthermore, the research team aimed to recruit a range of schools from various geographic regions for the study and used a stratified randomization scheme when allocating schools to conditions to improve the generalizability of the findings.

An additional limitation of this study involves the need to obtain active consent from participants, as this might introduce selection bias. We aim to overcome this risk of selection bias with a robust study design. As this is an RCT, both participants in the intervention condition and control condition will volunteer to participate; therefore, the impact of volunteering is likely to be spread evenly across the two conditions. Although active or voluntary consent procedures can introduce selection bias [61], previous studies have found no differences in alcohol or illicit drug use among students with passive or active consent [62]. Moreover, we aim to minimize the chance of selection bias by offering support for participants, to ensure their understanding of the consent form and what is required if they participate in the study (ie, consent forms will be offered in both electronic and hard-copy forms, and if required, the form can be translated into the preferred language of the participants). Ideally, passive consent procedures would be used to maximize the number of participants taking part in the trial; however, ethical restrictions meant that we were required to use active consent procedures in this study. As such, future research would benefit from the use of passive consent procedures to reduce the impact of selection bias on the outcomes in the study.

Conclusions

The CSP program was developed to address an unmet need for an integrated, internet-based program for students and parents to prevent alcohol and cannabis use. The CSP program fits within the school PDHPE curriculum and overcomes barriers to the implementation through online delivery, making it scalable to meet the needs of students and parents across Australia. If proven to be effective, this comprehensive program could be implemented widely, as part of a national strategy to significantly reduce the burden of disease, social costs, and disability associated with early substance use in adolescents.

Acknowledgments

This study is supported by funding from the Australian Government Department of Health and a Society for Mental Health Research Early Career Research Award to NCN. This study was also funded by the NHMRC through the NHMRC Centre of Research Excellence (APP1041129).

Conflicts of Interest

MT and NCN are two of the developers on the *Climate Schools* student program in Australia, which is distributed on a cost-recovery basis through Climate Schools Pty Ltd. The other authors declare that they have no competing interests.

Multimedia Appendix 1

Peer-reviewer report – Society for Mental Health Research.

[PDF File (Adobe PDF File), 100KB - resprot_v7i8e10849_app1.pdf]

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Abbreviations

APSALS: Australian Parental Supply of Alcohol Longitudinal Study
CSP: *Climate Schools Plus*
HREC: Human Research Ethics Committee
NHMRC: National Health and Medical Research Council
PAS: Prevention of Alcohol Use in Students
PDHPE: Personal Development Health and Physical Education
RCT: randomized controlled trial
SHAHRP: School Health and Alcohol Harm Reduction Project

Edited by G Eysenbach; submitted 23.04.18; peer-reviewed by N Lee, M Yap, S Gandhi; comments to author 06.06.18; revised version received 20.06.18; accepted 21.06.18; published 17.08.18.

Please cite as:
Newton NC, Chapman C, Slade T, Conroy C, Thornton L, Champion KE, Stapinski L, Koning I, Teesson M
Internet-Based Universal Prevention for Students and Parents to Prevent Alcohol and Cannabis Use Among Adolescents: Protocol for the Randomized Controlled Trial of Climate Schools Plus
JMIR Res Protoc 2018;7(8):e10849
URL: http://www.researchprotocols.org/2018/8/e10849/
doi:10.2196/10849
PMID:30120084

Protocol

A Co-Designed, Culturally-Tailored mHealth Tool to Support Healthy Lifestyles in M ori and Pasifika Communities in New Zealand: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: New Zealand urgently requires scalable, effective, behavior change programs to support healthy lifestyles that are tailored to the needs and lived contexts of Māori and Pasifika communities.

Objective: The primary objective of this study is to determine the effects of a co-designed, culturally tailored, lifestyle support mHealth tool (the OL@-OR@ mobile phone app and website) on key risk factors and behaviors associated with an increased risk of noncommunicable disease (diet, physical activity, smoking, and alcohol consumption) compared with a control condition.

Methods: A 12-week, community-based, two-arm, cluster-randomized controlled trial will be conducted across New Zealand from January to December 2018. Participants (target N=1280; 64 clusters: 32 Māori, 32 Pasifika; 32 clusters per arm; 20 participants per cluster) will be individuals aged ≥18 years who identify with either Māori or Pasifika ethnicity, live in New Zealand, are interested in improving their health and wellbeing or making lifestyle changes, and have regular access to a mobile phone, tablet, laptop, or computer and to the internet. Clusters will be identified by community coordinators and randomly assigned (1:1 ratio) to either the full OL@-OR@ tool or a control version of the app (data collection only plus a weekly notification), stratified by geographic location (Auckland or Waikato) for Pasifika clusters and by region (rural, urban, or provincial) for Māori clusters. All participants will provide self-reported data at baseline and at 4- and 12-weeks postrandomization. The primary outcome is adherence to healthy lifestyle behaviors measured using a self-reported composite health behavior score at 12 weeks that assesses smoking behavior, fruit and vegetable intake, alcohol intake, and physical activity. Secondary outcomes include self-reported body weight, holistic health and wellbeing status, medication use, and recorded engagement with the OL@-OR@ tool.

Results: Trial recruitment opened in January 2018 and will close in July 2018. Trial findings are expected to be available early in 2019.

Conclusions: Currently, there are no scalable, evidence-based tools to support Māori or Pasifika individuals who want to improve their eating habits, lose weight, or be more active. This wait-list controlled, cluster-randomized trial will assess the effectiveness of a co-designed, culturally tailored mHealth tool in supporting healthy lifestyles.

Trial Registration: Australia New Zealand Clinical Trials Register ACTRN12617001484336; http://www.ANZCTR.org.au/ACTRN12617001484336.aspx (Archived by WebCite at http://www.webcitation.org/71DX9BsJb)

Registered Report Identifier: RR1-10.2196/10789

(JMIR Res Protoc 2018;7(8):e10789) doi:10.2196/10789

KEYWORDS

behavior change; randomized controlled trial; co-design; mHealth; health behavior; noncommunicable diseases; New Zealand; Māori; Pasifika

Introduction

New Zealand is ranked third in the developed world with respect to obesity rates, with almost one in three New Zealand adults being obese (31.2%) [1]. High body mass index is now the second-ranked avoidable risk to health (after unhealthy diet) for the New Zealand population, accounting for 9.2% of total disability-adjusted life years [2]. Substantial ethnic inequalities exist, with Māori (indigenous New Zealanders; 15% of total population) and Pasifika (collective group of people representing different Pacific Island nations, predominantly from the South Pacific region; 7% of total population) adults living in New Zealand experiencing obesity rates 1.7 and 2.4 times higher than those of non-Māori and non-Pasifika adults, respectively [3].

The determinants of obesity are complex, and Māori and Pasifika are disproportionately affected by socioeconomic and dietary factors that predispose obesity and obesity-related illness [4]. Interventions designed for the general population tend to be less effective for Māori and Pasifika communities [5,6] and may contribute to increased health inequalities [7]. Culturally-tailored interventions are generally more effective [8] and have shown beneficial effects in other countries [9-12]. Nevertheless, funding pressures make it difficult to sustain resource-intensive interventions and maintain long-term health promotion activities.

The broad population penetration of mobile and wireless technologies and advancements in their app offers a potential solution. In total, 92% of New Zealanders own a mobile phone (67% own a mobile phone) [13] and 80% have internet access [14]. Further, there are no significant differences in mobile phone ownership or internet access by ethnicity or education and few differences by age (for those aged <65 years) [13]. Formative research in New Zealand indicates that the majority of Māori would be keen to use an mHealth intervention for weight loss [15], and systematic reviews indicate that mHealth interventions can lead to behavior change [16-19].

mHealth programs (ie, the usage of mobile and wireless technologies designed to achieve medical objectives) [20] have been shown to effectively help people change various health behaviors [19,21-26] and improve other secondary risk factors for cardiovascular diseases, such as blood pressure and medication adherence [27]. Nevertheless, most mHealth programs are designed with minimal input from end-users and lack tailoring to cultural needs. As a result, such interventions often have poor uptake and low rates of use by these communities and end-users [28].

The OL@-OR@ (pronounced “ola ora”) project (ACTRN12617001484336) consists of two stages: a co-design phase and a trial phase. The co-design phase focused on the development of a culturally-tailored, lifestyle support mHealth tool (mobile phone app and website) for Māori and Pasifika communities in New Zealand (conducted between June 2016 and October 2017). Subsequently, a systematic and theory-driven approach was applied to the selection of relevant culturally-tailored behavioral determinants and change techniques, informed by the co-design data gathered. The cluster-randomized trial described in this protocol was co-designed with communities to measure the impact of the OL@-OR@ mHealth tool on key preventable risk factors for noncommunicable disease, specifically diet, physical activity, smoking, and alcohol use.

Methods

Co-Design

The trial was designed using the same participatory co-design principles that underpinned the first phase of the OL@-OR@ study. An academic-community partnership has been established guided by the principles of participation and protection and aligned with New Zealand’s Treaty of Waitangi (founding document). Māori- (ie, *kaupapa*) and Pasifika-specific research approaches have been applied throughout the design of the mHealth tool and the trial [29]. Toi Tangata, a Māori health promotion provider, led the engagement process with Māori (involving communities in the Wellington and Auckland regions), and two Pasifika health providers, The Fono in Auckland and South Waikato Pacific Islands Community Services Trust in Tokoroa, led the engagement processes with their local communities. This paper focuses on the OL@-OR@ trial phase. During several *hui* (meetings) attended by Māori and Pasifika community representatives and academics, decisions were made regarding the trial design, including the community-based cluster trial design, the control condition, primary and secondary outcome measures, recruitment methods, and timelines.

Study Design

This trial protocol adheres to the SPIRIT guidelines (Multimedia Appendix 1). A two-arm, parallel, cluster-randomized controlled trial will be conducted in New Zealand between January and December 2018. The aim is to recruit 1280 participants from 64 clusters (32 Māori, 32 Pasifika); 32 clusters per arm (16 Māori, 16 Pasifika); 20 participants per cluster.

Eligibility Criteria

The clusters consist of Māori or Pasifika groups or communities identified by the community partners (Multimedia Appendix 2). A cluster was defined as any distinct location or setting in New Zealand where likeminded people or those with shared interests congregate, including a church, *marae* (meeting grounds), school, workplace, sports club, or community group. Individual participants are eligible if they are a member of a participating cluster; reside in New Zealand; are aged ≥18 years; have regular access to a mobile phone, tablet, laptop, or computer; have regular access to internet (at least once a week); are able to provide written consent (e-consent); and have an email address or are prepared to create an email account. Although people within clusters may self-identify as both Māori and Pasifika, for the purposes of the analysis, they will be recorded as Māori if they are part of a Māori cluster and as Pasifika if they are part of a Pasifika cluster.

Recruitment

Recruitment will be community-led, that is, Māori and Pasifika community coordinators will identify eligible clusters and approach a potential leader within these clusters. Once initial contact has been made with the identified cluster leaders, they will be given information on what is required to be involved with the study, including outlining the process of being randomized to control or intervention conditions. Cluster leaders will then provide informed consent for participation of their group or community in the study. The next step will be for the cluster leaders to begin recruiting individual participants for the trial. Specific recruitment methods will include inviting potential participants to face-to-face information sessions on the trial using social media (eg, Facebook), posters, brochures, other advertising material, and word-of-mouth and inviting established networks and groups previously formed with the community partners.

Potential participants will also be able to enroll in the trial if they are invited by an existing trial participant via the OL@-OR@ tool or if they share a phone with a trial participant who has downloaded the OL@-OR@ tool on that phone.

Study Procedures

People who are identified as part of a cluster by their local community coordinator will be invited to participate in the study. An information meeting will be organized to provide details about the study and answer any questions that potential participants may have. Potential participants will be provided with a copy of the participant information sheet and brochure. Those who are interested and meet the inclusion criteria may sign up for the study with their local community coordinator. Potential participants who indicate interest will be sent an email with study registration details. By clicking on a link in the email, they will be able to complete their registration details and provide e-consent (participants consenting using a computer-based consent form). They will then complete baseline questions online. Once all questions are complete and the terms of use are accepted, participants will be able to download the OL@-OR@ tool (intervention) or a data collection version of the app (control) on their device. If they do not have a mobile phone or tablet, participants will be able to access a Web version through a link provided. All participants will be asked to use the app (or Web version) for 12 weeks and keep the app running on their device for (at least) the whole 12-week period. At 4- and 12-weeks, Web-based follow-up assessments will take place. After 12 weeks, participants in intervention clusters can continue using the app if they wish. Participants assigned to the wait-list control condition will be able to download the full app or use the Web version once they have completed the 12-week questionnaire.

Randomization, Allocation Concealment, and Blinding

Clusters will be randomly assigned in a 1:1 ratio to either the intervention or control condition using a computer-generated randomization list prepared by the study statistician. Block randomization will be used with variable block sizes of 2 and 4, stratified by locality (Auckland or Waikato) for Pasifika clusters and by region (rural, urban, or provincial) for Māori clusters to ensure these factors are balanced across the two randomized groups. The randomization list will be concealed until the point of randomization for all clusters. Randomization codes will be kept secure in a restricted computer-based project file and will only be accessible to the project manager and project coordinator who will disclose these to community coordinators when clusters have been identified and participants have signed their agreements. Due to the nature of the intervention, it will not be possible to blind participants or research staff to the use of the different intervention conditions of full versus basic (data collection only) version of the OL@-OR@ tool. The risk of contamination between cluster arms is minimized via selection of distinct clusters located in different settings and communities around New Zealand. The OL@-OR@ system has also been designed so that it is not possible for participants in one arm of the trial (control or intervention) to invite participants in the other arm.

Study Intervention

Intervention Design

The OL@-OR@ tool is designed to help Māori and Pasifika and their *whānau* (extended family) to improve their health and wellbeing by making small positive, culturally relevant changes to their lifestyle. Co-design methods were used to capture and understand the needs of members of Māori and Pasifika communities. These methods fostered expression, reflection, and sharing and informed the development of the intervention.

Ethnic-specific models of health and wellbeing [30-33] were used to interpret the co-design data and to select relevant enablers and barriers of health behavior change, behavior change techniques, and intervention features that align with the cultural needs and wants of its users. The Theoretical Domains Framework [34] and Behavioral Change Taxonomy [35,36]

were used to map similarities and differences in identified behavioral determinants and change techniques to those confirming that the OL@-OR@ intervention aligns with evidence-based behavior change principles [37].

Feedback from community focus groups on desired content (physical activity, family, and healthy eating) and themes (holistic wellbeing, connecting, motivation and support, and health literacy) were integrated with established behavioral determinants and change techniques to create the mHealth tool content and features. The design features and proposed functions were presented using wireframes. These were taken back to communities in a continuous two-way iterative improvement process until an agreement was reached that the final wireframe design reflected community wants and needs. A cross-platform (iOS, Android, and Web-based) prototype of the app was created in-house by a team of developers using Apache Cordova and Drupal 8 platforms. The final app was released on Google Play and the App Store.

The tool supports users to set goals and specific steps to reach those goals. Users are encouraged to invite others to join them on their journey and can collect online reward tokens as they achieve their goals. The tool also provides information concerning healthy eating, physical activity, local activities, and health services. Lifestyle trackers help users to monitor their progress (see Multimedia Appendix 3 for screenshot examples of tool features). Regular culturally-tailored reminders and motivational messages (4-5 messages each week) are also sent to motivate users to reach their goals. These messages are delivered via notifications through the app and are stored in the message section of the app. At the beginning of each week, one *whakatauk*ī (motivational message) will be sent. Lifestyle messages including culturally-tailored tips on eating more healthily, doing more physical activity, reducing stress, improving sleep, and weight loss will be sent weekly. Also, any participants who report that they smoke will receive weekly messages about smoking cessation. Participants will also receive messages highlighting how to use specific features of the tool (weekly) and goal reminders at the end of each week reminding them to review or set new goals (see Multimedia Appendix 4 for examples of motivational messages).

Control Condition

Clusters assigned to the control condition will receive a basic version of the OL@-OR@ tool. This version will only collect data (baseline and 4-week and 12-week questionnaires) and provide a weekly motivational message thanking participants for partaking in the study and counting down the weeks until they receive the full OL@-OR@ tool at the end of the 12 weeks. The countdown is to help motivate those in the control group to complete the study. At the end of the study, when all assessments are completed, participants in the control clusters will be able to download the full OL@-OR@ tool to use for as long as they wish. Example screenshots from the control app can be seen in Multimedia Appendix 5.

Recompense for Involvement in the Study

To acknowledge participants' time and involvement in the study, *koha* (gift or donation) will be available for each cluster (NZ $500 per cluster of 20 participants, prorated per number of participants recruited for clusters of fewer than 20 participants). The community partners will decide the best way to provide *koha* to the communities involved (eg, provision of a voucher, cash for the community, a donation to a named charity, or purchasing of equipment for the community). Some clusters may elect to share the *koha* equally between enrolled participants.

Baseline Assessments

At baseline, data will be collected from each cluster concerning the community type (eg, a church community or a sports club), predominant ethnicity in the community, approximate number of community members, approximate number of cluster members interested in participating in the study, and cluster leader and contact details.

In addition, the following data will be collected at baseline from each study participant:

- Sociodemographic data: date of birth, gender, ethnicity, hapu (Māori subtribe) and iwi (Māori tribe) where relevant, highest education level, and annual household income.
- Anthropometric data: self-reported weight (in kilograms) and height (in centimeters).
- Health status: self-reported health condition(s) defined as being told by a doctor that they have high blood pressure, high cholesterol, diabetes, or heart disease.
- Physical activity: measured by the Godin Leisure Time Physical Activity Questionnaire [37].
- Smoking behavior: measured by 7-day point prevalence of self-reported smoking abstinence [38].
- Alcohol intake: measured by the Alcohol Use Disorders Identification Test Consumption [39].
- Fruit and vegetable consumption: measured by items used in the New Zealand Health Survey [40].
- Kava consumption: questions include "Do you consume Kava?," "How often do you consume Kava?," and "How many Kava drinks do you consume in a typical week?"
- Holistic wellbeing (for Māori participants only): Tūhononga (cultural connections), *Mauri* (life force or essence), wellbeing, whanaungatanga (family wellbeing and social connectedness) and Rangatiratanga (self-determination, motivation, and management), measured by 16 questions informed by Māori health models Te Whare Tapa Whā [30] and Te Pae Mahutonga [27] and adapted in part from the Hua Oranga Māori mental health assessment questionnaire [31]. Answers are measured on a 6-point Likert scale.
- Holistic wellbeing (for Pasifika participants only): spiritual, physical, mental, and family wellbeing measured by 10-items designed for the purpose of this study based on the Fonofale Model [33], the Ottawa Charter and Hua Oranga [32]. All answers are measured on a 5-point Likert scale.
- Pacific and Kiwi-New Zealand Heritage and Lifestyle (Pasifika participants only): Attitudes and beliefs about Pacific and Kiwi-New Zealand heritage and lifestyle measured using an 8-item cultural affiliation questionnaire [41,42]. Answer categories consist of a 5-point Likert scale.

Primary Outcome Measure

The primary outcome for the trial is participant adherence at 12-weeks to the recommended health guidelines, as defined by a self-reported composite health behavior score based on the European Prospective Investigation into Cancer-Norfolk Prospective Population Study [38] and as used in a previous trial evaluating the effectiveness of an mHealth-delivered comprehensive cardiac rehabilitation program [43]. This composite score includes: smoking (1: not currently smoking, 0: had ≥1 cigarettes in past 7 days), fruit and vegetable intake (1: ≥5 servings daily, 0: ≤4 servings daily), alcohol intake (1: ≤13 units per week, 0: ≥14 units per week), and physical activity (1: ≥14 units of moderate to vigorous activity/week, 0: ≤13 units of moderate to vigorous activity/week). Scores range from 0 to 4 based on the number of health guidelines met. Participants are classified as adherent if they score 3 or more out of 4 and nonadherent if they score 2 or less. These measures are assessed at an individual level but analyzed and reported at a cluster level (as are the secondary measures).

Secondary Outcome Measures

Secondary outcome measures will be collected at 4- and 12-week follow-up assessments via a Web-based questionnaire and include the same health behavior outcomes as those assessed at baseline (physical activity, smoking, alcohol intake, and fruit and vegetable consumption) and holistic wellbeing. At 12-week follow-up, user engagement and interaction with the mobile phone app will be quantified using an engagement index [44]. The index is an adapted version of the Web Analytics Demystified Visitor Engagement Index [45]. The original index comprised 7 subindices (click depth, loyalty, recency, interaction, feedback, brand, and duration indices). Although measuring all indices is ideal, the Web Analytics Demystified Visitor Engagement Index protocol emphasizes that the calculation can be adapted to suit the project [45]. Therefore, in line with a previous study assessing user engagement of an mHealth intervention [44], we will select relevant Web metrics to develop a composite engagement index for users of the OL@-OR@ tool. These metrics will include session duration, page views per session, and the number of push notifications. They will be used to calculate the following subindices: (1) click depth index: the number of pages participants view per session in the app, (2) loyalty index: the frequency of participants accessing the app after they commence the intervention, (3) interaction index: the number of push notifications sent through the app that are opened, (4) recency index: time lag between each session when the participant accessed the app, and (5) feedback index: self-reported 20-item measure of participant satisfaction with the app (questions relate to ease of navigation, usefulness of information, helpfulness of notifications, and satisfaction with the look of the app) [44].

The overall engagement index summarizes the subindices from date of registration to 12-week follow-up. The overall index will provide a score for each participant that measures overall engagement with the app during this period. Cutoff points will be developed based on the distribution of the total sample's index scores using tertiles. Participants will then be categorized as either poorly, moderately, or highly engaged. A summary of all assessments and the stage at which each will be measured is outlined in Table 1.

Sample Size

Recruiting 640 participants (16 clusters per arm, 32 clusters in total) will provide 80% power at a 5% level of significance (two-sided) to detect a between-group difference of 15% in the primary outcome at 12 weeks postrandomization, assuming the proportion of participants adherent to healthy lifestyle behaviors in the control group is 30% [43] and an intracluster correlation coefficient of 0.05 [46]. The inflation factor is approximately 3, that is, (1+40−1×0.05), which inflates n=160 per arm in a standard randomized controlled trial to n=480 per arm in a cluster-randomized trial under the same assumption. However, we aim to recruit 1280 participants in total from 64 clusters (32 Māori clusters and 32 Pasifika clusters). This sample size will provide 80% power for the analysis of Māori and Pasifika participants separately if our recruitment target is met.

Statistical Analyses

Baseline data collected from all participants will be summarized by treatment group, overall, and by ethnic-specific clusters (Māori and Pasifika). Information collected at the cluster level will also be reported. Continuous variables will be presented as numbers observed, means, and SDs. Categorical variables will be presented as frequencies and percentages. Since any differences between randomized groups at baseline could only have occurred by chance, no formal significance testing of baseline differences will be conducted.

The effect of the intervention will be evaluated using an intention-to-treat analysis including all clusters and participants in the group they are randomized to, regardless of whether they receive or complete that treatment. The proportion of participants who are adherent to lifestyle change (≥3 of 4 behaviors) at the end of the 12-week intervention period will be compared between the two treatment groups using generalized linear mixed models with a random cluster effect and adjusting for important baseline confounders. Missing participant data will be taken into account in the mixed model estimates by maximum likelihood, assuming they are missing at random. Similar regression analyses will be conducted on secondary outcomes using the link function appropriate to a continuous or categorical variable. Intracluster correlation coefficients will be estimated. Subgroup analysis will be conducted for Māori and Pasifika clusters separately. Statistical analysis will be performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA). All statistical tests will be two-sided at a 5% significance level.

Table 1. Schedule of enrollment, interventions, and assessments.

Time point	Enrollment (Week 0)	Allocation (Week 0)	Postrandomization (Week 4)	Close-out (Week 12)
Enrollment				
Eligibility screen	X[a]			
Informed e-consent[b]	X			
Contact details	X			
Interventions[c]				
OL@-OR@ mHealth tool		X	X	X
Wait-list control		X	X	X
Assessments				
Age, sex, ethnicity		X	X	X
Socioeconomic details		X	X	X
Contact details		X	X	X
Smoking behavior		X	X	X
Physical activity		X	X	X
Alcohol intake		X	X	X
Fruit and vegetable intake		X	X	X
Anthropometry (self-reported weight, height)		X		X
Health status		X		X
Medication use		X		X
Kava consumption		X		X
Holistic wellbeing		X		X
Pacific and New Zealand heritage and lifestyle[d]		X		X
Click depth index				X
Loyalty index				X
Interaction index				X
Recency index				X
Feedback index				X

[a]X indicates the presence of assessments required at particular time periods during the trial.

[b]Consent using a computer-based consent form.

[c]Intervetion was continuous from week 0 to week 12.

[d]Pasifika participants only.

Engagement Index

Basic descriptive data analysis will be performed on the metrics and components of the engagement index as well as the final index score [44]. To analyze the index score, cutoff points will be developed based on the distribution of the index scores of the total sample using tertiles. Participants will be categorized as either poorly, moderately, or highly engaged. Group comparisons between poorly, moderately, or highly engaged participants will be conducted using generalized linear mixed models. Additional analyses will be performed to determine the association between the index and sociodemographic characteristics of the participants including their education level, ethnicity, age, annual household income, device type (Android or iOS), and system type (app only, Web only, or app and Web).

Data Management

Data from the trial will be entered into the Drupal database at the study center (National Institute for Health Innovation, University of Auckland, New Zealand). Information about study subjects will remain confidential in keeping with the obligations set out in the Privacy Act 1993, the Health Information Privacy Code 1994 and Section 22B-221 of the Health Act 1956. Access to all study data will be restricted to research staff directly involved in conducting or monitoring the study. Confidentiality will be protected using study registration numbers, and only aggregated and deidentified data will be reported. Computerized

information will be password protected, and hard copy information (such as cluster agreements) will be kept in a locked filing cabinet under the responsibility of community coordinators. All reports from the study will be written such that no individuals can be identified. Paper records, electronic files, and source documents will be retained for 6 years from the termination date of the study, in accordance with the requirements of the Privacy Legislation and the Health (Retention of Health Information) Regulations 1996.

Ownership of Data

Individual study data will remain the property of individual study participants. The study center will have the responsibility for storage, protection, and retrieval of the study data. The University team will have the responsibility for the safe guardianship and use of the data in consultation with the wider project team. The Māori community partners will have guardianship over the data for Māori participants. Access to the data, all analyses, and dissemination of the data will be the joint responsibility of the University team and the Māori Community partners. Māori community partners will review and interpret all analyses involving Māori data and agree on key findings before dissemination.. The same principles apply to data for Pacific participants where Pacific community partners will have guardianship.

Ethical Approval and Informed Consent

Ethics approval for the trial was obtained from the Northern B Health and Disability Ethics Committee of New Zealand (17/NTB/152/AM01, approved on November 17, 2017). Ethics approval for any amendments to the study protocol will be sought prior to the implementation of the changes (information on the trial registry will be updated accordingly). Maintenance of confidentiality and compliance with the Privacy Act will be emphasized to all study participants. Study participation will be entirely voluntary, and participants may withdraw from the study at any time, without having to provide a reason, by contacting the research team. A participant information sheet and consent form will be given to participants who are identified as being part of a cluster by the local community coordinator during an information meeting. E-consent will be obtained at the time of registration once participants have had the opportunity to read the participant information sheet and ask any questions to their local community coordinator or other members of the study team. If any participants suffer harm from trial participation (which is unlikely), they should be eligible for compensation via their private health or life insurance or via New Zealand's Accident Compensation Corporation scheme.

Trial Governance

Trial governance includes a steering committee (on which all authors sit) and a trial management team who will manage the day-to-day processes of the trial, including data management. This trial does not meet two or more of the criteria required for the establishment of a Data Safety and Monitoring Committee [47].

Dissemination Policy

Results will be disseminated regardless of the magnitude or direction of treatment effect. Dissemination will include adding trial results to trial registration within 1 year of trial completion, feedback to trial participants, publication in an international journal and national and international media releases (including Māori, Pacific, and mainstream media channels) at the time of journal publication, and presentations to participating communities and relevant local, national, and international audiences (including health service funders and providers). In New Zealand, this will include but will not be limited to the Ministry of Health, District Health Boards, Māori and Pacific health provider organizations, general primary health organizations, nongovernment organizations, and health professionals. Criteria for authorship of any papers arising from the trial will be taken from the International Committee of Medical Journal Editors [48].

Extended Follow-Up of Study Participants

Longer-term follow-up (beyond the 12-week follow-up period of the trial) will be via the New Zealand Integrated Data Infrastructure (IDI) [49]. Participants will be asked if they consent to data gathered in this trial being linked to IDI using their unique national identifier to facilitate longer-term follow-up and assessment of health information that may be influenced by this study, for example, blood tests (blood glucose and cholesterol), visits to health professionals, and diabetes and heart disease medication use. IDI is a large national database containing microdata about people and households in New Zealand. Data is derived from a range of government agencies, Statistics New Zealand surveys, and nongovernment organizations. We have ethics approval to examine such data once a year for a maximum of 5 years after the study ends. All information will be anonymized and will not be linked to information that could identify participants. Written consent will be sought from study participants.

Results

Trial recruitment opened in January 2018 and will close in July 2018. Trial findings are expected to be available early in 2019.

Discussion

Most mHealth interventions are designed with minimal input from end-users and lack tailoring to specific (cultural) needs [50]. A culturally-tailored mHealth tool (mobile phone app plus website) aimed at supporting healthier lifestyles among Māori and Pasifika communities in New Zealand was co-designed by an academic and community partnership team [24]. This ground-up work informed a theory-driven approach to content development, including identification of key themes and content domains, selection of behavioral determinants and change techniques, and development of features and functionalities of the mHealth tool.

Comparable user-centered principles were applied to co-designing a community-led, cluster-randomized, wait-list controlled trial to evaluate the impact of the mHealth tool on health behavior change. As such, this project is engaging with communities in a meaningful way throughout the research process, from development to evaluation of the mHealth intervention. This approach has not only resulted in an mHealth

tool that aligns with the needs, wants, and lived (cultural) contexts of Māori and Pasifika communities but also anticipated increased engagement and empower communities to make positive lifestyle changes.

Acknowledgments

We would like to thank everyone who was involved in the study for the time and help given throughout. This includes community partners Rangimarie Mules, Leonie Matoe, and the Waiwhetu community; Janell Dymus and Te Runanga Ngati Whatua community; The Fono Trust local community; and South Waikato Pacific Islands Community Services Trust local community. From the National Institute for Health Innovation, we would like to thank the project coordinator, Jodie Schumacher, and app developers Dongho Park and Mohammad Rahman. Also, we give special thanks to Koda Web for helping us design the app.

This project is funded by the New Zealand Government Healthier Lives He Oranga Hauora National Science Challenge (HL-T1CR-E). The funder will not be involved in the design of the study and collection, analysis, and interpretation of data.

Authors' Contributions

LTM, RTF, AJ, RW, and CNM conceived the original idea for the study and sought and obtained funding. MT, SD, TF, and AH are Māori and Pasifika community partners. They recruit clusters and liaise with the cluster leaders in the study. SB, CP, M Vano, and EH are Māori and Pasifika cluster leaders. They recruit and register participants for the study. JG is the project manager responsible for the day-to-day running of the project, DG is a PhD student on this project, M Verbiest is the research fellow, and YJ is the project statistician. This paper was written by M Verbiest with input from all coauthors. CNM is the guarantor for this paper. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

SPIRIT checklist.

[PDF File (Adobe PDF File), 113KB - resprot_v7i8e10789_app1.pdf]

Multimedia Appendix 2

Trial cluster locations in New Zealand.

[PNG File, 39KB - resprot_v7i8e10789_app2.png]

Multimedia Appendix 3

Screenshots of OL@-OR@ app.

[PDF File (Adobe PDF File), 622KB - resprot_v7i8e10789_app3.pdf]

Multimedia Appendix 4

Motivational Messages.

[PDF File (Adobe PDF File), 38KB - resprot_v7i8e10789_app4.pdf]

Multimedia Appendix 5

Control App.

[PDF File (Adobe PDF File), 179KB - resprot_v7i8e10789_app5.pdf]

Multimedia Appendix 6

Peer-review report from the funding agency.

[PDF File (Adobe PDF File), 320KB - resprot_v7i8e10789_app6.pdf]

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Abbreviations

IDI: Integrated Data Infrastructure

Edited by G Eysenbach; submitted 15.04.18; peer-reviewed by S Gandhi, T Fleming; comments to author 23.05.18; revised version received 06.06.18; accepted 19.06.18; published 22.08.18.

Please cite as:
Verbiest M, Borrell S, Dalhousie S, Tupa'i-Firestone R, Funaki T, Goodwin D, Grey J, Henry A, Hughes E, Humphrey G, Jiang Y, Jull A, Pekepo C, Schumacher J, Te Morenga L, Tunks M, Vano M, Whittaker R, Ni Mhurchu C
A Co-Designed, Culturally-Tailored mHealth Tool to Support Healthy Lifestyles in Māori and Pasifika Communities in New Zealand: Protocol for a Cluster Randomized Controlled Trial
JMIR Res Protoc 2018;7(8):e10789
URL: http://www.researchprotocols.org/2018/8/e10789/
doi:10.2196/10789
PMID:30135054

Protocol

Empowering With PrEP (E-PrEP), a Peer-Led Social Media–Based Intervention to Facilitate HIV Preexposure Prophylaxis Adoption Among Young Black and Latinx Gay and Bisexual Men: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Young black and Latinx, gay, bisexual, and other men who have sex with men (YBLGBM, aged 18-29 years) have among the highest rates of new HIV infections in the United States and are not consistently reached by existing prevention interventions. Preexposure prophylaxis (PrEP), an oral antiretroviral regimen taken daily by HIV-uninfected individuals to prevent HIV acquisition, is highly efficacious in reducing HIV acquisition and could help stop the HIV epidemic in YBLGBM. Use of social media (eg, Facebook, Twitter, online dating sites) is ubiquitous among young people, providing an efficient avenue to engage YBLGBM to facilitate PrEP adoption.

Objective: Our overall goal was to develop and pilot test a theoretically grounded, social media–based, peer-led intervention to increase PrEP uptake in YBLGBM. We used diffusion of innovation and information-motivation-behavioral skills frameworks to (1) identify potential factors associated with interest in and adoption of PrEP among YBLGBM; (2) develop Empowering with PrEP (E-PrEP), a social media–based, peer-led intervention to increase PrEP uptake in YBLGBM; and (3) pilot test the feasibility and acceptability of E-PrEP, and determine its preliminary efficacy for increasing adoption of PrEP by YBLGBM. We describe the development and protocol for E-PrEP.

Methods: Using a participatory research approach, we partnered with YBLGBM intervention development partners to develop a social media–based behavioral intervention to facilitate PrEP uptake, which involved an online messaging campaign disseminated by YBLGBM peer leaders to their existing online networks. We designed the 6-week campaign to provide education about PrEP, increase motivation to use PrEP, and facilitate access to PrEP. We then conducted a cluster-randomized trial of E-PrEP compared with an attention-matched general health control condition (E-Health) among YBLGBM aged 18 to 29 years to assess E-PrEP's feasibility, acceptability, preliminary efficacy for increasing self-reported intention to use PrEP, PrEP uptake, and impact on knowledge and attitudes about PrEP at 12-week follow-up (6 weeks after the end of the online campaign).

Results: From October 2016 to March 2017, we developed, pretested, and refined E-PrEP with 6 YBLGBM intervention development partners. From May to June 2017, we recruited, enrolled, and randomly assigned 10 peer leaders (n=5 for each condition). The 10 peer leaders then recruited and enrolled 152 participants from their existing online networks (range 3-33 per peer leader), during June and July 2017. Intervention follow-up was completed after 12 weeks, in November 2017, with analyses underway.

Conclusions: We hypothesize that, compared with E-Health, participants randomly assigned to E-PrEP will be more likely to express intention to use PrEP and greater PrEP uptake, and will also show changes in potential mediators of PrEP uptake (knowledge, attitudes, stigma, and access). A Web-based biobehavioral intervention model such as E-PrEP could be rapidly scaled even with limited resources and have significant population-level impact.

Trial Registration: ClinicalTrials.gov NCT03213366; https://clinicaltrials.gov/ct2/show/NCT03213366 (Archived by WebCite at http://www.webcitation.org/71onSdcXY)

Registered Report Identifier: RR1-10.2196/11375

(JMIR Res Protoc 2018;7(8):e11375) doi:10.2196/11375

KEYWORDS

pre-exposure prophylaxis; HIV; social media interventions; HIV prevention; social network intervention; social media; social networking; telemedicine

Introduction

The Role of Social Media in HIV Prevention

Gay, bisexual, and other men who have sex with men (GBM) make up 2% to 3% of the adult population [1] and continue to account for the majority of the 40,000 new HIV infections occurring annually in the United States. HIV disparities affecting young GBM, and particularly young black and Latinx (a gender-neutral term sometimes used in lieu of Latino or Latina), gay, bisexual, and other men who have sex with men (YBLGBM), are even more pronounced. YBLGBM have some of the highest rates and incidences of HIV [2-5]. While many effective behavioral HIV prevention interventions have been developed, these programs often do not reach an estimated three-quarters of young GBM [6]. This lack of reach may be partly explained by the inability to engage YBLGBM who do not identify as gay or bisexual, or who are unlikely to present in person to lesbian, bisexual, gay, and transsexual– or HIV-affiliated settings or sexually transmitted infection clinics, where most interventions have traditionally taken place. To reduce the burden of HIV in YBLGBM, rapid development and implementation of new prevention strategies with a broader reach are urgently needed [7-10].

Preexposure prophylaxis (PrEP) with oral antiretroviral medication is a highly effective biomedical HIV prevention strategy. In clinical trials, daily PrEP has been found to be extremely efficacious (>95% when taken daily) in preventing HIV infection in men who have sex with men, heterosexuals, and injection drug users [11-14]. Less is known about the real-world impact of PrEP on YBLGBM. Current data indicate that young black and Latinx men have lower rates of PrEP uptake than other groups of men [15], suggesting disparities in knowledge, interest, or access to this new prevention tool. Ensuring access to PrEP by YBLGBM is paramount [16,17], including facilitating access to information and resources to support decision making about PrEP use [17-20]. New scalable interventions that can rapidly disseminate information and support PrEP uptake are needed to achieve this goal and to reduce the burden of HIV in this population.

Social media may be one such tool that could help support PrEP adoption by YBLGBM. As a tool for behavioral interventions, social media employs internet-based technologies (eg, Facebook, Instagram, and Twitter) to support interactive dialogue through the exchange of user-generated content in online networks [21]. Social media access and use by young people is ubiquitous, and disparities in use by race/ethnicity or income are minimal among youth [22-24]. A prior study in low-income YBLGBM in New York , NY, USA, showed universal access to and daily use of multiple social media sites, even among homeless YBLGBM [25]. Other studies showed that YBLGBM are readily identifiable and accessible through social media, and that many use these sites to seek sex partners [26,27]. Given their high risk of acquiring HIV [24,28-32], their extensive use of mobile phones and the internet, and the failure of traditional HIV interventions to reach YBLGBM, social media may be particularly efficient for engaging this population [33].

Objective

Although several studies of social media–based health interventions have been published [8,29,30,34-37], best practices in this field for HIV prevention are unknown and evolving. The overall goal of this study was to develop a culturally tailored, peer-led, social media–based behavioral intervention to support PrEP uptake in YBLGBM. Our aims were to use a diffusion of innovation (DOI) framework to (1) determine potential factors associated with interest in and adoption of PrEP among YBLGBM; (2) develop Empowering with PrEP (E-PrEP), a social media–based, peer-led intervention to increase PrEP uptake in YBLGBM aged 18 to 29 years in New York City; and (3) pilot test feasibility and acceptability, and determine preliminary efficacy of E-PrEP for increasing adoption of PrEP by YBLGBM. This paper describes the development of the E-PrEP intervention and the study protocol.

Methods

Overview

We first developed, pretested, and refined the Web-based intervention (E-PrEP) (intervention development phase). We then conducted a 2-arm cluster-randomized controlled trial to evaluate the feasibility, acceptability, and preliminary efficacy of E-PrEP, compared with an attention-matched general health control condition (E-Health). We randomly assigned YBLGBM peer leaders to either the E-PrEP intervention or the E-Health control condition. Peer leaders were trained to deliver the intervention or control condition in their assigned arm, and then recruited YBLGBM individuals from their existing online networks (network participants) to complete a Web-based screening and baseline survey. Eligible network participants were enrolled into the trial and assigned to either a private Facebook group (Facebook, Inc, Menlo Park, CA, USA) or Instagram (Instagram Inc, Menlo Park, CA, USA) feed, connected to the peer leader who recruited them. Network participants were thus assigned to the intervention or control condition based on their peer leader's assignment. Peer leaders then launched an online campaign by posting intervention or control condition content (eg, articles, video clips, and infographics) almost daily to their respective private groups, and by attempting to engage their network participants in discussions of the materials being posted. The online campaign occurred over a 6-week period, after which participants completed an immediate postintervention assessment and another postintervention assessment after 6 additional weeks (12 weeks after the start of the campaign).

Theoretical Models

We developed E-PrEP based on DOI [38] and information-motivation-behavioral skills (IMB) [39] models. The DOI model posits that a new innovation (eg, PrEP) is adopted over time through communication among members of a similar social system in a staged process, involving changes in norms and perceived attributes about the innovation [40,41]. Stages in the process include acquiring knowledge of the innovation, which may lead to interest and then a decision to adopt or reject the innovation, followed by actual adoption or rejection. In Figure 1 [42,43], we highlight elements of the innovation (PrEP) that may influence adoption, based on DOI theory. These are relative advantage (the benefits of using PrEP relative to other HIV prevention strategies), compatibility (PrEP fitting into potential users' routines or existing behaviors), perceived simplicity (PrEP being relatively easy to acquire and use), and trialability (ability to try PrEP without long-term commitment).

While the DOI framework is highly informative, it does not explicitly provide a pathway to develop skills for adoption of an innovation (eg, navigating health care systems to obtain PrEP). Therefore, we also incorporated all components of the IMB framework [44]. The IMB model posits that fostering information acquisition, increasing motivation, and building behavioral skills are needed to change HIV prevention behaviors (eg, PrEP use) [45] and has been recently proposed as a model for guiding PrEP uptake interventions [46].

Using these 2 models as guides, we selected relevant behavioral targets to increase PrEP adoption focusing on (1) communication channels and messengers, (2) sociocultural factors and norms, and (3) perceived attributes (Figure 1). We then used a community-based participatory research approach [47-49] to develop E-PrEP messages targeting the DOI and IMB domains, and stages of knowledge and information, interest and motivation, acquisition of behavioral skills, and decision (to adopt PrEP).

Setting

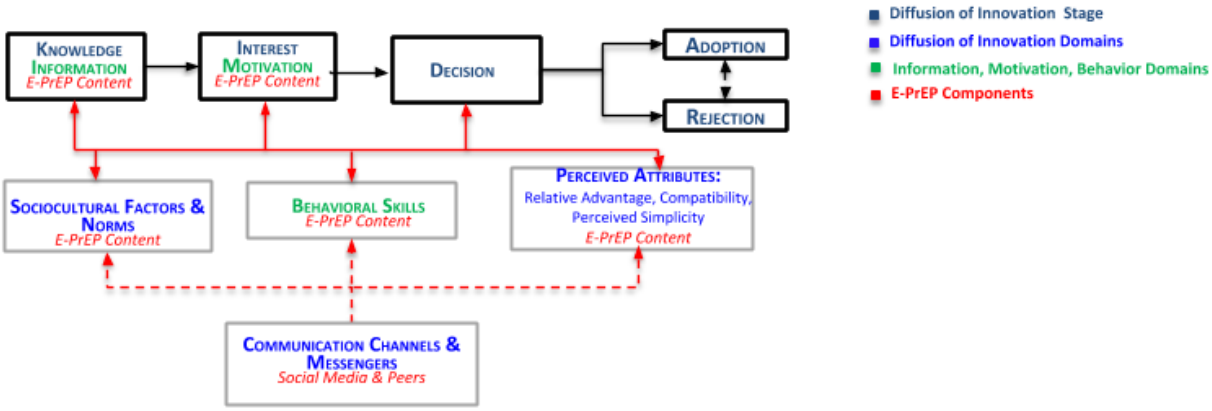
All aspects of the study took place in New York City. The HIV epidemic in New York City mirrors US national trends, with new infections disproportionately occurring among YBLGBM [50]. PrEP, which is covered by Medicaid and most other insurers in New York State, is now widely accessible in New York City. New York State has a PrEP assistance program to help with costs associated with clinical services (eg, office visits, laboratory tests) for uninsured and underinsured patients, and there is a large network in New York City of lesbian, gay, bisexual, transgender, and queer (or questioning) (LGBTQ)-affirming and -competent medical providers who prescribe PrEP.

Development of the E-PrEP Intervention and Attention-Matched Control Conditions

Intervention Development Overview

We designed E-PrEP based on formative work conducted by our team [51], in which peers used multiple social media platforms to promote HIV testing using creative messaging and led other social media–based HIV interventions [52,53]. Community-based participatory research methods [47-49,54] guided the development of E-PrEP, with input from a group of 6 YBLGBM intervention development partners experienced in HIV and PrEP outreach in New York City, whom we recruited through an existing HIV outreach initiative for YBLGBM. We selected Facebook and Instagram as the platforms for the intervention, as these are the 2 general social media sites most frequently used by the target population. We did not restrict the intervention to a single platform to provide flexibility, as not all YBLGBM use both sites equally. We developed all contents for both E-PrEP and the control condition (E-Health), and created a content posting and activity guide for all 6 weeks (see Multimedia Appendix 1 for additional details). We standardized E-PrEP in its mode of delivery, types of digital media and contents, and sequence of topics posted and discussed, but during the intervention each peer leader tailored the exact language of each post based on their individual communication style. All materials, including assessments, were mobile phone optimized.

Figure 1. Empowering with PrEP (E-PrEP) conceptual model. DOI: diffusion of innovation; IMP: information, motivation, behavioral skills; PrEP: preexposure prophylaxis. Adapted from Fisher and Fisher [42] and Rogers [43].



Selection of Targets for E-PrEP

We selected potentially modifiable targets to inform message content based on the DOI and IMB models. We also incorporated findings from a qualitative study of local YBLGBM [55], a systematic review of barriers to and facilitators of PrEP, which included a systematic content analysis of online posts about PrEP by men who have sex with men [56], and input from our intervention development partners. Messages were presented using digital media (eg, text, pictures, infographics, and video clips) and posted online based on findings from prior Web-based interventions[57,58] and on social media marketing principles [59]. We designed the content to engage participants in online discussions about HIV prevention, PrEP, and health care [57]. To retain YBLGBM and prevent intervention fatigue [7,60], peer leaders and participants were encouraged to post other items of interest, regardless of their relevancy to HIV or PrEP (eg, pop-culture posts, pictures from recent events, or discussion of current news) [10,61].

Development of E-PrEP Intervention Contents

We used an iterative and participatory approach to inform the contents of each E-PrEP online post. First, the research team and our intervention development partners created a digital media library of PrEP educational contents by searching social media (Facebook, Instagram, Twitter, and YouTube) and websites with publicly posted and shareable information about PrEP and accessing health care in the United States. Next, we elicited feedback from the intervention development partners about the following attributes for each media item: their overall thoughts, the comprehensibility, aesthetic appeal, engagability, and informativeness of the item, whether the intervention development partners would actually share the media item, and whether they thought their YBLGBM friends would be likely to view or click on the media item. Then, we took the highest-rated items and mapped them onto a matrix including DOI and IMB domains, as well as barriers to and facilitators of PrEP, to ensure that all relevant topics were covered.

Specific E-PrEP Components

Table 1 [62-70] lists examples of E-PrEP intervention contents. The content, formats, and mode and timing of delivery of E-PrEP were informed by the intervention development partners during the intervention development phase, with ongoing input from the peer leaders during intervention implementation. Existing local resources, LGBTQ-friendly clinics, and an existing LGBTQ patient navigator in New York City were highlighted as part of the online content to ensure that people knew how to access care if desired. We only listed clinical resources that accepted new patients, accepted Medicaid or uninsured patients, and were already prescribing PrEP.

Development of the Attention-Matched Control Condition

E-Health focused on a broad range of health topics prioritized by the peer leaders assigned to this arm, but did not include any contents about HIV or PrEP. The peer leaders randomly assigned to the E-Health control condition were informed at the first meeting that they would be creating a 6-week social media campaign focusing on health issues they viewed as a priority for YBLGBM within their communities. They chose to cover the following topics: depression, anxiety, suicide, intimate partner violence, drug use, social acceptance, and awareness of sexually transmitted infections (excluding HIV). We designed the E-Health timeline to match the E-PrEP intervention timeline for both time and day of posts and frequency of posts. Similarly to the development of E-PrEP, peer leaders compiled publicly available digital media contents addressing the selected health topics, and then as a group finalized materials to be posted during the online campaign. As with E-PrEP, standardized E-Health contents were posted by peer leaders, framed using their own words. At the end of the trial, peer leaders and participants randomly assigned to E-Health were exposed to all E-PrEP contents.

Setup of Web-Based Intervention Sites

We established E-PrEP (intervention) and E-Health (control) private online communities (either a private Facebook group or a private Instagram feed) for each peer leader. We also formed 2 separate private Facebook groups (1 for each condition) for

peer leaders, led by a peer facilitator. In these groups, peer leaders could share additional materials, troubleshoot potential issues, and communicate with other peer leaders, the peer facilitator, and a research assistant assigned to that condition. We used third-party content management software (Buffer [71]) to facilitate content posting so that all posts could be prescheduled by peer leaders for the 6-week intervention duration and published at the same day and time in both conditions.

Table 1. Empowering with PrEP[a] (E-PrEP) weekly topics, theoretical domains, and barriers or facilitators targeted.

Week	Weekly theme	DOI[b] stage	DOI or IMB[c] domains [62]	Potentially modifiable barrier or facilitator targeted	Example of messaging or contents posted by peer leaders
1	PrEP awareness	Knowledge, Interest	Perceived attributes, Sociocultural norms (DOI); Information, Motivation (IMB)	• Lack of PrEP knowledge • Low perceived risk	• "The government wouldn't want half the world to contract HIV [emoji face with rolling eyes]. What other myths have you heard about PrEP?" [63] • "If you're dtf let's talk about it #get-prepped #lets talk about it #nycgay" [64] (peers facilitate ongoing discussions on ways to protect, including PrEP)
2	How to talk about sex and PrEP	Knowledge	Perceived attributes, Sociocultural factors (DOI); Information, Behavioral skills (IMB)	• Do not know how to get PrEP	• "There are some things to consider when taking PrEP, but there are people to answer your questions What questions do you have? #askyourdoctor #getprepped" [65]
3	Talking to partners and friends	Interest	Sociocultural factors (DOI); Motivation (IMB)	• Perceived stigma of using PrEP	• "Having a positive partner could be the new norm. What makes it hard to bring up PrEP with your partners? #preplove #hivlove #grindrlovestory #getprepped" (clip from video with serodiscordant couple) [66]
4	Overcoming barriers to PrEP	Interest	Perceived attributes (DOI); Information, Motivation (IMB)	• Potential side effects	• "If you take it at night, how will you feel side effects? Get protected while you sleep #getprepped, What other tips do you have to avoid side effects?" [67]
5	How to get on PrEP?	Knowledge, Decision	Information, Behavioral skills (IMB)	• Ability to navigate health care system	• "What information should you have handy before you call to make a doctor's appointment?? Your home address, phone number, date of birth, and insurance information. You'll be asked why you are making the appointment. They just need the basics, like 'I want to make an appointment to get on PrEP to prevent HIV.' Tell the scheduling person if you're only available certain days or times." [68]
6	Finding a doctor to prescribe you PrEP and affording PrEP	Decision, Implementation	Perceived attributes (DOI); Behavioral skills (IMB)	• Accessing PrEP- or LGBTQ[d]-friendly provider • Cost	• "DM us your zip code if you want to get on PrEP, and we'll send you a list of docs in your area! Or Follow this link to find PrEP providers in your county." [69] • "In New York most people can get PrEP for free or cheap, regardless of your insurance status! If you have insurance, including Medicaid, your PrEP will likely be covered. If not, we can help you figure out your options, even if you're uninsured! Call/text Eric at xxx if you have questions." [70]

[a]PrEP: preexposure prophylaxis.

[b]DOI: diffusion of innovation model.

[c]IMB: information-motivation-behavioral skills model.

[d]LGBTQ: lesbian, gay, bisexual, transgender, and queer (or questioning).

Pretesting and Refining of E-PrEP

To pretest and refine E-PrEP, the intervention development partners each recruited 2 YBLGBM participants from their networks. These participants completed an online consent process and baseline survey, and then received an additional link to join an unlisted private Facebook group where all E-PrEP contents were posted over a 6-week period. The pretest participants provided feedback about contents, process, and acceptability, and also provided suggestions for improvement to all aspects of the intervention through three ways: (1) ongoing feedback elicited by the intervention development partners on the posted E-PrEP contents using open-ended questions in the Facebook group, (2) a brief online acceptability and usability survey at the end of the 6-week period, and (3) an in-person focus group with the intervention development partners and 8 of the pretest participants. Pretest participants received a US $25 debit card as an incentive for their participation. Based on feedback from pretest participants, we refined the E-PrEP intervention by modifying post contents (eg, replacing contents that elicited negative reactions or were considered stigmatizing).

Implementation of the Intervention

Peer Leader Recruitment and Randomization

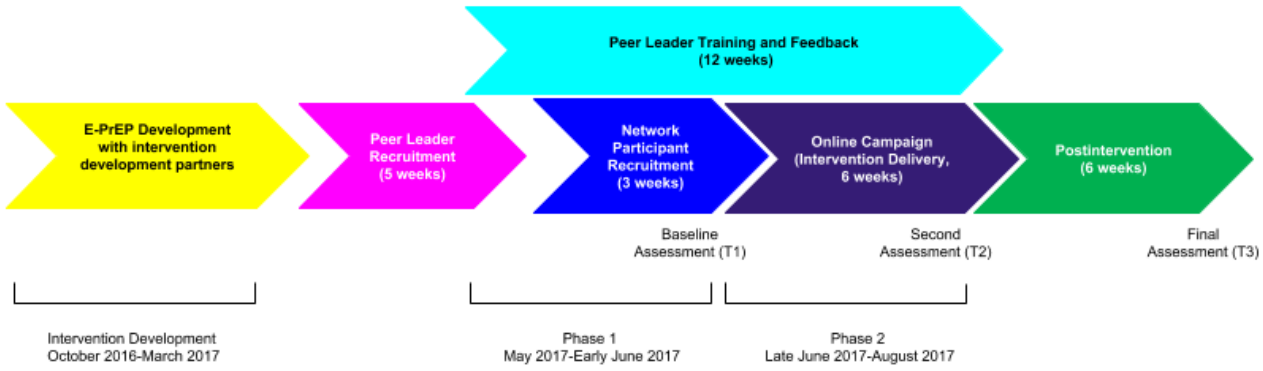
We recruited 10 YBLGBM peer leaders through advertisements via emails to local youth and LGBTQ-focused community organizations, word-of-mouth through key informants in local YBLGBM communities, and targeted advertisements on Facebook and Instagram. All advertisements directed potential peer leaders to a brief online screening survey. Inclusion criteria for peer leaders were (1) having more than 500 online friends or followers on Facebook or Instagram, (2) using either Facebook or Instagram daily, (3) having positive attitudes about PrEP, (4) residing in New York City, (5) identifying as black or Latino, (6) being sexually active with men in the past year, (7) being fluent in English, (8) being between 18 and 34 years of age, (9) being willing to and feeling comfortable posting and discussing health issues (including sexual health and HIV) with friends on Facebook or Instagram, (10) being able to commit to meeting weekly for 12 weeks for training and intervention implementation, and (11) being able to provide consent. A study coordinator telephoned individuals meeting eligibility to provide further information about the study (eg, that this was a research study and they were study participants as well) and to assess interest and availability. After recruiting peer leaders over a 5-week period, we randomly assigned them to the 2 arms. Peer leaders were blinded to their study condition and were informed that their participation was to help refine and launch an online health promotion campaign for YBLGBM in their online social networks. Each arm was facilitated by a peer facilitator (who also identified as a black or Latinx GBM and was experienced in group facilitation for HIV prevention with YBLGBM in New York City) and supported by a research staff member.

Training and Finalizing Intervention Contents for E-PrEP (Intervention Arm)

We used a participatory process to refine and implement the study. Peer leaders met weekly over a 12-week period. Meetings took place for 3 hours in the evenings at a Wi-Fi–equipped community health center that was easily accessible by public transportation. As Figure 2 displays, the first 6 weeks were dedicated to training and intervention refinement activities (phase 1) and the second 6 weeks were the active intervention delivery period (phase 2).

At the first training session (phase 1), peer leaders randomly assigned to E-PrEP were informed that the overall goal of the campaign was to help prevent HIV in our communities by disseminating accurate information about PrEP to their networks and help link individuals to primary care or PrEP care through an online outreach campaign. During phase 1, peer leaders received training in online recruitment, HIV prevention outreach, PrEP, social media–based outreach and engagement, Buffer software (for scheduling the online posts), and research ethics. As part of the training and intervention refinement, peer leaders reviewed the previously selected and prepiloted E-PrEP digital media materials and made changes or additions as they deemed necessary. During the intervention period (phase 2), peer leaders posted content and provided ongoing feedback to the investigators (see Intervention Procedures, below). In addition to eliciting ongoing feedback during the intervention period (phase 2), we obtained feedback on peer leaders' experiences participating in the study after study completion using a structured Web-based survey and a semistructured focus group discussion. We collected this information to guide future online outreach practices and capture any relevant issues that emerged during the intervention period but was not captured in our weekly discussions.

Figure 2. Timeline for intervention development and trial implementation. E-PrEP: Empowering with PrEP; T: time.



Training in Research Ethics for Peer Leaders

Peer leaders went through a community research ethics training adapted from a World Health Organization training for lay community members [72]. The training covered topics in the history of research ethics, confidentiality, vulnerable participants, ethical recruitment practices, protecting against risks, minimizing risks, and personal safety and conduct. This training had previously been used with community partners for whom the Collaborative Institutional Training Initiative course [73] was inaccessible due to literacy or language barriers. We also had ongoing discussions throughout the project period in online privacy and security issues. Peer leaders were informed that if there were any clinical questions or questions they did not know the answers to posted, they should send a message with a copy of the question to their peer facilitator and research staff associated with their group, who would obtain the answers to the questions.

Compensation for Peer Leader Participants

Peer leaders were considered to be research participants and were compensated for their time and incentivized to actively participate, by receiving increasing amounts of incentive for each week they attended the weekly in-person meetings (up to US $485 via a debit card) over the course of phases 1 and 2. Peer leaders could participate in makeup sessions if needed by meeting one-on-one with the research staff member assigned to their arm. Because peer leaders prescheduled all posts using the Buffer scheduling software, intervention delivery did not have to rely on peer leaders conducting core intervention activities (ie, daily posts in the private online group) outside of the weekly meetings. Peer leaders were encouraged, though, to foster discussions on each post by posing questions to their groups or sharing their thoughts and eliciting feedback from group members.

Network Study Participants, Recruitment, and Randomization

Peer leaders, after completing training, recruited network study participants via their existing online social networks to complete an online eligibility screener and baseline survey, using individualized links (Figure 2). Potential network study participants were directed to a Web-based informed consent form, followed by a screener that continued seamlessly into the baseline survey (for eligible network study participants) (using Qualtrics survey software) or an exit page indicating ineligibility. After completion of the baseline survey, network study participants were directed to join the private online intervention group of the peer leader who had recruited them (either a Facebook private group or a private Instagram feed as selected by the peer leader) and were considered to be enrolled after joining the group. Network study participants received an incentive of US $20 after joining the online group.

Inclusion criteria for network study participants were (1) identifying as or assigned male at birth, (2) self-identifying as black or Latino, (3) being 18 to 29 years of age, (4) being fluent in English, (5) being HIV uninfected or unknown by self-report, (6) residing in New York City, (7) having a Facebook or Instagram account, (8) having had insertive or receptive anal sex with a male partner in the past 12 months, and (9) having had 1 of the following in the past 12 months: condomless anal intercourse, anal sex with more than 3 men, bacterial sexually transmitted infection diagnosis (syphilis, gonorrhea, or chlamydia), or a sex partner who was at least 10 years older [74].

We used a cluster-randomized design [34] for several reasons. As we are testing a peer-based social network intervention, keeping study participants clustered with the peer leaders who recruited them maintains ecologic validity and approximates real-world circumstances. This approach also helps minimize contamination within peer networks and is consistent with the DOI model, which highlights social connections in the diffusion process [41,62]. The main drawback to this design is intracluster correlation, such that we cannot assume independence among participants within peer groups. To address this, we will conduct a series of sensitivity analyses (see Analytic Plan, below).

Fraudulent or Duplicate Responses

To address potentially fraudulent or duplicate responses, we excluded individuals from the same internet protocol address, recognizing that this approach may inadvertently exclude individuals who simply were sharing a Wi-Fi network. Additionally, we asked for Facebook and Instagram usernames to verify participant identity [75-80]. A research assistant reviewed and approved all requests for entry to the private groups by (1) verifying that the Facebook or Instagram account was already connected to the peer leader who recruited them, (2) asking participants to respond to a private direct message from the research assistant, and (3) insuring that participants had more than 50 friends or followers. We used this last criterion to avoid potentially fraudulent participants who may have developed a new social media account just for the intervention and would thus be unlikely to regularly log in and be exposed to contents being published during the intervention period.

Intervention Procedures

After completing recruitment (over a 3-week period), YBLGBM peer leaders launched the intervention by posting materials according to the timeline developed during the training and intervention refinement period (Multimedia Appendix 1). We held weekly project meetings with peer leaders assigned to both E-PrEP and E-Health to ensure appropriate implementation and to discuss logistic, ethical, or other issues that may have arisen. Each group met on different days of the week with different research staff members to help minimize potential contamination. Content for both arms was posted over a 6-week period using Buffer [71], which allowed all the posts to be prescheduled and published in the private groups using the peer leaders' existing accounts. This approach ensured standardized publication of contents (ie, at the same time and day for each post) and reduced reliance on peer leaders being asked to post contents every day. We collected outcome data from the network study participants via online surveys at baseline, 6 weeks, and 12 weeks. Participants were given US $20, $30, and $40 online gift cards as incentives after completion of assessments at baseline, 6 weeks, and 12 weeks, respectively.

Measures

Online Surveys

We administered online surveys to collect self-reported data at the 3 time points (baseline, 6 weeks, and 12 weeks). We collected data on PrEP use and intention to use, PrEP knowledge and attitudes, self-efficacy for PrEP care, sexual behaviors, sexually transmitted infection and HIV testing, and other covariates listed in Table 2. At each assessment period, participants were sent automated email reminders, followed by direct social media or text message reminders (sent by study staff 24 hours later if surveys were not completed). We repeated these reminders every 2 days until assessments were completed, for a period of 2 weeks. To assess possible contamination between study arms, the 6-week assessment displayed random samples of campaign posts from both E-PrEP and control arms to all participants and assessed recall [34,81,82].

Online Engagement Metrics

We collected number of posts viewed, comments, and likes for each participant at 6 weeks. For each post in each of the private peer Facebook groups, we manually collected view data in a spreadsheet by documenting whether a participant had viewed the post or not, coded as 0 (not viewed) and 1 (viewed). For participants using Instagram, we used the same approach to document likes and comments for each of the posts. We also extracted additional engagement data (comments, likes, and reactions) using Grytics software (1339 SAS) for the Facebook groups (not available for Instagram). Grytics is a third-party analytics app that extracts Facebook group engagement data. At the time of the intervention, Grytics did not extract group members' profile data such as age or gender. Sharing of posts on Facebook was disabled for the trial to reduce potential contamination.

Outcomes

Our primary outcomes are (1) self-reported PrEP uptake or intention (measured by indicating either current use of PrEP or intention to use PrEP in the next month) [83], and (2) change on the PrEP motivational cascade [84] at 12 weeks. Secondary outcomes are PrEP knowledge [85], PrEP-related stigma [86], attitudes about PrEP, and access to primary or sexual health care [87]. We will also explore potential changes in social network factors (eg, social support) and whether social media engagement correlated with the primary and secondary outcomes.

Analytic Plan

Feasibility

To test feasibility, we will assess online process measures, including participation rate (number of individuals screening eligible and then ultimately joining the study) and retention metrics (number of participants actively leaving or "unjoining" a social media study site and number of respondents completing follow-up assessments).

Acceptability

We will evaluate acceptability by assessing engagement activity (eg, number of posts viewed, number of individuals commenting or liking posts), satisfaction with the intervention, and willingness to continue participating if it were an option, joining a similar study again, and likelihood of recommending friends to join this study if it were an option.

Primary and Secondary Outcomes Analysis

First, we will compare groups for equivalence at baseline, using chi-square test, *t* tests, or nonparametric tests as appropriate. In addition, we will determine whether subgroups (eg, grouped by social media platform used, peer leader group, race/ethnicity, and sexual orientation) differ with respect to the primary and secondary outcomes. Relevant differences will be used as covariates in subsequent models. To compare differences in outcomes between arms over time, we will use repeated-measures mixed-effects logistic models, with the treatment arm as a fixed effect, peer leaders as a random intercept, repeated measures from a same participant as another random intercept, and time (as a linear term) as an independent variable. We will also look at residual plots to determine whether we need to include nonlinear terms for time.

Table 2. Survey domains for the Empowering with PrEP[a] (E-PrEP) cluster-randomized controlled trial.

Measures	Week		
	0	6	12
Sociodemographic information	Yes	No	No
Social media access and use	Yes	Yes	Yes
PrEP knowledge, attitudes, and self-efficacy	Yes	Yes	Yes
Stigma (HIV, PrEP, and sexuality related)	Yes	Yes	Yes
Social network factors (social support, PrEP use among friends or partners, relationship with peer leader)	Yes	Yes	Yes
Health care access and use	Yes	Yes	Yes
Sexual health (partners, condom use, sexually transmitted infection history, and HIV testing)	Yes	Yes	Yes
Mental health, alcohol, and substance use	Yes	Yes	Yes
Contamination measures	No	Yes	Yes
Intervention satisfaction	No	Yes	Yes

[a]PrEP: preexposure prophylaxis.

Next, we will use hierarchical models to examine the role of secondary outcomes as potential mediators of change over time; for example, are there differences by condition in PrEP knowledge or attitudes that account for differences in the outcomes? Finally, we will assess the impact of the exposure arm (E-PrEP or E-Health control) and selected covariates (significant in the bivariate analysis at $P<.15$) on the primary and secondary outcomes using mixed-effects models.

Online Engagement

To assess the impact of online process and engagement metrics on the outcomes, we will assess in the E-PrEP arm whether intervention exposure and engagement metrics correlate with the primary outcomes of uptake of PrEP and intention to use PrEP. In exploratory analyses, we will assess whether group activity (ie, total number of network participant reactions and posts) correlate with the primary outcomes. To overcome possible limitations due to intracluster correlations, we will also include a modified sensitivity analysis that examines outcomes in relation to participants' network size and perceived affinity to the peer leaders.

Challenges and Limitations

Attrition

Unlike in prior internet-based interventions, we proposed to use online venues already frequented by YBLGBM and to push intervention components to private home pages, visible only to participants, thus obviating the need to return repeatedly to specific study sites and potentially facilitating engagement. Peer leaders were familiar to participants and served as both recruiters and messengers, delivering contents framed in the peer leader's communication style. We believe these design considerations will help mitigate attrition, observed in prior Web-based interventions.

Contamination

The internet's strength is that it delivers multidimensional intervention components [88]. Social media's strength in diffusing innovations is that it facilitates information sharing within and between networks at a pace not previously possible. The nature of social media means there may likely be contamination between study arms. We minimize this to the extent possible by randomizing by peer leader, blinding peer leaders and study participants, and limiting access to the private study sites and contents. Additionally, peer leaders all agreed to not share any contents of materials being posted in their private Facebook or Instagram study groups until after the 12-week assessment.

Results

Over a period of 5 weeks, from May to June 2017, we recruited, enrolled, and randomly assigned 10 peer leaders (Table 3). From June to July 2017, over a period of 3 weeks, the 10 peer leaders recruited and enrolled a total of 152 network participants (range 4-33 per peer leader; Table 4). Intervention follow-up was completed in November 2017, with analyses ongoing.

Table 3. Baseline characteristics of peer leaders in the Empowering with PrEP[a] (E-PrEP) study.

Characteristics	E-PrEP group (n=5)	Control group (n=5)
Age (years), mean (SD)	24.6 (6.23)	26.4 (5.74)
Gender identity, n (%)		
Male	5 (100)	4 (80)
Gender nonbinary or gender queer	0	2 (40)
Residence, n (%)		
Bronx	3 (60)	3 (60)
Brooklyn	0	1 (20)
Manhattan	2 (40)	1 (20)
Race/ethnicity, n (%)		
Latinx/Hispanic	3 (60)	4 (80)
Non-Hispanic black	2 (40)	1 (20)
Sexual orientation, n (%)		
Gay/homosexual	3 (60)	3 (60)
Queer	2 (40)	1 (20)
Bisexual	1 (20)	1 (20)
Education level, n (%)		
High school or less	1 (20)	2 (40)
Some college and higher	4 (80)	3 (60)
Employment[b], n (%)		
Full-time	1 (20)	1 (20)
Part-time	3 (60)	0
Unemployed	0	3 (60)
Student	2 (40)	1 (20)
No. of Facebook friends, mean (SD)	2532 (1657)	3021(1269)
No. of Instagram followers, mean (SD)	2242 (1455)	1443 (644)
PrEP status		
Ever taken PrEP	1 (20)	0
Never taken PrEP	4 (80)	5 (100)

[a]PrEP: preexposure prophylaxis.

[b]Results may add up to more than 100%, as participants could choose multiple categories.

Table 4. Baseline sociodemographic characteristics of network participants in the Empowering with PrEP[a] (E-PrEP) study.

Characteristics	E-PrEP group (n=81)	Control group (n=71)
Age (years), mean (SD) *t* test	24.28 (2.8)	23.32 (3.4)
Gender identity, n (%)		
Male	68 (84)	64 (90)
Female/transfemale	7 (9)	3 (4)
Transmale	1 (1)	0
Gender nonconforming or nonbinary	2 (3)	0
Queer	3 (4)	4 (6)
Residence, n (%)		
Bronx	44 (54)	35 (49)
Brooklyn	18 (22)	14 (20)
Manhattan	16 (20)	13 (18)
Queens	2 (3)	8 (11)
Staten Island	1 (1)	1 (1)
Race/ethnicity, n (%)		
Latinx/Hispanic	26 (32)	47 (66)
Non-Hispanic black	55 (68)	24 (34)
Sexual orientation, n (%)		
Gay/homosexual	60 (74)	56 (79)
Queer	12 (15)	3 (4)
Bisexual	7 (9)	10 (14)
Heterosexual/straight	1 (1)	1 (1)
Other	1 (1)	1 (1)
Education level, n (%)		
High school or less	36 (44)	19 (38)
Some college	28 (35)	35 (49)
College and higher	17 (21)	9 (13)
Income (US $), n (%)		
None	12 (15)	14 (20)
<10,000	26 (32)	15 (21)
10,000-19,999	11 (16)	10 (14)
20,000-29,999	13 (16)	6 (8)
30,000-39,999	11 (14)	16 (23)
≥40,000	8 (10)	10 (14)
Employment[b], n (%)		
Full-time	24 (30)	29 (41)
Part-time	17 (21)	15 (21)
Unemployed	31 (38)	15 (21)
Disabled	3 (4)	2 (3)
Student	12 (15)	13 (18)
Living situation, n (%)		
Don’t have a place to live	4 (5)	2 (3)

Characteristics	E-PrEP group (n=81)	Control group (n=71)
Temporary living situation	15 (19)	7 (10)
Parents or family	29 (36)	36 (51)
Partner, boyfriend, or husband	2 (3)	7 (10)
Roommates	20 (25)	14 (19.7%)
Alone	11 (14)	4 (5.6%)
Female partner, girlfriend, or wife	0	1 (1.4%)
Health insurance, n (%)		
Yes	61 (75)	59 (83.1%)
No	18 (22)	10 (14.1%)
Don't know	2 (3)	2 (2.8%)
Type of health insurance, n (%)		
Medicaid	33/61 (54)	29/59 (49)
Your employer or someone else's employer	18/61 (30)	18/59 (31)
Medicare	6/61 (10)	2/59 (3)
Some other source	2/61 (3)	6/59 (10)
Don't know or not sure	2/61 (3)	0

[a]PrEP: preexposure prophylaxis.

[b]Results may add up to more than 100%, as participants could choose multiple categories.

Discussion

Existing behavioral interventions have had limited success in reducing HIV infections in YBLGBM. The promise of PrEP to reduce HIV transmission will be realized in YBLGBM only if uptake, high adherence, and continued engagement in PrEP care is achieved. A social media–based approach to facilitate PrEP uptake may efficiently identify and reach YBLGBM at high risk and may therefore enhance PrEP adoption by helping foster education, motivation, and skills, and linking individuals to sites where they can receive PrEP. Additionally, the use of peer leaders can help influence PrEP uptake by overcoming barriers to engagement and changing social norms and attitudes [89]. Behavioral interventions using peer leaders have been associated with fostering HIV preventive behaviors [90] and in increased viral suppression in HIV-infected individuals [91]. Thus, an intervention model such as E-PrEP, which leverages both peers and social media, could be rapidly scaled up to help accelerate PrEP uptake.

Rather than being simply another medium for adaptation and implementation of existing interventions designed for in-person contact, social media may be a true game changer [7,9,10,81,88] to engage hard-to-reach individuals. While many studies of Web-based behavioral interventions exist, including some that use social media [53], this is, to our knowledge, one of the first to use social media and peer leaders to facilitate uptake of a biomedical intervention. This study is among the first to design and implement a theoretically grounded and completely Web-based intervention codeveloped by peer leaders to accelerate PrEP uptake. Given the paucity of data regarding social media–based interventions to change health behaviors, specifically about a biomedical HIV prevention tool, E-PrEP highlights an important behavioral intervention strategy for existing and future biobehavioral innovations.

Social media offers the power of scale and efficiency for a large potential impact, even with relatively low-intensity interventions [10,81,92]. Similarly, PrEP, if widely adopted in populations at high risk of HIV, could markedly decrease HIV infection rates. Social media–based, peer-led approaches such as E-PrEP could be used to enhance efforts by community-based and other organizations that use internet-assisted or peer outreach strategies to improve health [9]. Findings from this study may help elucidate diffusion processes and factors affecting PrEP adoption, and will lead to the development of a refined social media–based, peer-led intervention, which can then be tested in a fully powered trial. The insights gained from this study may help produce meaningful interventions for YBLGBM, as well as needed data regarding the application of social media- and technology-based interventions to facilitate health behavior change.

Acknowledgments

We'd like to thank all of the participants, the peer leaders, Sage Rivera, Justin Toro, Reginal Juste, Ernie Jason, Tony Ostolaza, Sean Donegan, Lawrence Gross, Yashesh Parikh, Donna Futterman, and the Montefiore Adolescent AIDS Program. This study was supported by US National Institutes of Health (NIH) K23MH102118 (principal investigator VVP) and the

Einstein-Rockefeller-CUNY Center for AIDS Research (NIH P30AI051519). Funding agencies had no role in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Empowering with PrEP (E-PrEP) 6-week online content posting guide.

[PDF File (Adobe PDF File), 284KB - resprot_v7i8e11375_app1.pdf]

Multimedia Appendix 2

Review from funding agency.

[PDF File (Adobe PDF File), 237KB - resprot_v7i8e11375_app2.pdf]

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Abbreviations

DOI: diffusion of innovation
E-Health: attention-matched general health control condition
E-PrEP: Empowering with PrEP
GBM: gay, bisexual, and other men who have sex with men
IMB: information-motivation-behavioral skills
LGBTQ: lesbian, gay, bisexual, transgender, and queer (or questioning)
PrEP: preexposure prophylaxis
YBLGBM: young black and Latinx gay, bisexual, and other men who have sex with men

Edited by N Kuter; submitted 11.07.18; peer-reviewed by E Elliot, J Rhoton; comments to author 26.07.18; revised version received 08.08.18; accepted 09.08.18; published 28.08.18.

Please cite as:
Patel VV, Ginsburg Z, Golub SA, Horvath KJ, Rios N, Mayer KH, Kim RS, Arnsten JH
Empowering With PrEP (E-PrEP), a Peer-Led Social Media–Based Intervention to Facilitate HIV Preexposure Prophylaxis Adoption Among Young Black and Latinx Gay and Bisexual Men: Protocol for a Cluster Randomized Controlled Trial
JMIR Res Protoc 2018;7(8):e11375
URL: http://www.researchprotocols.org/2018/8/e11375/
doi:10.2196/11375
PMID:30154071

Protocol

Intra-Arterial TheraSphere Yttrium-90 Glass Microspheres in the Treatment of Patients With Unresectable Hepatocellular Carcinoma: Protocol for the STOP-HCC Phase 3 Randomized Controlled Trial

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Abstract

Background: Globally, hepatocellular carcinoma is the second most common cause of cancer deaths. It remains challenging to intensify cancer treatment without impairing liver function.

Objective: The objective of the TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (STOP-HCC) study is to examine the hypothesis that transarterial radioembolization (TheraSphere yttrium-90 glass microspheres) combined with standard first-line treatment with sorafenib will improve outcomes over treatment with sorafenib alone in unresectable hepatocellular carcinoma. The STOP-HCC study is the largest international, multicenter, prospective study of intra-arterial treatment in combination with sorafenib in unresectable hepatocellular carcinoma. Here we report the study design.

Methods: STOP-HCC is a prospective, phase 3, open-label, randomized controlled study conducted across up to 105 sites in North America, Europe, and Asia. Eligible adults have unresectable hepatocellular carcinoma and a life expectancy of at least 12 weeks, 1 or more unidimensional measurable lesions, Child-Pugh score 7 points or less, and Eastern Cooperative Oncology Group Performance Status score 1 or lower, and are candidates for treatment with sorafenib. Presence of branch portal vein tumor thrombosis is permitted. Patients were randomly assigned in a 1:1 ratio to receive either sorafenib alone or transarterial radioembolization followed by sorafenib within 2 to 6 weeks. The primary outcome is overall survival. Secondary outcomes are time to progression, time to untreatable progression, time to symptomatic progression, tumor response, quality of life, and adverse event occurrence. The study is an adaptive trial, comprising a group-sequential design with 2 interim analyses with 520 patients, and an option to increase the sample size to 700 patients at the second interim analysis. The sample size of 520 patients allows for 417 deaths to give 80% power to detect an increase in median overall survival from 10.7 months for the sorafenib group (based on the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol [SHARP] trial) to 14.2 months for the transarterial radioembolization+sorafenib group (hazard ratio 0.754) with 2-sided alpha of .05. The increased sample size of 700

patients allows for 564 deaths to give 80% power to detect a smaller difference in median overall survival from 10.7 months for the sorafenib group to 13.7 months for the transarterial radioembolization+sorafenib group (hazard ratio 0.781).

Results: Enrollment for the study completed in September 2017. Results of the first and second interim analyses were reviewed by the Independent Data Monitoring Committee. The recommendation of the committee, at both interim analyses, was to continue the study without any changes.

Conclusions: The STOP-HCC study will contribute toward the establishment of the role of combination therapy with transarterial radioembolization and sorafenib in the treatment of unresectable hepatocellular carcinoma with and without branch portal vein tumor thrombosis.

Trial Registration: ClinicalTrials.gov NCT01556490; https://clinicaltrials.gov/ct2/show/NCT01556490 (Archived by WebCite at http://www.webcitation.org/7188iygKs).

Registered Report Identifier: RR1-10.2196/11234

(JMIR Res Protoc 2018;7(8):e11234) doi:10.2196/11234

KEYWORDS

sorafenib; hepatocellular carcinoma; microspheres; yttrium radioisotopes; research design; clinical trial, phase III; randomized controlled trial; carcinoma, hepatocellular

Introduction

Background

Primary liver cancer (hepatocellular carcinoma [HCC] and intrahepatic bile duct cancer) is the fifth most common cancer in men and ninth most common in women worldwide [1]. Globally, HCC is the second most common cause of cancer deaths [1]. The selection of therapeutic strategy and prediction of survival are guided by disease staging systems, of which the most widely used is the Barcelona Clinic Liver Cancer (BCLC) classification system [2-4]. The system determines cancer stage (BCLC A, B, C, and D) and prognosis based on 3 major prognostic factors of HCC: tumor burden, liver function, and Eastern Cooperative Oncology Group (ECOG) Performance Status score. This allows differentiation of patients with early-stage disease, who could benefit from curative treatments, from those with intermediate, advanced, and end-stage disease, who mostly receive palliative therapies or best supportive care.

Early-stage disease is often asymptomatic and unlikely to be diagnosed unless patients are enrolled in a surveillance program. Most HCC is diagnosed after patients have progressed beyond early-stage disease and, thus, they receive palliative treatments (intra-arterial treatment, systemic therapies, and external radiation), with the goal to improve life expectancies and maintain a good of quality of life. Median survival in this group of patients varies widely, ranging from approximately 3 months for patients with metastatic disease and portal vein thrombosis to up to 33 months for patients with good prognosis [5,6]. The patients with a diagnosis of BCLC D disease are not expected to derive a significant therapeutic benefit from HCC treatment unless they are bridged to transplantation. Even among those for whom treatment remains possible, most patients receive only best supportive care [7].

Patients with unresectable HCC are primarily treated with locoregional therapies and systemic agents. The systemic treatment sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals Inc, Wayne, New Jersey, USA) is the only approved systemic therapy in the first-line treatment of patients with unresectable HCC [8,9]. It is the standard-of-care treatment for patients with advanced HCC (BCLC C), as recommended by the European Association for the Study of the Liver [3]; however, some regional differences exist for patient selection for sorafenib treatment [10]. Two placebo controlled, randomized, phase 3 trials (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol [SHARP] and the Asia-Pacific trial) demonstrated that sorafenib provided a significant improvement in median overall survival [11,12]. In the SHARP trial, median overall survival improved from 7.9 months in the placebo group to 10.7 months in the sorafenib group (hazard ratio [HR] 0.69, 95% CI 0.55-0.87) and, in the Asia-Pacific trial, median overall survival improved from 4.2 months in the placebo group to 6.5 months in the sorafenib group (HR 0.68, 95% CI 0.50-0.93). Individual responses to sorafenib may be affected by baseline characteristics, such as disease etiology, tumor burden, performance status, tumor stage, and prior therapy. Sorafenib consistently increased median overall survival across these different subgroups, compared with placebo, as reflected by HRs of 0.50 to 0.85, which were similar to that of the overall group (HR 0.69) [13]. The subgroups with HRs in the lower end of this range were patients with an ECOG Performance Status score of 1 to 2 (median overall survival 8.9 months with sorafenib vs 5.6 months with placebo; HR 0.71, 95% CI 0.52-0.96); patients with both extrahepatic disease and portal vein invasion (median overall survival 8.9 months with sorafenib vs 6.7 months with placebo; HR 0.77, 95% CI 0.60-0.99); and BCLC C patients (median overall survival 9.7 months with sorafenib vs 7.0 months with placebo; HR 0.70, 95% CI 0.56-0.89) [13].

The use of sorafenib in clinical practice was assessed in over 3000 patients in the global observational registry study of sorafenib, Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment With Sorafenib (GIDEON) [14]. Median overall survival in GIDEON ranged from 8.5 months (95% CI 7.6-9.6) in the United States to 14.5 months (95% CI 13.2-17.4) in Japan [10]. Despite the indisputable benefit of sorafenib, 85% of patients experienced at least one adverse event, and the incidence of drug-related adverse events leading to discontinuation was around 31% in the GIDEON registry [10].

After the marketing of sorafenib was approved in North America, numerous studies that evaluated other molecular therapies did not demonstrate their superiority or noninferiority to sorafenib [15,16]. The combination of locoregional therapy with transarterial chemoembolization (TACE) and targeted agents (sorafenib, brivanib, and orantinib) initially appeared to be an attractive strategy; however, the combinations did not improve overall survival in 5 large randomized trials [17]. Recent significant advancements were the approval of regorafenib (Stivarga, Bayer HealthCare Pharmaceuticals Inc, Whippany, NJ, USA) and nivolumab (Opdivo, Bristol-Myers Squibb Co., Princeton, NJ, USA) for patients who have been previously treated with sorafenib [18-21]. Additional recent developments were phase 3 trials that demonstrated superiority of cabozantinib over placebo in the second-line treatment of advanced HCC and noninferiority of lenvatinib to sorafenib in the first-line treatment of unresectable HCC, as well as a phase 2 trial in which pembrolizumab showed encouraging results [22-24].

Transarterial radioembolization (TARE) could be an alternative to TACE treatment [25]. The 2 available TARE devices are TheraSphere microspheres (Biocompatibles UK Ltd, Surrey, UK) and SIR-Spheres resin microspheres (Sirtex Medical Ltd, North Sydney, Australia). Favorable survival outcomes with TheraSphere microspheres were reported for a large prospective cohort of 1000 patients over a 15-year period ending in March 2017 [26]. The majority (89%) of patients were treatment naïve. Median overall survival ranged between 8.0 and 47.3 months depending on disease stage and liver function. Also, TARE was well tolerated, and the adverse events rate was low compared with rates with systemic treatment or TACE: grade 3/4 albumin and bilirubin toxicities, respectively, were observed in 49 (5%) and 110 (11%) patients [26].

There is more rationale to combine sorafenib with TARE than with TACE. First, TARE is better tolerated than TACE, which may allow a higher dose and longer length of therapy with sorafenib. Additionally, sorafenib may be potentially more synergistic with yttrium-90, as antiangiogenic agents potentiate the effects of radiation on tumor regression [27].

Several small nonrandomized studies that investigated combination treatment with TARE and sorafenib reported favorable results among patients with BCLC A and B status. Median overall survival ranged between 12 and 20 months, and disease control was achieved in up to 100% of patients [27-30]. The most common toxicities reported were fatigue, diarrhea, and hand-foot syndrome. These toxicities are similar to those reported with sorafenib monotherapy. Sorafenib doses were reduced in up to 65% of patients and administration was interrupted in up to 13.8%.

Two large randomized multicenter trials were designed to evaluate combination treatment with TARE and sorafenib, with the primary end point of overall survival. The Evaluation of Sorafenib in Combination With Local Micro-Therapy Guided by Primovist Enhanced MRI in Patients With Hepatocellular Carcinoma (SORAMIC) trial compared sorafenib alone against TARE using resin yttrium-90 microspheres combined with sorafenib in patients with advanced HCC [31]. Recently reported results of the study, conducted primarily in Europe, showed that in a total of 419 patients, the combination of TARE and sorafenib did not improve overall survival over treatment with sorafenib alone (12.1 vs 11.5 months; HR 1.018, *P*=.87) and resulted in an increased rate of adverse events of grade 3 or higher (73% vs 65%) [32]; however, an overall survival benefit was observed in some subgroups.

Objective

The TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (STOP-HCC) study is the largest phase 3 prospective study of TARE in combination with sorafenib in unresectable advanced HCC. Compared with the SORAMIC trial, STOP-HCC has a larger sample size and so should have greater statistical power to detect a difference in overall survival; additionally, STOP-HCC uses glass yttrium-90 microspheres and is being conducted worldwide. At the time the STOP-HCC study was designed (in 2011), sorafenib was the only systemic agent approved for use as first-line treatment in HCC and, since then, there have been several trials reporting positive outcomes [10,33]. The primary purpose of the STOP-HCC study is to compare overall survival in patients who receive sorafenib alone with overall survival in patients who receive TARE with TheraSphere yttrium-90 microspheres followed by sorafenib. Here we report the protocol for the STOP-HCC study.

Methods

Overview

The STOP-HCC study, also known as the BTG TS-103 study, was registered with ClinicalTrials.gov (NCT01556490) on March 13, 2012. Textbox 1 describes eligibility criteria for the STOP-HCC study. Participating institutions obtained institutional review board approval of the protocol and informed consent form and obtained written informed consent from patients (Multimedia Appendix 1). Each institution has qualified investigators and support staff who conduct the study according to Good Clinical Practice guidelines, have adequate expertise in the treatment of patients with HCC, and are experienced with and trained in the use of TheraSphere yttrium-90 microspheres. A list of sites is available on the study's ClinicalTrials.gov registration page (linked in the abstract).

Textbox 1. Patient eligibility for the TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (STOP-HCC) study.

Inclusion criteria

- Patients aged >18 years with unresectable hepatocellular carcinoma (HCC; confirmed by histology or noninvasive American Association for the Study of Liver Diseases criteria) who have a life expectancy ≥12 weeks.
- Measurable disease defined as at least one unidimensional measurable lesion by computed tomography or magnetic resonance imaging (according to Response Evaluation Criteria in Solid Tumors v1.1).
- Child-Pugh score ≤7 points and Eastern Cooperative Oncology Group Performance Status score of ≤1.
- Eligible to receive standard-of-care sorafenib.
- Platelet count >50×10^9/L or >50% prothrombin activity; hemoglobin ≥8.5 g/dL (≥85.0 g/L); bilirubin ≤2.5 mg/dL (≤42.8 μmol/L); alanine aminotransferase and aspartate aminotransferase <5 times the upper limit of normal; amylase or lipase ≤2 times the upper limit of normal; serum creatinine ≤1.5 times the upper limit of normal; international normalized ratio for prothrombin time <2.0.

Exclusion criteria

Key exclusions:

- Eligible for curative treatment (eg, ablation or transplantation).
- Main portal vein thrombosis (branch portal vein thrombosis is permissible).
- Extrahepatic disease, except lung nodules and mesenteric or portal lymph nodes ≤2.0 cm each.

Other exclusions:

- Must not have tumor replacement >70% of total liver volume based on visual estimation by the investigator or must not have tumor replacement >50% of total liver volume in the presence of albumin <3 g/dL (<30 g/L).
- History of previous or concurrent cancer other than HCC unless treated curatively ≥5 years prior to entry.
- Contraindication to TheraSphere administration according to package label.
- Patients infected with HIV can be considered; however, they must be well managed and well controlled with an undetectable viral load.
- Contraindications to sorafenib, angiography, and selective visceral catheterization.
- Concurrent treatment with substrate agents for cytochrome P450 2B6, uridine diphosphate glucuronosyltransferase 1A1 or 1A9, and P-glycoprotein; rifampicin; St John's wort; phenytoin; carbamazepine; phenobarbital; dexamethasone; other systemic anticancer agents (eg, docetaxel, doxorubicin, or irinotecan); other locoregional therapies (other than study treatment).
- Prior treatment with transarterial chemoembolization (TACE) or bland embolization must have occurred >2 months prior to randomization and must have been applied to a treatment field or lobe that is not to be treated under this protocol. For patients with tumor progression in the treatment field or lobe previously treated with TA(C)E, vessels feeding the tumor(s) must be assessed for adequate blood flow using angiography (cone beam computed tomography strongly recommended), and the TACE or bland embolization must have been applied >6 months prior to randomization.
- Prior receipt of external beam radiation treatment to the chest, liver, or abdomen.

Overview of Study Design

STOP-HCC is an ongoing phase 3, randomized, parallel-group, multicenter, prospective, open-label study evaluating treatment with TheraSphere microspheres in patients with unresectable HCC in whom sorafenib therapy is already planned. Patients were recruited at up to 105 sites in the United States, Canada, Europe, and Asia. Eligible patients were randomly assigned in a 1:1 ratio to the sorafenib and TARE+sorafenib groups. The sorafenib group receives planned sorafenib according to the product label. The TARE+sorafenib group receives TheraSphere microspheres prior to the initiation of sorafenib. All patients are followed prospectively from randomization to death until the predefined number of deaths, to allow the final analysis to be conducted, have occurred.

Site investigators are from departments of radiology, nuclear medicine, and interventional radiology. Investigators are experienced in radioembolization with radioactive microsphere products. For sites with investigators with low or no experience with TheraSphere microspheres, before inclusion in the trial, the site team must have completed training that included 3 to 5 administrations of TheraSphere microspheres. Administration of TheraSphere microspheres is generally considered to be an outpatient procedure in the United States and Canada and an inpatient procedure in Europe and Asia. The physical location for aftercare and recovery was determined by individual institutional policies and facility configurations. The sites are collecting the data.

An Independent Data Monitoring Committee (IDMC), led by the IDMC chairperson, was established to oversee the conduct of the study. The IDMC met periodically to review enrollment, protocol deviations, and safety events. In addition, the IDMC conducted and reviewed an initial feasibility safety analysis and will evaluate the overall survival data at interim analyses for consideration of stopping the study for efficacy and for the option to increase the sample size at the second interim analysis.

The IDMC is tasked to make formal recommendations to the study sponsor at the time of the feasibility safety analysis, at the time of the interim analyses, and during the conduct of the study based on detailed decision rules specified in the IDMC charter. An IDMC member or designate can act as the study independent medical monitor. The IDMC will evaluate the final study report.

Screening

On day –14 to day 0, the following assessments were conducted: review of eligibility criteria, demographics, medical history, physical examination, medication and prior treatment history, serum pregnancy test for women, ECOG Performance Status, hematology (white blood cells, hemoglobin, hematocrit, and platelets), coagulation (prothrombin time, partial thromboplastin time, and international normalized ratio for prothrombin time), chemistry panel, liver function tests, tumor markers for HCC (alpha-fetoprotein), triple-phase magnetic resonance imaging and spiral computed tomography (CT) of abdomen, Child-Pugh score, spiral CT of chest and pelvis, quality-of-life questionnaire, assessment and report of adverse events, and review and recording of concurrent medications. Informed consent was obtained at screening.

Randomization and Stratification

Eligible patients were randomly assigned on day 0 using a computer-generated randomization scheme, and investigators had the option to randomly assign patients using either a Web-based electronic system or telephone. To create a balance between the 2 study groups, patients were stratified based on region (North America and Europe vs Asia), ECOG Performance Status (0 vs 1), and presence or absence of branch portal vein tumor thrombosis (PVTT). Randomly assigned patients who were unable to receive the planned study treatment continued to be followed under their assigned study group and will be included in the statistical analysis.

Treatment

Figure 1 shows the STOP-HCC treatment schema.

Table 1 shows the schedule of assessments and treatment. For patients who discontinued the study treatment due to progressive disease and were unable to maintain routine clinic visits, investigative sites should maintain telephone contact until death.

Sorafenib Group

Patients randomly assigned to the sorafenib group start sorafenib as soon as possible after randomization, in accordance with the product labeling. Doses are adjusted over several visits as needed. Every 8 weeks after randomization, assessments are conducted as Table 1 describes.

Figure 1. Clinical trial schema for the TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (STOP-HCC) study. TARE: transarterial radioembolization; TS: TheraSphere microspheres.

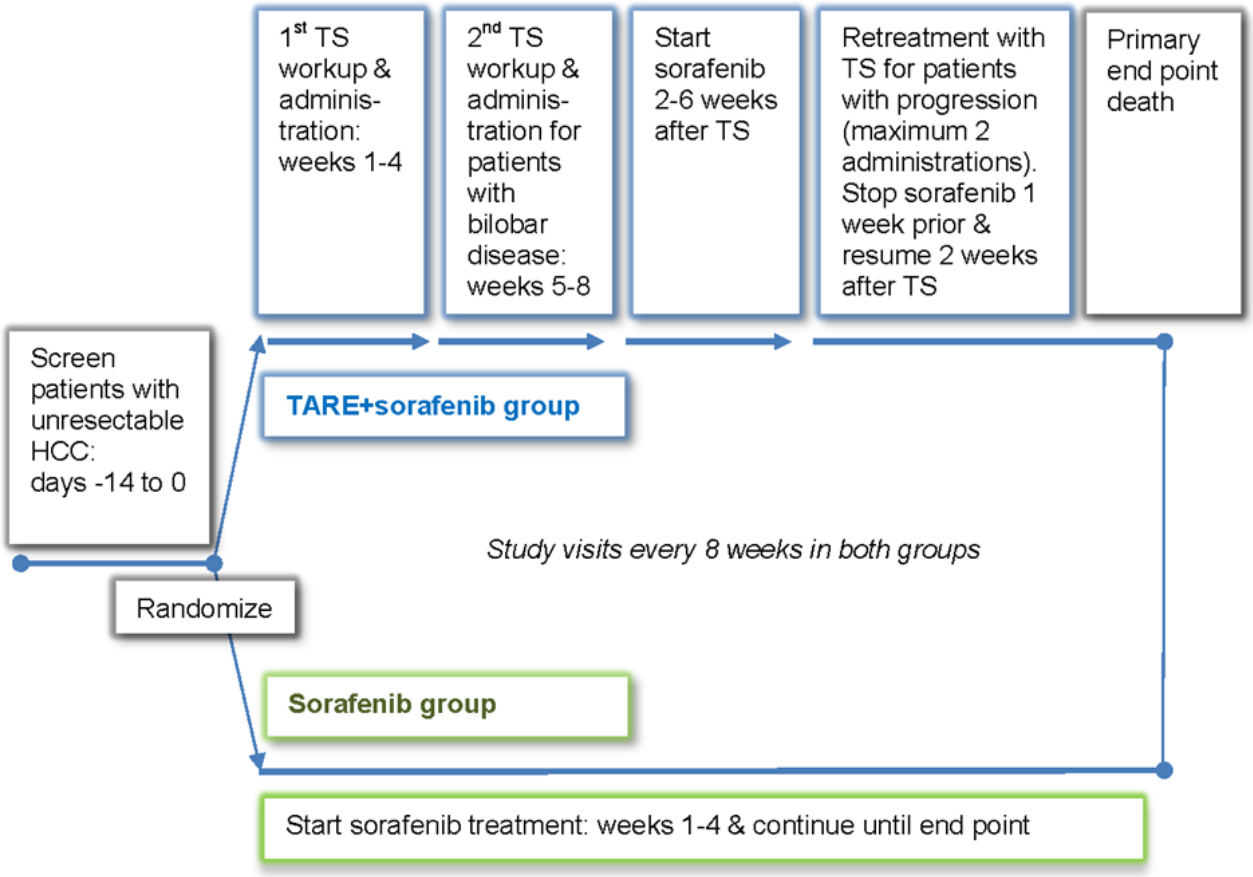

Table 1. TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (STOP-HCC) study schedule of assessments and events.

Interventions and Assessments	Sorafenib group: initiate treatment weeks 1-4; continue therapy weeks ≥5	TARE[a]+sorafenib group				Follow-up every 8 weeks ±14 days[c] (for both groups)
		First workup and TARE treatment: Weeks 1-4	Second workup and TARE treatment for patients with bilobar disease: Weeks 5-8	Sorafenib treatment: initiate and continue sorafenib treatment >2 to <6 weeks after TARE	Workup and retreatment[b] for patients with hepatic progression	
Interventions						
Administer sorafenib[d]	✓			✓	✓[c]	
Calculate liver volume and mass		✓			✓	
Hepatic angiogram, ^{99m}Tc-MAA scan[f], calculate TARE dose, administer TARE[g]		✓	✓		✓	
Assessments						
ECOG[h] Performance Status		✓	✓		✓	✓[i]
Hematology[j], coagulation[k], chemistry panel, liver function tests	✓[l]	✓[l]			✓	✓[m]
Tumor markers for hepatocellular carcinoma (alpha-fetoprotein)	✓	✓				✓[m]
Triple-phase MRI[n]/spiral CT[o] abdomen, Child-Pugh score, spiral CT chest and pelvis, quality-of-life questionnaire						✓[m]
Assess and report adverse events, review and record concurrent medication	✓	✓	✓		✓	✓[m]
Final end point, efficacy and safety documentation, and exit patient						✓[i]

[a]TARE: transarterial radioembolization.

[b]Additional TARE workup and administration in lesions amenable to further TARE.

[c]The follow-up visits should be scheduled from the day of randomization. A window of ±14 days is permissible from the scheduled date.

[d]According to package insert at weeks 1-4 for sorafenib group patients and after all initial TARE administrations for TARE+sorafenib group patients only.

[e]Sorafenib to be stopped 7 days before subsequent TARE administration in disease progression and restarted 2 weeks after TARE is administered.

[f]^{99m}Tc-MAA scan: technetium-99m macroaggregated albumin.

[g]Additional TARE may be administered only after progression if lesions are amenable to treatment.

[h]ECOG: Eastern Cooperative Oncology Group.

[i]Both before and after progression of disease resulting in termination of further treatment.

[j]Hematology tests: white blood cells, hemoglobin, hematocrit, and platelets.

[k]Coagulation tests: prothrombin time, partial thromboplastin time, and international normalized ratio for prothrombin time.

[l]If treatment commences within 14 days of randomization, the clinical laboratory assessments are not required to be repeated.

[m]Prior to progression of disease resulting in termination of further treatment.

[n]MRI: magnetic resonance imaging.

[o]CT: computed tomography.

TARE+Sorafenib Group

All patients in the study have liver volume measurements and mass calculations with triple-phase CT (Table 1). Eligibility for TARE with TheraSphere microspheres included a pretreatment angiography with administration of technetium-99m macroaggregated albumin (^{99m}Tc-MAA) followed by a ^{99m}Tc-MAA single-photon emission computed tomography (SPECT) or SPECT/CT scan to determine catheter positioning for treatment, to assess the potential for extrahepatic shunting

requiring use of angiographic occlusion techniques, and to determine the lung shunt fraction.

Patients deemed unsuitable for such treatment can proceed to treatment with sorafenib as described above. For eligible patients, TARE is started within 28 days of randomization, prior to the initiation of sorafenib.

Patients with unilobar disease receive a lobar TARE. Patients with bilobar disease receive TARE to the first lobe, and then TARE to the second lobe after at least 28 days after the first treatment but still within 5 to 8 weeks after randomization.

The treatment approach for TARE with TheraSphere microspheres is lobar. Target liver mass and volume are determined by the positioning of the delivery catheter in the hepatic vasculature and the resulting liver area (Couinaud segments) infused. Since there is considerable individual variation in hepatic vascular anatomy, the determination of target liver mass and volume depends on the variant encountered. TheraSphere microspheres are administered at a dose of 120 Gy ±10% to each lobe. If radiation exposure to the lungs exceeds 30 Gy (or 50 Gy cumulative across all planned infusions, estimated during the dose calculation), the TARE dose is reduced to a minimum dose of 90 Gy ±10%. If, after consideration of dose reduction, radiation exposure to the lung continues to be more than 30 Gy (or 50 Gy cumulative), TARE is not administered and sorafenib treatment is initiated. ^{99m}Tc-MAA angiography and ^{99m}TC-MAA SPECT or SPECT/CT can be repeated after 4 weeks of continuous treatment with sorafenib to reassess lung shunting. If radiation exposure to the lung is less than 30 Gy for a single treatment (or 50 Gy cumulative over all planned infusions) within a target dose of 90 to 120 Gy ±10%, TARE can be administered.

Sorafenib treatment is initiated at least 2 weeks and up to 6 weeks following administration of TARE (Table 1), rather than concurrently, in order to minimize the risk of additive or synergistic adverse events. Sorafenib is administered according to the package insert. Every 8 weeks after randomization, follow-up is conducted as Table 1 shows.

During follow-up, patients in the TARE+sorafenib group who had hepatic progression with lesions amenable to TARE can be retreated under investigator judgment. In that case, sorafenib is discontinued 7 days prior to TARE (equivalent to approximately 5 to 7 half-lives) and resumed 2 weeks after TARE.

For TARE with TheraSphere microspheres, the catheter is placed under image guidance at the same position as for ^{99m}Tc-MAA administration. Prophylaxis with a gastric inhibitor (H2 blocker) is recommended.

After the first 20 patients in the TARE+sorafenib group received both TheraSphere microspheres and sorafenib and completed at least 2 weeks of sorafenib therapy, a feasibility safety assessment was conducted. The IDMC reviewed the safety results of both groups in an unblinded fashion. Stopping further enrollment to trial could have been considered if there was either (1) an unanticipated patient death definitely or probably related to the sequential administration of TARE followed by sorafenib, or (2) a pattern of serious toxicity clearly related to the sequential administration of TARE followed by sorafenib as assessed by the IDMC experts based on the severity of disease of the study population.

Outcome Measures and Definitions

The primary outcome measure of the STOP-HCC study is overall survival time. The secondary outcomes are time to progression, time to untreatable progression, time to symptomatic progression, tumor response, quality of life, and adverse events. Definitions of these outcomes are as follows:

Overall survival is the time from the randomization date to death from any cause.

Time to progression is the time from randomization to radiological progression according to Response Evaluation Criteria in Solid Tumor (RECIST) v1.1.

Time to untreatable progression is the time from randomization to predefined criteria for untreatable progression. For patients randomly assigned to the TARE+sorafenib group, any liver lesion still amenable to TARE is not considered untreatable progression. Untreatable progression is defined as any of the following: intolerance to sorafenib; occurrence of specific contraindications to sorafenib; assessment of progression in the target lesions or occurrence of new lesions after treatment (for patients randomly assigned to the TARE+sorafenib group, a maximum of 2 retreatments with TARE); occurrence of specific contraindications to TheraSphere microspheres or the appearance of lung or intestinal shunts or anatomical constraints not correctable by radiological procedures; confirmed extrahepatic metastases; deterioration of liver function (Child-Pugh score >B7); and clinical progression to ECOG Performance Status score greater than 1. Such deterioration in performance score is observed at 2 subsequent evaluations at 8-week intervals.

Time to symptomatic progression is the time from randomization to ECOG Performance Status greater than 1 with or without tumor progression based on RECIST v1.1; deterioration in ECOG status is confirmed at 2 subsequent evaluations at 8-week intervals.

Tumor response is categorized according to RECIST v1.1 (change in the sum of diameter of target lesions) based on investigator assessment of baseline versus subsequent follow-up images [34]. The tumor response, according to the modified RECIST and based on a blinded centralized independent imaging assessment, is recorded as an exploratory end point.

Quality-of-life assessment is based on the patient-reported Functional Assessment of Cancer Therapy-Hepatobiliary questionnaire. A deterioration in quality of life is a 7-point decline in the total score or death, whichever occurs first.

The time to deterioration in quality of life is calculated as the time from randomization to deterioration in quality of life.

The following additional efficacy variables will be assessed.

Progression-free survival is defined as the time from randomization until date of radiological progression according to RECIST v1.1 or death due to any cause, whichever occurs first.

Duration of objective response will be determined for patients who have a best response of complete response or partial response. Duration of objective response is defined as the time from first date of response of complete response or partial response until date of progression or death due to any cause, whichever occurs first.

Duration of disease control will be determined for patients who had a best response of complete response, partial response, or stable disease. Duration of disease control is defined as the time from the first date of response of complete response, partial response, or stable disease until date of progression or death due to any cause, whichever occurs first.

Depth of response is defined as the percentage change from baseline to the nadir in the sum of the longest diameters of target lesions.

Posttreatment tumor shrinkage is defined as the proportion of patients achieving a 20% or greater decrease in the sum of the longest diameters of target lesions.

Adverse events, serious adverse events, and unanticipated adverse device effects are collected throughout the study and assessed using version 4.0 of the National Cancer Institute Common Terminology for Adverse Events [35].

Planned Statistical Analysis

Study Design and Sample Size

The STOP-HCC study is a phase 3 adaptive trial using a group-sequential design with overall survival as the primary efficacy end point. The study was designed to detect a 3.5-month increase in median overall survival, from 10.7 months in the sorafenib group to 14.2 months in the TARE+sorafenib group (HR 0.754), using a log-rank test. Due to uncertainty in the expected treatment effect, we planned a sample size reestimation, which would allow the sample size to increase in order to detect a 3.0-month increase in median overall survival time, from 10.7 months in the sorafenib group to 13.7 months in the TARE+sorafenib group (HR 0.781).

A maximum of 417 deaths would yield 80% power to detect the target difference in median overall survival (HR 0.754) with a 2-sided alpha of .05 using a group-sequential design with 2 interim analyses. It was estimated that a maximum of 520 patients would need to be recruited over 60 months, with an 18-month additional follow-up period. This includes an adjustment to take account of an assumed 5% of patients who would be lost to follow-up and for whom a date of death was not recorded, and an assumed additional 5% of patients who would be erroneously randomly assigned because they did not meet the eligibility criteria at randomization.

Interim and Final Analyses of the Primary End Point

The IDMC will evaluate the overall survival data during 2 interim analyses, which are planned at the observance of approximately, but no less than, 188 and 250 events, with a 2-sided $P \leq .0151$ at either point allowing the study to be stopped early for efficacy. The efficacy stopping boundaries are based on the rho family error spending function with the parameter value $\rho=1.5$. If the interim analyses do not occur at exactly 188 or 250 deaths, the corresponding efficacy boundaries will be calculated using the rho family spending function with $\rho=1.5$.

Sample size modification will be considered at the second interim analysis according to a simplification of the promising zone approach described in Mehta and Pocock [36]. The conditional probability boundaries for the decision rules at the second interim analysis are as follows: unfavorable zone ($CP2<z$): study size to remain at 417 deaths; promising zone ($z \leq CP2<0.8$): study size to increase to 564 deaths; favorable zone ($CP2 \geq 0.8$): study size to remain at 417 deaths, where CP2 is defined as the conditional probability of rejecting the null hypothesis at the final analysis, given the results at the second interim analysis, and z is a predefined cutoff defined according to the Müller and Shäffer [37] principle to ensure that type I error is controlled.

The final analysis, without a sample size modification, is planned when approximately, but no less than, 417 deaths have occurred. A 2-sided $P \leq .0363$ is required to declare a statistically significant improvement in median overall survival at the final analysis. If the final analysis does not occur at exactly 417 deaths, the corresponding efficacy boundary will be calculated using the rho family spending function with $\rho=1.5$.

If the sample size increases after the second interim analysis, the final analysis is planned when approximately, but no less than, 564 deaths have occurred, which gives 80% power to detect an improvement in median overall survival from 10.7 to 13.7 months using a log-rank test with a 2-sided $P \leq .0363$ required to declare statistical significance. We estimated that recruitment of approximately 700 patients over 66 months with an 18-month follow-up period would allow for 564 deaths, yielding 80% power to detect a statistically significant improvement in median overall survival with a 2-sided $P \leq .0363$. This includes an adjustment to take account of an assumed 5% of patients lost to follow-up with no recorded date of death, and an assumed additional 5% of patients erroneously randomly assigned because they did not meet the eligibility criteria at randomization.

Statistical Analyses

All efficacy end points will be analyzed using a modified intention-to-treat population, defined as patients who met the study eligibility criteria and were randomly assigned. The per-protocol population is defined as the patients in the modified intention-to-treat population without any major protocol deviations that could affect efficacy evaluation; analysis using the per-protocol population will be according to the treatment actually received. The safety population included all randomly assigned patients who received study treatments at least once; analysis will be according to the treatment actually received.

For the primary end point, the Kaplan-Meier method will be used to estimate overall survival curves, and the log-rank test will be used to compare groups. For all secondary end points, comparison between groups will be conducted at a 2-sided alpha of .05, with analyses occurring only at final analysis to determine statistical significance between the groups. For the secondary time-to-event end points (time to progression, time to untreatable progression, time to symptomatic progression,

and time to deterioration in quality of life), the Kaplan-Meier method will be used to estimate curves, and comparisons between groups will be conducted using the log-rank test. Tumor response rates will be compared between groups using the continuity-adjusted Newcombe-Wilson test.

Poolability and Other Analyses

Univariable Cox regression analyses of the primary efficacy end point, overall survival, and all other time-to-event end points (ie, time to progression, time to untreatable progression, time to symptomatic progression, and time to deterioration in quality of life) will be conducted with the following baseline factors, one at a time, together with randomized group: age group, race, ethnicity, unilobar versus bilobar disease, region, ECOG Performance Status, presence of branch PVTT, duration from date of initial diagnosis of HCC to randomization, tumor burden, presence of extrahepatic lesions, Child-Pugh score, BCLC stage, HCC etiology, prior oncologic treatment for HCC, bilirubin, albumin, albumin-bilirubin score, and alpha-fetoprotein. This will allow an assessment of each of these factors on the study outcomes.

To address the poolability of data across regions, study sites, and sex, multivariable Cox regression analyses of the time-to-event end points will be conducted with the following factors, together with treatment group, and the factors from the univariable analyses that have a 2-sided $P<.15$: region and treatment group by region interaction, enrolling site and treatment group by site interaction, and sex and treatment group by sex interaction, respectively.

Logistic regression analyses of binary end points (ie, objective response rate and disease control rate) will be conducted in the same way as the Cox regression analyses described above.

Results

Enrollment for the study completed in September 2017. Results of the first and second interim analyses were reviewed by the IDMC; the recommendation of the committee, at both interim analyses, was to continue the study without any changes.

Discussion

Overview

TARE has gained a place in various guidelines and consensus recommendations for the treatment of unresectable HCC. A consensus panel report by the Radioembolization Brachytherapy Oncology Consortium states that TARE can be considered for patients with unresectable hepatic primary cancer or metastatic hepatic disease with liver-dominant tumor burden, and a life expectancy of at least 3 months [38]. TARE is recommended in the Asia-Pacific Primary Liver Cancer Expert consensus guidelines in early and intermediate HCC when standard treatment is not compatible and in locally advanced HCC [39]. The Taiwan Liver Cancer Association and the Gastroenterological Society of Taiwan recommend TARE as an option in patients who are refractory to TACE or have either a large tumor burden or major vascular invasion (such as PVTT) [40].

PVTT is the most common form of macrovascular invasion in HCC, and it is a common complication [41]. TACE and other forms of embolic treatment are generally considered contraindicated or not relevant in HCC patients with PVTT. The reason is that multiple TACE treatments could embolize the hepatic artery, leaving the compromised portal vein as the only source of blood supply to the liver and, thus, raise the risk of liver failure [42]. Treatment of HCC associated with PVTT would be a good indication for TheraSphere microspheres because the small size and number of TheraSphere microspheres administered makes them less embolic than other devices, and the ensuing effect on vascular dynamics is smaller than with other devices [43-45]. TARE with TheraSphere microspheres was found to be tolerable and effective in HCC patients with branch or lobar PVTT [44,46,47].

We expect the STOP-HCC study to be the largest study of sorafenib alone versus sorafenib combined with TARE. We chose overall survival as the primary end point; overall survival is the primary end point recommended by the American Association for the Study of Liver Diseases Panel of Experts for the design of clinical trials in HCC patients because it is the most clinically relevant and the one that is least subject to investigator bias [48]. The major factors that may affect overall survival in this trial are the pattern of progression, access to postprogression therapy, tolerance of the combination of TARE and sorafenib, and underlying cirrhosis and hepatitis.

When the study was designed there was no standard second-line treatment available. Now that at least three new drugs are available in second-line treatment (regorafenib, cabozantinib, and the checkpoint inhibitor nivolumab), it is possible that postprogression treatment may affect overall survival. Subsequent treatments that are equally effective in the treatment arms would not be expected to affect the absolute overall survival benefit of the experimental treatment but will make the relative improvement in overall survival smaller, provided that the subsequent therapies used in both treatment arms follow the current standard of care [49]. There is a low risk that postprogression treatment could be a factor influencing the end point. No crossover was permitted in this trial. It is unlikely that TheraSphere, which has a low toxicity profile, will influence the rate of administration of further anticancer treatment at progression or decrease the efficacy of second-line treatment compared with the treatment in the control group [50]. In the recently published REFLECT trial, the median overall survival in sorafenib-treated patients was 12.3 months (95% CI 10.4-13.9) versus 10.7 months in the SHARP trial [11,51]. One explanation could be the proportion of patients receiving treatments after sorafenib (39%) in the REFLECT trial [51].

Another factor that may affect overall survival is the tolerance to the treatment. In the randomized controlled trials of TACE versus TACE plus sorafenib (Sorafenib or Placebo in Combination With Transarterial Chemoembolization for Intermediate-Stage Hepatocellular Carcinoma [SPACE], Sorafenib in Combination With Transarterial Chemoembolisation in Patients With Unresectable Hepatocellular Carcinoma [TACE 2], and Transcatheter Arterial Chemoembolization Therapy in Combination With Sorafenib [TACTICS] trials [52-54]) and of sorafenib versus TARE plus

sorafenib (SORAMIC) [32], the combination treatments did not impair TACE or TARE administration. However, SPACE, TACE 2, and SORAMIC did not meet their primary end points. While the TACTICS trial was successful, it could be argued that the favorable results of the combination were mostly related to the low dosage and duration of sorafenib, which was given for a median of 38.7 weeks [55,56] compared with 17.1 weeks (TACE 2), 21 weeks (SPACE), and 29 weeks (SORAMIC). In the TACTICS study, patients received sorafenib 400 mg/day prior to TACE, then 800 mg/day during TACE sessions until time to untreatable progression; the median doses of sorafenib in the TACE 2, SPACE, and SORAMIC trials were 660 mg/day, 566 mg/day, and 485 mg/day [32,52-54], respectively. This low dose in the TACTICS trial allowed for less treatment interruption due to adverse events and a longer duration of treatment. The STOP-HCC study addresses a slightly different population of patients (only advanced, as compared with intermediate stage in TACE 2 and SPACE and 50% at intermediate stage in SORAMIC), and the sensitivity to sorafenib could be different according to the disease stage. Also, to avoid the cumulative side effect of the treatments and allow an effective duration of sorafenib, treatment with sorafenib is started after completion of TARE and dose reduction is planned.

Overall survival should be improved by the control of the different risks of progression. Treatment failure could be the consequence of new intrahepatic lesions, intrahepatic growth, and new extrahepatic lesions (including portal vein thrombosis). TARE should mitigate the first two risks and sorafenib, the third risk.

Finally, survival in HCC patients is confounded by underlying cirrhosis and hepatitis, so while there may be a treatment effect, there are other elements at play that determine survival.

Although the SORAMIC trial did not show an improvement in overall survival, there are some design differences between that trial and the STOP-HCC trial: the STOP-HCC study has a larger sample size and so should have greater statistical power to detect an overall survival difference, the TARE devices used in the 2 studies are different (resin yttrium-90 microspheres vs glass yttrium-90 microspheres), and the SORAMIC trial was conducted in Europe and Turkey with 38 sites, whereas STOP-HCC is being conducted in North America, Europe, and Asia with approximately 100 sites.

We chose secondary end points to determine whether improvement in response affects overall survival and quality of life. The secondary end points of time to progression, time to symptomatic progression, and tumor response rate are also recommended by the American Association for the Study of Liver Diseases Expert Panel [48]. Additionally, this study is assessing time to untreatable progression and quality of life.

Limitations

Limitations of the study include the unblinded design, but other limitations were minimized as much as possible. Blinding for the sorafenib group would have been difficult to achieve due to its well-known and extensive toxicity profile. There are uncertainties in the assumptions of median overall survival for the sample size calculation (eg, since the population enrolled may include more PVTT patients than expected, and the literature suggests that a larger difference in median overall survival may exist for PVTT patients vs non-PVTT patients), hence the choice of an adaptive study design, which allows the sample size to be increased to detect a smaller difference in median overall survival. The STOP-HCC study addresses this issue in terms of providing a large patient population in a well-designed trial.

Conclusion

It is important to establish an effective, tolerable, and affordable treatment to improve patient survival for unresectable HCC. One challenge in the treatment of patients with HCC at the advanced stage is providing an efficient treatment of the cancer without impairment of liver function and quality of life. TARE has a limited toxicity profile when used appropriately and, consequently, a low impact on sorafenib dose intensity and duration and is, thus, an attractive concomitant treatment. Enrollment for the STOP-HCC study completed in September 2017 [57], and the estimated follow-up period is 18 months. Data from this trial will enhance the knowledge regarding optimal treatment options for patients with unresectable HCC.

Acknowledgments

The authors thank all the individuals who participated in the design of the study (TheraSphere STOP-HCC Protocol Study Group), the IDMC, and Tuli Ahmed, Accelera Communications, LLC (King of Prussia, PA, USA) and Gretchen Pezza, BTG International, Inc (West Conshohocken, PA, USA) who provided medical writing support. The TheraSphere STOP-HCC Protocol Study Group consisted of the following members: H Kevin Kim and Bassel El-Rayes (Emory University Hospital, Atlanta, GA, USA); Jorg Schlaak (University Hospital, Essen, Germany); Stephen Cohen (Fox Chase Cancer Center, Philadelphia, PA, USA); Jean-Luc Raoul (Centre Eugène Marquis, Rennes, France); Jonathan Strosberg, Bulent Arslan, and Ravi Shridhar (H Lee Moffitt Cancer Center, Tampa, FL, USA); Matt Johnson and Mary Maluccio (Indiana University, Indianapolis, IN, USA); Dan Brown (Thomas Jefferson Hospital, Philadelphia, PA, USA); Jeff Geschwind, David Cosgrove, and Michael Choti (Johns Hopkins University, Baltimore, MD, USA); Andrew Zhu (Massachusetts General Hospital, Boston, MA, USA); Lewis Roberts (Mayo Clinic, Rochester, MN, USA); Bill Rilling (Medical College of Wisconsin, Milwaukee, WI, USA); Ravi Murthy and Ahmed Kaseb (MD Anderson, Houston, TX, USA); Vincenzo Mazzaferro (Istituto Nazionale Per Lo Studio e La Cura dei Tumori, Milan, Italy); Laura Kulik, Mary Mulcahy, Riad Salem, Bob Lewandowski, and Al Benson III (Northwestern Memorial Hospital, Chicago, IL, USA); Mark Bloomston, Tony Saab, and Hooman Khabiri (Ohio State University Medical Center, Columbus, OH, USA); Daniel Sze (Stanford University, Palo Alto, CA, USA); Wells Messersmith and Jan Durham (University of Colorado, Denver, CO, USA); Nicholas

Fidelman (University of California San Francisco, San Francisco, CA, USA); and HuaChing Zhao (MedTrials Inc, Media, PA, USA).

TheraSphere is a registered trademark of Theragenics Corporation used under license by Biocompatibles UK Ltd, a BTG International Group Company. TheraSphere microspheres are manufactured for Biocompatibles UK Ltd.

Conflicts of Interest

This study was sponsored by Biocompatibles UK Ltd, a BTG International Group Company. The sponsor was involved in the design of the study. The sponsor funded professional medical writers for the writing of the manuscript. All authors met International Committee of Medical Journal Editors authorship criteria. NC, JB, EB, BH, and FM are employed by BTG International Group Companies; NC and BH own company stock. JE received research grants from and acted as a consultant for BTG. DC was compensated for work on a speakers' bureau for BTG and advisory board for Bristol-Myers Squibb. LK has been compensated for work on advisory boards for Bristol-Myers Squibb, Bayer, Gilead Sciences, and Eisai and as a nonpromotional speaker for BTG. RS receives research grant funding from and is a consultant to BTG.

Multimedia Appendix 1

IRB approval of the global principal investigator's site, Northwestern.

[PDF File (Adobe PDF File), 921KB - resprot_v7i8e11234_app1.pdf]

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Abbreviations

^{99m}Tc-MAA: technetium-99m macroaggregated albumin
BCLC: Barcelona Clinic Liver Cancer
CT: computed tomography
ECOG: Eastern Cooperative Oncology Group
GIDEON: Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment With Sorafenib
HCC: hepatocellular carcinoma
HR: hazard ratio
IDMC: independent data monitoring committee
MRI: magnetic resonance imaging
PVTT: portal vein tumor thrombosis
RECIST: Response Evaluation Criteria in Solid Tumors
SHARP: Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol
SORAMIC: Evaluation of Sorafenib in Combination With Local Micro-Therapy Guided by Primovist Enhanced MRI in Patients With Hepatocellular Carcinoma
SPACE: Sorafenib or Placebo in Combination With Transarterial Chemoembolization for Intermediate-Stage Hepatocellular Carcinoma
SPECT: single-photon emission computed tomography
STOP-HCC: TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma
TACE: transarterial chemoembolization
TACE 2: Sorafenib in Combination With Transarterial Chemoembolisation in Patients With Unresectable Hepatocellular Carcinoma
TACTICS: Transcatheter Arterial Chemoembolization Therapy in Combination With Sorafenib
TARE: transarterial radioembolization

Edited by G Eysenbach; submitted 07.06.18; peer-reviewed by P Bansal; accepted 09.07.18; published 15.08.18.

Please cite as:
Chauhan N, Bukovcan J, Boucher E, Cosgrove D, Edeline J, Hamilton B, Kulik L, Master F, Salem R
Intra-Arterial TheraSphere Yttrium-90 Glass Microspheres in the Treatment of Patients With Unresectable Hepatocellular Carcinoma: Protocol for the STOP-HCC Phase 3 Randomized Controlled Trial
JMIR Res Protoc 2018;7(8):e11234
URL: http://www.researchprotocols.org/2018/8/e11234/
doi:10.2196/11234
PMID:30111528

Original Paper

Psychosocial Assessment Using Telehealth in Adolescents and Young Adults With Cancer: A Partially Randomized Patient Preference Pilot Study

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Abstract

Background: Adolescent and young adults with cancer are at increased risk of psychosocial difficulties relative to their healthy peers. Current models of inpatient face-to-face psychosocial care might limit the capacity for clinicians to provide timely and personalized assessment and intervention for this group. Telehealth offers a promising alternative toward increasing access to the provision of evidence-based psychosocial assessment and treatment for adolescent and young adults with cancer.

Objective: This pilot study aimed to assess the feasibility and acceptability for both patients and clinicians of providing a psychosocial assessment via telehealth to adolescents and young adults currently receiving treatment for cancer, relative to face-to-face delivery.

Methods: We included patients who were aged 15-25 years, currently receiving treatment, could speak English well, and medically stable. Patients were recruited from oncology clinics or wards from 5 hospitals located across Sydney and Canberra, Australia, and allocated them to receive psychosocial assessment (Adolescent and Young Adult Oncology Psychosocial Assessment Measure) with a clinical psychologist or social worker through face-to-face or telehealth modalities using a partially randomized patient preference model. Patients completed a pre- and postassessment questionnaire comprising validated and purposely designed feasibility and acceptability indices, including the impact of technical difficulties, if patients had their own devices; number of patients who were content with their group allocation; self-reported preference of modality; Treatment Credibility and Expectations Questionnaire; and Working Alliance Inventory. Clinicians also completed a postassessment questionnaire rating their impressions of the acceptability and feasibility of intervention delivery by each modality.

Results: Of 29 patients approached, 23 consented to participate (response rate: 79%). Participants were partially randomized to either telehealth (8/23, 35%; mean age 16.50 years, range 15-23 years; females: 4/8, 50%) or face-to-face (11/23, 62%; mean age 17 years, range 15-22 years; females: 8/11, 72%) conditions. Four participants withdrew consent because of logistical or medical complications (attrition rate: 17.4%). Most participants (6/8, 75%) in the telehealth group used their computer or iPad (2 were provided with an iPad), with minor technical difficulties occurring in 3 of 8 (37.5%) assessments. Participants in both groups rated high working alliance (Working Alliance Inventory; median patient response in the telehealth group, 74, range 59-84 and face-to-face group, 63, range 51-84) and reported positive beliefs regarding the credibility and expectations of their treatment group. Postassessment preferences between face-to-face or telehealth modalities varied. Most patients in the telehealth group (5/8, 63%) reported no preference, whereas 6 of 11 (55%) in the face-to-face group reported a preference for the face-to-face modality.

Conclusions: Telehealth is acceptable as patient comfort was comparable across modalities, with no significant technological barriers experienced. However, patients varied in their preferred interview modality, highlighting the need to tailor the treatment to patient preference and circumstances.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12614001142628; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=366609 (Archived by WebCite at http://www.webcitation.org/721889HpE)

(JMIR Res Protoc 2018;7(8):e168) doi:10.2196/resprot.8886

KEYWORDS

telehealth; videoconferencing; psychosocial; psychological assessment; adolescent and young adult; cancer

Introduction

There has been growing recognition that psychosocial needs of adolescent and young adult (AYA) patients with cancer aged 15-25 years are different from both adults and younger children and warrant specialized services, including timely psychosocial assessment [1,2]. A cancer diagnosis during adolescence has the potential to significantly impact many aspects of normal development, including physical, psychological, social, sexual, educational, and financial domains [3]. In addition, the AYA years are a time during which individuals are at an increased risk of developing mental health disorders, even without the severe stress of a cancer diagnosis [4]. The combination of these factors means that compared with other age groups, young people with cancer often experience more complex psychological distress and social challenges, which might require more long-term, time-intensive psychosocial assessment and intervention [5-10]. Recent studies have reported that clinical-level distress is observed in 23%-27% of AYAs within the first year postdiagnosis [6,8]. Without appropriate assessment and intervention, this might translate into serious long-term mental health risks. A recent study reported that AYAs with cancer are at a significantly higher risk of suicidal behavior (both attempts and completed attempts) in the year after, and up to 5 years postdiagnosis, compared with their peers without cancer [10].

Besides being associated with a poorer quality of life in its own right [11], elevated distress among AYAs with cancer is also likely to have adverse impact on other clinical factors, such as treatment adherence [12], and their ability to communicate effectively about their symptoms, which might delay or exacerbate treatment complications [13,14]. In addition, distress contributes to delays in the postcancer treatment of AYAs reintegrating into normal life, potentially affecting schooling or work and relationships for years into survivorship [15,16]. Ensuring that AYAs with cancer suffering from elevated distress have access to the services they need (eg, psycho-oncology) at the time they need it is therefore important.

AYAs with cancer have unique psychosocial needs [17], and the provision of quality care needs to respect their preferences and provide appropriate emotional support, information, and physical comfort. The experience AYAs have with their care affects their functional, emotional, and social adjustment [18]. The provision of timely psychosocial assessment and intervention for AYAs with cancer is another fundamental component of best practice care [3,19] and is recommended as part of gold standard AYA clinical care in several international jurisdictions, including the UK and Australia [20]. However, considerable barriers exist for this group of patients accessing assessment and intervention. Although Australian rural and remote patients with cancer often need to travel long distances for specialist care, at great expense, time, and inconvenience to their jobs and family [21-23], AYAs are at a particular disadvantage. Many hospitals lack specialist AYA services or health professionals with AYA expertise, and the available specialized services are typically located in metropolitan centers [24,25]. AYAs are a dispersed population, and sometimes live a great distance from their treating hospital. These barriers sometimes mean patients avoid traveling for less “urgent” or compulsory aspects of their care altogether (such as receiving psychosocial assessment or intervention), potentially affecting clinical outcomes.

One method of ensuring higher access to appropriate psychosocial assessment and intervention in AYA patients with cancer is telehealth. Telehealth “involves the use of modern information technology, especially two-way interactive audio/video communications, computers, and telemetry (ability to exchange data), to deliver health (and mental health) services to remote patients” [26]. Previous reviews have highlighted that telehealth might allow for the provision of specialist assessment and intervention to previously inaccessible and remote populations. Telehealth is also valuable in urban areas,

especially for those who find it difficult to travel because of logistical or treatment-related constraints. Moreover, providing care using telehealth stands to benefit health providers, as Web-based consultations might reduce clinicians' travel time costs when caring for patients in diverse locations and increase the efficiency of limited clinician resources, facilitating an increased capacity in service delivery [27]. Finally, AYAs can be difficult to engage in psychosocial services because of barriers such as the stigma of accessing mental health services [28]. Telehealth offers flexibility to the delivery modality of psychosocial care and might assist in enhancing their engagement, by allowing them to talk to a mental health clinician in a truly private setting, and not being seen by a clinician in a ward or an outpatient clinic.

A key part of providing quality psychosocial care to AYAs is regular psychosocial screening and assessment, which enables members of the health care team to identify patients in distress, as well as those at risk of poor psychosocial outcomes, while detecting specific unmet needs that could be exacerbating patient distress. Ongoing assessment throughout treatment ensures unmet needs are addressed, even when those needs change [2,29]. Telehealth offers a promising avenue to ensure that adequate psychosocial assessment is delivered to AYA patients at appropriate time points throughout their cancer journey and into survivorship.

At present, no research has specifically examined the feasibility and acceptability of using telehealth to provide psychosocial assessment for AYAs with cancer. However, in the intervention literature, several studies have suggested that AYA patients might be amenable to receiving psychosocial assessment through telehealth [30,31]. The provision of psychosocial support using telehealth in adult patients with cancer has been found to be satisfactory and feasible [32]. Telehealth interventions can achieve therapeutic alliance and rapport (ie, the relational bond between a clinician and a patient) equivalent to face-to-face therapy [33], and telehealth interventions for childhood and AYA cancer survivors implemented by phone, website, and Facebook have demonstrated feasibility and acceptability [34-38]. Finally, telehealth interventions have shown similar efficacy to face-to-face intervention in improving the quality of life of cancer survivors [39]. Despite these promising findings, no previous studies have investigated the feasibility or acceptability of using telehealth technology to provide psychosocial assessments to AYA patients regarding the treatment of cancer; this is critical to establish given that the literature to date has been mixed regarding whether telehealth is an appropriate, acceptable, or feasible modality through which psychologically distressed patients' needs can (or should) be met [40,41]. As part of one of the first clinical consultations during which a patient's distress, illness adjustment, and mental health history might be fully explored, establishing the feasibility and acceptability of telehealth for psychological assessment is crucial to future development and expansion of AYAs' access to these services as part of best practice clinical care.

This study aimed to evaluate the feasibility and acceptability of telehealth-delivered psychosocial assessment among AYAs undergoing treatment for cancer compared with patients receiving face-to-face assessment. Both patients and clinicians provided feedback for this evaluation. Specifically, the objectives were to assess the feasibility of using telehealth to deliver psychosocial assessments to AYAs during cancer treatment by examining the frequency of technical difficulties experienced in the telehealth group and how many patients in the telehealth group had access to their own devices compared with how many required one. The acceptability of using telehealth to deliver psychosocial assessments to AYAs during cancer treatment was determined by examining (1) how many patients were content with their group allocation and how many patients requested the alternative modality; (2) patients' subjective frustration with technical difficulties if or when these occurred in the telehealth condition; (3) self-reported preference of modality for all patients and to explore reasons for the stated preference; (4) patient outcome expectations and credibility beliefs about receiving the psychosocial assessment via telehealth or face-to-face; (5) patient-reported levels of working alliance across both telehealth and face-to-face; and (6) clinicians' impressions of patients' engagement, comfort, rapport, and openness across both modalities. We hoped that indexing these feasibility and acceptability indices could directly inform the design and planning of a future, larger randomized trial of telehealth-delivered psychosocial assessment for AYA patients with cancer across Australia.

Methods

Participants

This study was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee. We recruited patients (both inpatients and outpatients) from the following 5 sites in the state of New South Wales (NSW), Australia: Westmead Hospital and The Children's Hospital at Westmead (Western Sydney), Prince of Wales Hospital and Sydney Children's Hospital (East Sydney), and Canberra Hospital (Canberra). While the 5 sites are situated in urban centers, they capture both urban and rural patients. Patients were eligible to participate in this study if they had a cancer diagnosis, were on treatment, and were aged 15-25 years. Patients presenting with skin cancer diagnoses were ineligible to participate. Consistent with the New South Wales Health Policy and the clinical care model provided within the AYA services the study recruited from, patients aged <18 years were invited to provide their consent, independent of a legal parent or guardian. The additional inclusion criteria included speaking and being able to read English well and being medically stable. Patients were determined to be medically stable using clinical judgment, liaising with the treating team as appropriate. If patients in the telehealth group did not have access to a necessary device (eg, a computer or an iPad), they were provided one. No compensation was offered for participation in this study. Furthermore, 3 clinicians were involved in delivering the study, one at each site—two clinical psychologists and one social worker.

Design

This pilot study was a partially randomized patient preference trial (ACTRN12614001142628) [42-44], which allowed participants to opt out of the randomized allocation and choose

their preferred group. This design enables individual differences or biases to be accounted for among those who elect to be randomized, while also being better in assessing the manner in which clinical services are offered and selected by patients in real clinical contexts. We randomized patients who consented to participate in the study to receive their psychosocial assessment via face-to-face or telehealth modalities. If patients were not comfortable being randomized, they were offered the choice to select their preferred assessment modality.

Procedure

A Masters-level clinical psychologist or social worker approached patients in person bedside or before or after a clinic appointment for introducing the study and providing the study information form. This necessitated patients having some degree of face-to-face contact with the clinician before the assessment, regardless of the group allocation. The clinicians had limited previous experiences with using telehealth in a clinical setting and were provided training in the use of telehealth and the software before using it with patients. Following informed consent, patients indicated whether they were comfortable being randomized to either condition. Based on their decision, patients were either randomized (using a simple randomization method with random numbers generated by independent personnel) or chose to receive their psychosocial assessment via face-to-face or telehealth. Patients then completed a preassessment questionnaire battery.

Next, a Masters-level clinical psychologist or social worker assessed patients within 4 weeks using the AYA Oncology Psychosocial Assessment Measure, developed by CanTeen [45]. Patients allocated to telehealth were joined to Web-based videoconferencing software (Cisco Webex), a secure, password-protected videoconferencing application. Immediately following the assessment, care plans were developed collaboratively with patients, as per the AYA Oncology Psychosocial Care Manual [45].

Then, patients immediately completed a postassessment questionnaire battery. Both pre- and postassessment batteries were completed either on paper or online, depending on the patient's preference. If a patient was identified to be experiencing elevated distress or was assessed to be at acute risk (eg, experiencing suicidal ideation with intent or plan), the clinician responded as appropriate depending on the level of risk and the modality through which the patient was being assessed. This study utilized the same risk management protocol as reported in other recent Australian trials using videoconferencing, which have been shown to be appropriate in terms of screening for and managing mental health risks [41]. Specifically, if assessed face-to-face, risk management procedures were in keeping with standard clinical care (eg, walking patient to emergency, contacting a general practitioner [GP] or community crisis team etc). In contrast, risk management strategies for patients assessed via telehealth were determined by the level of risk. The protocol included actions such as confirming the AYAs' location and contacting 000 (Australian emergency phone number), liaising with the AYA's GP or community crisis team, contacting the AYA's primary caretaker and treating team, and providing the AYA with crisis telephone numbers to contact if they begin to feel less safe and encourage them to talk to their GP.

Psychosocial Assessment

The AYA Oncology Psychosocial Assessment Measure [45] is a modified version of the HEADSS (Home, Education/Employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment [46], a widely used adolescent psychosocial assessment measure administered by semistructured clinical interview, adapted to suit the circumstance and needs of AYA patients with cancer. It includes the assessment of home environment, education or employment status, social history, drug or alcohol use, sexuality, and mental health status (eg, suicidal or depressed) [45]. Furthermore, the Psychosocial Measure informs the development of a care plan with patients, which might involve ongoing psychosocial support or referral to appropriate services [45].

Measures

Demographics

The preassessment questionnaire battery included demographic information, including age, gender, employment status, diagnosis, and treatments received. We included the Youth Satisfaction Questionnaire [47], measuring satisfaction with overall psychosocial care, in the preassessment battery; this measure has adequate internal consistency [47] and has previously been used among AYAs with cancer [48]. Scores range from 3 to 9, with higher scores denoting higher patient satisfaction.

Feasibility

Patients were asked to report whether technical difficulties occurred, and if so, how many minutes of interruption these caused. Our benchmark for feasibility was the resolution of any technical difficulties within 5 minutes (assessed in the postassessment battery).

Patients in the telehealth group also reported whether they had their own device or not. Our benchmark for feasibility was for ≥75% patients to have their own device (assessed in the postassessment battery).

In terms of recruitment rate and attrition, our benchmark for feasibility was for >50% patients approached to consent and participate in this study (assessed in the postassessment battery).

Acceptability

We used the number of patients who were content with their group allocation versus the number of patients who requested an alternative modality as an index of acceptability. Our benchmark for acceptability was for 80% patients to be content with their group allocation (assessed in the postassessment battery).

Patients were asked to rate how frustrated they were if they experienced technical difficulties on a scale of 1-10, where an average rating of ≤3 was deemed acceptable (assessed in the postassessment battery).

All patients indicated self-reported preference of modality, or whether they had no preference either way, and were then asked

to explain their preference in an open-ended written response. Our benchmark for acceptability was for >80% patients in the telehealth group to prefer their allocation over face-to-face or otherwise have no preference (assessed in the postassessment battery).

Patient outcome expectations and credibility beliefs about receiving the psychosocial assessment via telehealth or face-to-face were assessed with the Treatment Credibility and Expectations Questionnaire [49] in the preassessment battery. In addition, items were modified for this study as appropriate; for example, "treatment" was replaced with "consultation over the internet." This measure has high internal consistency and includes 6 items, of which, 4 employ a 9-point Likert scale ranging from 1 to 9 and 2 employ an 11-point Likert scale ranging from 0% to 100%; higher scores reflect higher credibility or expectations. Our benchmark for acceptability was for outcomes on this measure to be comparable across groups (assessed in the preassessment battery).

Patients reported levels of working alliance across both telehealth and face-to-face assessed using the Working Alliance Inventory (WAI) [50], which measured AYAs' perceptions of their relationship (ie, rapport and feeling understood) with the clinician who conducted the assessment. This measure employs a 7-point Likert scale ranging from 1 (not at all) to 7 (exactly), where the total score ranges from 12 to 84, with higher scores reflecting a stronger working alliance. Our benchmark for acceptability was for outcomes on this measure to be comparable across groups (assessed in the postassessment battery).

Upon completion of this study, we asked patients to rate how beneficial and how burdensome the study was respectively, on a scale ranging from 1 (not at all) to 5 (very much; assessed in the preassessment battery).

Clinicians' impressions of patients' engagement, comfort, rapport, and openness were assessed across both modalities, whereby clinicians completed a postassessment questionnaire asking them to rate their impression of patients' engagement, comfort, rapport, and openness on a 10-point Likert scale ranging from 1 (low) to 10 (high). We defined acceptability as outcomes on this measure being commensurate across groups. Our definitions of feasibility and acceptability are similar to other work assessing feasibility and acceptability of telehealth-delivered psychosocial care [51] (assessed in the postassessment battery).

Psychosocial State

The preassessment battery included measures of current psychosocial functioning used to characterize the sample, including the Kessler Psychological Distress Scale 10 [52], measuring anxiety and depression symptoms in the past 4 weeks. Scores in this measure range from 10 to 50, where scores <20 indicate normal functioning, 20-24 indicate mild difficulties, 25-29 indicate moderate difficulties, and >30 indicate severe difficulties [52,53]. In addition, patients completed the Pediatric Quality of Life Inventory for adolescents and young adults [54], measuring AYA cancer-specific quality of life. Scores range from 0 to 100, with higher scores indicating a higher quality of life.

Statistical Analysis

Data were analyses using SPSS Version 24.0 (IBM Corp, Armonk, NY, USA). We calculated descriptive statistics for all measures included. When the data is nonnormally distributed, medians as ranges are reported as a measure of central tendency. Between-group quantitative analyses were not conducted because of the small sample size and associated limited power.

Results

Participants

Of the 29 patients approached, 23 (79%) consented to participate and 6 (21%) declined as they were not interested in participating. In addition, 17% (4/23) participants did not complete the study following consent—2 were lost to follow-up, 1 changed mind, and 1 became too unwell and was withdrawn from the study by the investigators (this occurred following consent, but prior to any further participation in the study). Of the 19 remaining participants, 17 were randomized to either telehealth (8/17, 47%) or face-to-face (9/17, 53%) conditions, with 2 participants electing to be assessed face-to-face (Figure 1). The 2 patients who chose the face-to-face modality were collapsed in the data with other face-to-face group participants and not reported separately; this decision was made because of the small number (n=2) of patients who opted out of randomization.

Table 1 summarizes key patient characteristics. In this study, 19 participating AYAs represented a diverse range of ages, gender, employment status, diagnosis, and treatment. All patients were undergoing treatment for their first diagnosis (ie, had not relapsed). AYAs lived a median distance of 24 (range 13-414) km from their treating hospital. As a group, AYAs' average levels of distress according to Kessler Psychological Distress Scale 10 were in the "normal" range, although some in each group showed elevated distress (telehealth: 2/8, 25%; face-to-face: 3/11, 27%). In addition, our sample reported health-related quality of life scores in the moderate range, although their emotional or physical functioning was somewhat lower. Overall, AYAs reported very high satisfaction with their psychosocial care to date (median Youth Satisfaction Questionnaire score 8.5, range 6-9).

Feasibility

Technical difficulties occurred during a minority of assessments in the telehealth group (3/8, 37.5%); however, in each case, problems were resolved in <5 minutes, meeting our benchmark of feasibility. The technical difficulties that occurred were all because of inconsistent connection speeds in the context of patients' devices not being connected to Wi-Fi but relying on the 4G mobile connection. Of telehealth participants, 6 of 8 (75%) used their own computer or iPad and the other 2 (25%) were provided with an iPad as their assessment occurred during an inpatient stay, which met our benchmark of feasibility. Of all 29 patients approached, 19 (65.5%) consented to participate and also completed all components of the study, above our feasibility target of 50%.

Acceptability

Almost all (17/19, 89%) patients were content with their group allocation, above our acceptability target of 80%. In the telehealth group, all 3 patients who experienced technical difficulties rated their level of frustration because of this as 1 of 10, below our benchmark of 3/10. Table 2 outlines patients' experiences of the psychosocial assessment. Following the psychosocial assessment, 7 of 8 (87.5%) patients in the telehealth group reported a preference for telehealth or otherwise no preference between face-to-face or telehealth modalities (above our acceptability target of 80%). Evaluating differences in the modality preference across gender, among young men, 3 preferred face-to-face, 3 preferred telehealth, and 1 cited no preference. Among young women, 5 preferred face-to-face, 1 preferred telehealth, and 6 cited no preference. Table 3 outlines qualitative patients' responses accounting for their reported preference of the assessment modality. Patients reported their perceptions of the ease and comfort associated with each modality, as well as concerns about confidentiality and familiarity with the clinician conducting the interview. Table 4 outlines patients' expectations of the telehealth or face-to-face modality and their beliefs about the credibility of the modality. Overall, patients had similarly positive expectations for both telehealth and face-to-face modalities and rated high credibility. The median patient response on WAI was 74 (range 59-84) for the telehealth group and 63 (range 51-84) for the face-to-face group. WAI scores for young men (median 67, range 54-81) and young women (median 67, range 51-84) were comparable. In both groups, the median response to whether the study was burdensome was 1 (ie, not at all). The median response to whether the study was beneficial was higher in the telehealth group. Table 5 outlines clinicians' reports of patients' engagement, comfort, rapport, and openness. Overall, clinicians tended to report high levels of patient engagement and comfort across both the telehealth and face-to-face groups. Furthermore, clinicians' ratings of technical difficulties were commensurate with patients' ratings.

Figure 1. The Consolidated Standards of Reporting Trials (CONSORT) flowchart of participants. F/U: follow-up.

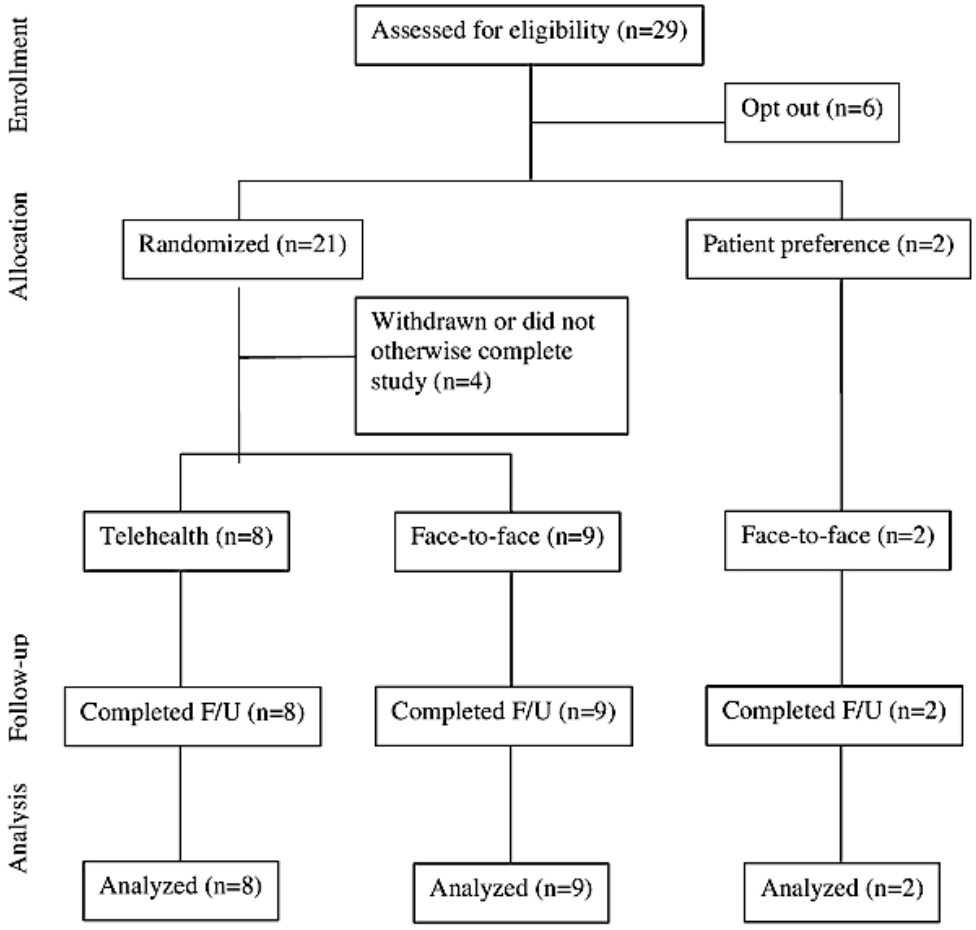

Table 1. Patient characteristics.

Variable	Telehealth (n=8)	Face-to-face (n=11)
Age (years), median (range)	16.50 (15-23)	17 (15-22)
Gender (female), n (%)	4 (50)	8 (73)
Live at home (yes), n (%)	8 (100)	11 (100)
Parents separated or divorced (yes), n (%)	2 (25)	3 (27)
Employed, n (%)	4 (50)	6 (54.5)
Speak another language other than English at home (yes), n (%)	2 (25)	3 (27)
Highest level of education completed, n (%)		
Year 10 or below	5 (62.5)	5 (45)
Technical and Further Education certificate	0 (0)	2 (18)
Year 12	3 (37.5)	4 (36)
Kilometers living from hospital, median (range)	22.50 (13-414)	24 (17-94)
Remoteness index[a]		
Major cities	7 (87.5)	10 (91)
Inner regional	1 (12.5)	1 (9)
Treatment factors		
Diagnosis, n (%)		
Acute lymphoblastic leukemia	0 (0)	1 (9)
Acute myeloid leukemia	0 (0)	2 (18)
Brain cancer	0 (0)	1 (9)
Hodgkin's Lymphoma	1 (12.5)	4 (36)
Non-Hodgkin's Lymphoma	1 (12.5)	1 (9)
Sarcoma of the bone	1 (12.5)	0 (0)
Soft tissue sarcoma	3 (37.5)	1 (9)
Other	2 (25)	1 (9)
Age at diagnosis, median (range)	16 (14-23)	16 (13-21)
Received chemotherapy, n (%)	6 (75)	9 (82)
Received radiotherapy, n (%)	1 (12.5)	4 (34)
Received surgery, n (%)	2 (25)	2 (18)
Bone-marrow transplant, n (%)	2 (25)	1 (9)
Youth Satisfaction Questionnaire, median (range)	9 (6-9)	8 (7-9)
Functioning		
Kessler Psychological Distress Scale 10[b], median (range)	17.50 (13-27)[c]	17 (12-37)[d]
Pediatric Quality of Life Inventory for adolescents and young adults[e], mean (SD)		
Total score	66.75 (14.84)	61.86 (14.90)
Physical health	39.84 (17.82)	42.33 (19.93)
Emotional	65.00 (22.36)	60.91 (18.14)
Social	83.75 (11.57)	77.73 (12.72)
Study or work	53.13 (26.98)	65.45 (26.31)
Pain and hurt	59.38 (17.36)	54.46 (17.02)
Nausea	61.88 (28.53)	58.18 (25.03)
Procedural anxiety	81.25 (29.12)	75.76 (31.94)

Variable	Telehealth (n=8)	Face-to-face (n=11)
Treatment anxiety	80.21 (16.02)	68.94 (26.64)
Worry	65.63 (24.98)	46.21 (29.67)
Cognitive problems	71.88 (21.87)	61.82 (31.09)
Physical appearance	87.50 (14.77)	64.40 (34.17)
Communication	82.29 (17.50)	71.97 (31.02)
In general, would you say your health is 1 (excellent)-5 (poor), median (range)	3 (2-4)	3 (2-3)
Before your diagnosis, had you ever seen a psychologist, social worker, counselor or psychiatrist at any time in the past (yes), n (%)	2 (25)	6 (54.5)

[a]The Australian Statistical Geography Standard Remoteness Structure.

[b]Scores range from 10 to 50, where higher scores indicate higher psychological distress.

[c]Two patients fell in the clinically elevated range (ie, moderate to severe, scores above 24).

[d]Three patients fell in the clinically elevated range (ie, moderate to severe, scores above 24).

[e]Scores range from 0 to 100, where higher scores indicate a higher quality of life.

Table 2. Patients' experience of psychosocial assessment (assessed in the postassessment battery).

Question/statement and response	Telehealth (n=8)	Face-to-face (n=11)
Were there any topics that you did not feel comfortable discussing with the psychologist during this consultation, n (%)		
Yes	1 (12.5)	0 (0)
No	7 (87.5)	11 (100)
Were you happy having your assessment online or in person or would you have preferred doing it the other way, n (%)		
Prefer online	1 (12.5)	3 (27.3)
Prefer face-to-face	2 (25)	6 (54.5)
No preference	5 (62.5)	2 (18.2)
Please rate your level of comfort in talking about personal issues online or in person (compared with in person or online)[a], median (range)	8.50 (3-10)	8.50 (6-10)
The consultation with the psychologist or social worker did not take too long to complete[b], median (range)	2 (1-4)	2 (1-3)
I did not have to wait too long for my consultation with the psychologist or social worker[b], median (range)	1.50 (1-2)	2 (1-2)
It was difficult to travel to my consultation with the psychologist or social worker[b], median (range)	4.50 (1-5)	4 (1-5)
The questions in the psychological consultation were easy to understand[b], median (range)	1.50 (1-2)	2 (1-3)
The consultation with the psychologist or social worker covered issues that were relevant to me[b], median (range)	1.50 (1-2)	2 (1-2)
I would have liked to have completed my psychological consultation in a more private location, median (range)	4 (1-5)	4 (2-5)
I would be happy to have a psychological consultation again as part of my future care[b], median (range)	2.50 (1-3)	2 (1-3)
Completing this psychological assessment has helped me to communicate my emotional needs to my medical care team[b], median (range)	2 (1-3)	2 (1-3)
Face-to-face only: How long did it take you to get to the hospital for your appointment today (min), median (range)	—	30 (20-120)
Online only: Did you experience any technical difficulties during today's online consultation[b], n (%)		
Yes	3 (37.5)	—
No	5 (62.5)	—
Online only: Technical difficulties; if yes, how long did it take to resolve[b], n (%)		
<5 min	3 (100)	—
>5 min	0 (0)	—
Online only: Technical difficulties; if yes, how much did these technical difficulties frustrate you[a], median (range)	1 (1-1)	—
Was participation in this study burdensome to you in any way[c], median (range)	1 (1-2)	1 (1-4)
Was participation in this study beneficial to you in any way[c], median (range)	4 (3-5)	1.5 (1-5)

[a]Response set: 1-10.

[b]Response set: 1 (strongly agree)-5 (strongly disagree).

[c]Response set: 1 (not at all)-5 (very much)

Table 3. Qualitative patient reports explaining their preference of modality for either telehealth, face-to-face, or no preference (assessed in the postassessment battery).

Preference	Quote
Telehealth	
Prefer online	• "Because it's a lot easier as I can just have my session done when I'm at home."
Prefer face- to-face	• "Because you want to familiarize who they are first and how they can help you." • "Face-to-face for me allows for deeper discussion, I felt slightly removed from the whole thing when doing it online. It is also a better setting face-to-face as I was aware of my housemate being around which limited some of the topics that I would talk about."
No preference	• "I do not have a preference as I personally believe that it didn't make a difference to our conversation." • "Personally, speaking to somebody via technology achieves the same result as speaking face-to-face." • "I'm comfortable in both situations." • "Either way works for me."
Face-to-face	
Prefer online	• "Yeah, only reason I prefer online is because my social worker is too far from my home." • "Because I live far away."
Prefer face-to-face	• "Easier." • "I just find it easier." • "Feel more comfortable discussing situations in person." • "It's good to talk to someone face-to-face." • "I prefer the face-to-face because I feel it more comfortable to talk to an actual person." • "Easier to talk to."
No preference	• "I don't mind either way." • "I think both are as good as each other."

Table 4. Treatment credibility and expectations questionnaire [49] (completed preassessment).

Question	Median (range)	
	Telehealth[a] (n=8)	Face-to-face[a] (n=11)
At this point, how logical does it seem to you to have a consultation over the internet or in person?	6.50 (2-9)	7 (2-9)
At this point, how successfully do you think this consultation over the internet or in person will be in helping you cope?	6.50 (4-9)	6 (1-9)
How confident would you be in recommending having a consultation with your psychologist over the internet or in person?	7 (4-9)	7 (1-9)
By the end of your consultation over the internet or in person, how much better do you think you will feel about your current situation?	70 (40-80)	70 (0-90)
At this point, how much do you really feel that your consultation over the internet or in person will help you cope with your current situation?	6.50 (3-9)	6 (1-9)
By the end of the consultation over the internet or in person, how much improvement in how you are coping with your situation do you really feel will occur?	55 (40-90)	60 (0-90)

[a]Four items employ a 9-point Likert scale ranging from 1 to 9, and 2 items employ an 11-point Likert scale ranging from 0% to 100%; higher scores reflect higher credibility or expectations.

Table 5. Clinicians' ratings (n=3) of clinicians' experience of psychosocial assessment (completed postassessment).

Question	Telehealth (n=8)	Face-to-face (n=11)
Please rate how active or vocal the patient was during the assessment today, median (range)	9 (6-10)	8 (4-10)
How comfortable did you feel conducting the assessment today, median (range)	9 (7-10)	9 (6-10)
Rate how good the rapport was between yourself and the AYA[a] patient overall, median (range)	9 (7-10)	8 (6-9)
How open did you feel the AYA patient was, median (range)	8 (6-10)	7 (4-10)
Online only: Did any technical difficulties arise during this session (yes), n (%)	3 (37.5)	—
If yes, how long did it take less than 5 minutes to resolve (yes), n (%)	3 (100)	—

[a]AYA: adolescent and young adult.

Discussion

Principal Findings

This study explored whether the administration of a psychosocial assessment would be both feasible and acceptable to AYAs currently receiving cancer treatment if delivered using telehealth. Overall, the delivery of psychosocial assessments via telehealth was found to be feasible. We were able to deliver telehealth-based psychosocial assessments to a broad patient group with a range of cancer diagnoses, ages, and varied distress levels and across both young men and women. All patients randomized to the telehealth group had their own device, which they used to connect to their Web-based assessment (unless they were inpatients, in which case a device was provided). Furthermore, while some patients did experience technical difficulties during their assessment, these were resolved quickly and resulted in minimal frustration, which is in keeping with other recent telehealth studies where technical difficulties and associated dissatisfaction were minimal [51,55]. Clinicians' scores indicated a high degree of acceptability from their perspective as well. It is important to note that clinicians did not have prior experience in using telehealth as a modality in providing clinical care, highlighting that when provided with appropriate training, telehealth is a feasible tool to implement even in settings where clinicians might not have had previous experience in doing so.

Psychosocial assessments delivered via telehealth were also found to be acceptable. The ability to effectively deliver an inherently interpersonal service through the medium of technology has been posed as one of the key ethical tensions involved in the expansion of telehealth services [6,56]. Our findings highlighted that both clinicians and patients felt comfortable with the telehealth modality and reported comparably high levels of patients' engagement and comfort across telehealth and face-to-face modalities. Critically, patients' perceptions of the therapeutic collaborative relationship with the psychologist or social worker were also comparable across groups. The high proportion of patients who were willing to be randomized to either condition (telehealth or face-to-face) at the outset further emphasizes that future trials will be able to employ this design with confidence. In the context of the partially randomized patient preference design used in this study, AYAs' openness to both models of care appears to reflect that both models of undertaking psychosocial assessments for AYA patients with cancer might be developmentally and clinically appropriate in different circumstances. Concerning gender, our results suggested that both males and females might be open to telehealth as a model of care; although our sample was quite small, this aligns with previous findings that report no impact of gender on the acceptability of telehealth technology [57,58].

The qualitative responses showed that patients who preferred telehealth indicated this was largely because of logistical issues, whereby telehealth reduced the burden of travel and increased ease of attending an assessment. Patients who preferred face-to-face assessment indicated it was simply more comfortable and easier to engage with a clinician in person. Although telehealth was the explicit preference among a minority of AYAs, of note, almost three times as many AYAs in the telehealth group expressed having "no preference" of modality. Despite ethical concerns in the literature regarding the potential for confidentiality and security issues in telehealth [40], we found little evidence of AYAs being overly concerned around these confidentiality aspects, and it did not appear to affect our participation rates. Like previous Australian studies, we used a more secure videoconferencing platform, with password-protected sessions, and liaised with patients to ensure that the session was undertaken in a private, confidential location [41,48]. Rather, our findings indicate that while AYAs may have a general tendency to prefer face-to-face interactions with psychosocial clinicians, they may become more open to the possibilities or potential benefits of telehealth once they have tried it for themselves. This notion agrees with previous literature that has found young people exposed to telehealth reported appreciation for the privacy it allows [59], which overcomes barriers to service utilization, such as mental health stigma, and the sense of empowerment and control patients have about terminating sessions [60]. Thus, future studies should investigate whether and how patients' (and clinicians') attitude toward telehealth may change with exposure to it. In order to better gauge AYAs' relative preferences for telehealth versus face-to-face delivered psychosocial services, a future trial employing a crossover design in which AYAs gain exposure to both models of care would be recommended. The variance in patients' preferences reported in this study (and the high proportion indicating no preference) highlights the importance of clinicians engaging collaboratively with AYAs to ensure that they offer a service that suits each patient's needs.

Although participants' preference for assessment modality varied, the median level of reported comfort talking about personal issues was comparable across groups. In addition, participants' perceptions of the working relationship with their psychologist appeared equally positive regardless of their gender or how far away they lived from the hospital. These findings echo other recent studies that have also found that young people report positive perceptions of psychological interactions that take place using telehealth [61,62]. For many patients, therefore, concerns about the quality of the rapport or working relationship over telehealth might not be the primary driving factor underlying preferences between the two treatment models.

Our sample also represented a group of AYAs with lower total health-related quality of life, and in particular lower emotional and physical functioning, relative to previously reported samples of AYA cancer survivors [11]. Telehealth technologies might be particularly helpful for individuals currently experiencing a great symptom burden and for whom additional travel to a hospital site to receive support would be difficult [18,48]. Indeed, satisfaction with telehealth is understandably very high in rural communities where the need to travel for face-to-face care is prohibitive [63]. As AYA psychosocial assessments are increasingly recognized as a key part of the best practice clinical care (Clinical Oncology Society of Australia guidelines [56]), this study shows the potential utility of incorporating telehealth into that delivery model and suggests that this would be feasible and acceptable to both patients and clinicians.

Strengths

This study has several strengths. To the best of our knowledge, this is the first study to explore the clinically important issue of whether using telehealth to provide psychosocial assessment is viable among AYAs with cancer. We had a high response rate and level of participation among patients approached to participate, highlighting the appeal and importance of the study to AYAs. Contrary to prior studies where AYAs' ownership of technology was a requirement for participation [51], we were able to provide AYAs with access to technological equipment if they needed it, ensuring equity of access to AYAs with varied socioeconomic and financial resources. Furthermore, the study demonstrated the feasibility and acceptability of using a telehealth modality to conduct psychosocial assessments among patients of varying levels of psychological distress. Prior work has questioned the appropriateness of using emerging technologies, including telehealth, with distressed populations, citing safety concerns [18,64]. This study provides a first step to supporting the acceptability and feasibility of telehealth psychosocial assessment for vulnerable and distressed groups and is in line with previous work demonstrating that distress can be assessed in clinically and ethically appropriate ways using Web-based telehealth technologies 41.

Limitations

This study also has several limitations. First, the small sample size and nonnormal data distribution restricted quantitative between-group analyses. Second, all patients received some degree of face-to-face engagement by the clinicians regardless of group randomization, which may have lessened the differences between the two groups. This occurred in the patient recruitment and consent process and was conducted by the assessing clinician because of resource limitations. However, recent research has reported that emerging technologies, such as telehealth, are likely to be best used as "adjuncts" or supplements to routine, face-to-face clinical care [13,14,18,65-68]. As such, the mix of face-to-face and telehealth care our sample received is likely to be a good approximation of how this might be incorporated into routine practice in clinical settings. In future, studies using a "crossover" design would assist in more rigorously comparing the relative feasibility and acceptability of these two modalities, whereby participants would have exposure to both face-to-face and telehealth modalities before providing feedback on these. In addition, although the psychosocial assessment used is manualized and clinicians engaged in self-reported fidelity checks where they ticked off each component of the assessment for each patient, we did not include a rigorous assessment of clinicians' fidelity to the AYA psychosocial assessment as one of our outcome measures; consequently, it is possible that the face-to-face and telehealth arms also differed in the delivery of this assessment between clinicians. Finally, as a pilot study, this study has inherent limitations with respect to the generalizability of the results without a future larger scale trial being undertaken.

Conclusions

Despite these limitations, this study represents the first attempt to investigate the acceptability and feasibility of telehealth in providing a psychosocial assessment to AYAs on cancer treatment, as well as clinicians' experience of patients' response to telehealth. Overall, telehealth was well received, patient comfort was comparable across modalities, and no significant technological barriers were experienced. While some patients will indicate a preference for a face-to-face assessment, a preference that needs to be respected, telehealth offers a feasible and acceptable alternative for patients who prefer it or otherwise would be burdened by accessing face-to-face assessment.

Acknowledgments

The authors wish to acknowledge contributions to this study from a number of collaborating AYA clinicians, including Rachel Bailey, Pip Eve, Katie Carlson, Tora Sibbald, Alison Baker, Robert Battisti, Cath O'Dwyer, and Fiona Maguire. We also wish to thank Holly Evans, Sarah Ellis, Brittany McGill, Stephanie Konings, Ellen Yanxiang Gan, and Sophie Champion from The Behavioural Sciences Unit for their assistance in preparing this manuscript for publication. This work is supported by Kids Cancer Alliance, a CINSW Translational Cancer Research Centre (15/TRC/1-04). US-D is supported by an Early Career Fellowship from the Cancer Institute of New South Wales (ID: 14/ECF/1-11) and an Early Career Fellowship from the National Health and Medical Research Council of Australia (APP1111800). The Behavioural Sciences Unit is supported by the Kids with Cancer

Foundation and the Kids Cancer Alliance as well as a Cancer Council New South Wales Program Grant PG16-02 with the support of the Estate of the late Harry McPaul.

Conflicts of Interest

None declared.

Multimedia Appendix 1

CONSORT - EHEALTH checklist (V 1.6.1).

[PDF File (Adobe PDF File), 532KB - resprot_v7i8e168_app1.pdf]

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Abbreviations

AYA: adolescent and young adult
WAI: Working Alliance Inventory

Edited by A Powell; submitted 01.09.17; peer-reviewed by C Valle, C Maheu; comments to author 15.11.17; revised version received 05.03.18; accepted 26.04.18; published 29.08.18.

Please cite as:
Chalmers JA, Sansom-Daly UM, Patterson P, McCowage G, Anazodo A
Psychosocial Assessment Using Telehealth in Adolescents and Young Adults With Cancer: A Partially Randomized Patient Preference Pilot Study
JMIR Res Protoc 2018;7(8):e168
URL: http://www.researchprotocols.org/2018/8/e168/
doi:10.2196/resprot.8886
PMID:30158103

Protocol

Web-Based Cognitive Bias Intervention for Psychiatric Disorders: Protocol for a Systematic Review

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Abstract

Background: Traditional psychological therapies focus mainly on modification of individuals' conscious decision-making process. Unconscious processes, such as cognitive biases, have been found accountable for various psychiatric psychopathologies, and advances in technologies have transformed how bias modification programs are being delivered.

Objective: The primary aim of this review is to synthesize evidence of Web-based cognitive bias modification intervention for bias reduction. The secondary aim is to determine the change in symptoms for individual psychiatric disorders following bias modification.

Methods: A systematic review will be conducted including only randomized trials. There will be no restrictions on participants included in the study. A search will be conducted on the respective databases until 2017. Selection of studies will be by the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA-P) guidelines. Quality assessment of included studies will be conducted using the Cochrane Risk of Bias tool. A narrative synthesis of identified articles will then be conducted. A meta-analysis will be considered only if there are sufficient articles in a domain for statistical analysis. Ethical approval for this protocol and the planned systematic review was not required.

Results: We expect that the review will be completed 12 months from publication of this protocol.

Conclusions: This review is of importance given how technology has transformed delivery of conventional therapies. Findings from this review will guide future research involving technology and cognitive bias modification interventions.

Trial Registration: International Prospective Register for Systematic Reviews (PROSPERO): 2017 CRD42017074754; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=74754 (Archived by WebCite at http://www.webcitation.org/71AvSgZGn)

Registered Report Identifier: RR1-10.2196/10427

(JMIR Res Protoc 2018;7(8):e10427) doi:10.2196/10427

KEYWORDS

cognitive bias modification; attention bias modification; psychology; psychiatry; internet; eHealth

Introduction

Advances in experimental psychology over the last decade have led to growing interest and further research in cognitive bias and cognitive bias modification. Cognitive bias includes attentional biases, approach bias, and interpretative biases [1], and the presence of these automatic biases results in individuals attending to or approaching certain stimuli in their environment or making negative interpretations when faced with ambiguity [2]. For instance, individuals with substance use disorders would attend to and approach substance-related cues and items in their natural environment more readily because of the presence of these automatic processes, and this might be responsible for them relapsing. Cognitive bias is involved in psychopathologies of several psychiatric disorders, ranging from social anxiety disorder [3] to alcohol [4] and tobacco use disorders [5]. Findings that these biases are present led to bias modification intervention to retrain these automatic attentional approach tendencies or interpretational tendencies toward certain stimuli [2]. These interventions are commonly referred to generally as cognitive bias modification. Attentional bias retraining involves use of either the dot-probe or visual probe task, and this involves pairing the probe with the neutral word or image all the time [6]. Approach biases retraining involves the use of the approach or avoidance task, which includes having the individual push away substance-related cues [7]. Interpretative bias retraining involves training participants to make positive interpretations using ambiguous scenarios or the word sentence association task [8].

To date, apart from increased recognition of cognitive biases and understanding of underlying theoretical approaches, several studies have examined the effectiveness of cognitive bias modification for various psychiatric disorders. Manning et al (2016) [9] reported the feasibility of delivering cognitive bias modification, targeting approach biases for inpatient individuals attending an alcohol detoxification program. They [9] also reported that cognitive bias modification aided individuals in maintenance of abstinence. They [9] reported no differences between experimental and control groups regarding secondary outcomes, such as the craving score, time to relapse, mean drinking days, and mean drinks per drinking day. Regarding performance on the bias modification task, participants' response to the task became faster with more sessions completed. Cognitive bias modification therapy has been investigated in other addictive disorders, such as that of cocaine use disorder [10]. Cognitive bias modification has also been evaluated among individuals with other psychiatric disorders, depressive disorders [11], and anxiety disorders [12]. Recent studies have attempted to synthesize the evidence base for cognitive bias modification for various disorders. Cristea et al's (2016) [13] prior meta-analytic review reported that cognitive bias modification was effective in reducing cognitive biases for participants with alcohol or tobacco use disorders. They reported that bias modification for both attentional and approach biases was moderately effective with an effect size of 0.60 (Hedge G) [13]. However, they also reported that changes in attentional biases did not lead to changes in symptomatology, such as cravings and other addiction outcomes. Jones et al's (2017) [2] review of meta-analysis reported that cognitive bias modification was most effective for anxiety disorders. Jones et al (2017) reported that among 10 studies they identified for anxiety disorder, 8 reported significant results. The effect size for anxiety disorders ranged from 0.13 to 0.74 [2]. They also reported that only 3 of 7 studies provided evidence for cognitive bias modification of depressive symptoms with effect sizes ranging from 0.35 to 0.85 [2]. They also reported that cognitive bias modification was effective (based on results from 2 meta-analyses) for eating disorders, smoking, and alcohol use with effect sizes ranging from 0.003 to 0.36 [2]. Thus, published studies to date have demonstrated the potential of cognitive bias modification in targeting cognitive biases intrinsic to various psychiatric disorders.

One of the key findings arising from Jones et al's (2017) [2] review was that contextual factors do influence the overall effectiveness of interventions. Although Jones et al's (2017) [2] prior review reported that cognitive bias paradigms are most efficacious when administered in a laboratory environment, there remains to date quite a number of cognitive bias modification interventions administered remotely. The increasing number of remote Web-based therapies has largely been attributed to major advances in eHealth technologies; eHealth is defined as the process in which health resources and health care are communicated and transferred by an electronic medium, and it includes Web-based interventions as well as telephone-delivered therapy and texting [14]. Since the advent of eHealth, various medical disciplines have evaluated these technologies for self-management of chronic diseases, thus facilitating individuals' participation in rehabilitation programs and supporting outreach efforts in rural areas [15]. Web-based technologies are widely utilized in mental health for delivery of various forms of psychological therapy, and they have been proven efficacious for disorders such as depression and anxiety. However, the growth of Web-based interventions is not limited to existing therapies. An increasing number of studies have examined the efficacy of Web-based cognitive bias interventions. Attentional control training and approach bias retraining were administered using a Web-based program to 136 problem drinkers in Wiers et al's (2015) [16] previous study. Similarly, cognitive bias modification targeting imagery and interpretation bias were administered to participants with depressive disorder using a Web-based program in Blackwell et al's (2015) [17] previous study. There are several distinct advantages of delivering cognitive bias modification via the Web. Use of web technologies removes geographical barriers that would traditionally hinder participants from or limit them to receiving such interventions [18]. Participants are also no longer confined in a laboratory environment and can undertake the same intervention in the comfort of their home environment [17]. Web-based interventions also remove the need for a therapist, and this will facilitate dissemination of the intervention to multiple individuals [19].

In their meta-meta-analyses, Jones et al (2017) [2] have included 2 meta-analytical articles [20,21] that have synthesized evidence for Web-based cognitive bias modification interventions. Both meta-analyses focused on the technology applied to cognitive bias modification for anxiety disorders. Also, only 4 of the

studies included in the Price et al (2016) meta-analysis were delivered in the home environment with the latest study published in 2014 [21]. For Kampmann et al's (2016) meta-analysis [20], only 7 studies delivered bias interventions outside a laboratory environment with the latest study published in 2015. For social anxiety disorder, there have been further evaluations, such as that by Hullu et al (2017) [22]. There has also been further evaluation of Web-based interventions for other disorders, such as for anxiety and depressive symptoms in adolescents [23,24,25] and for addictive disorders [19,26,27]. Given further studies for anxiety disorders and potentially more studies evaluating Web-based cognitive bias modification in other disorders, this review is crucial and pertinent. Understanding the efficacy of Web-based cognitive bias interventions would guide further research that seeks to harness technology in the delivery of cognitive bias modification interventions.

The primary aim of this review is to synthesize the evidence of Web-based cognitive bias modification intervention for bias reduction. The secondary aim is to determine the change in symptoms for individual psychiatric disorders following bias modification.

Methods

Search Strategy

To identify relevant articles, the following search terminologies will be used:

("Cognitive bias" OR "attention bias" OR "approach bias" or "interpretative bias") AND ("Internet" OR "Web" OR "Online"). Search terms within each concept will be combined using the Boolean operator "OR" and search terms between 2 disparate concepts will be combined using the Boolean operator "AND."

A comprehensive search will be conducted on PubMed, MEDLINE, EMBASE, PsycINFO, Science Direct, Cochrane CENTRAL, and Scopus databases. If full-text access is not available, original authors will be contacted. Proceedings from scientific meetings and conference abstracts will also be included.

Inclusion and Exclusion Criteria

Only articles in the English language will be included. Inclusion criteria are the condition examined must be a psychiatric disorder, the diagnosis must be made either by a structured clinical interview or by means of a questionnaire, cognitive bias modification must have been delivered using a Web-based modality, the study design is that of a randomized trial, and Web-based cognitive bias modification intervention must be delivered as a standalone (not in conjunction with other modalities of therapy).

Exclusion criteria are the intervention did not include a validated measure for attention bias or cognitive bias assessment, the intervention was delivered by a mobile phone device, the intervention was delivered by a mobile game, attention bias modification is part of a pharmacological trial, and Web-based cognitive bias modification is delivered in conjunction with other therapies

Condition or Domains Studied

This review seeks to determine the effectiveness of Web-based cognitive bias modification in psychiatric disorders.

Participants

Adult, child, and adolescent populations will be considered for inclusion in this systematic review. There are no restrictions on participants included in these studies. Participants could be either individuals from the general population or a treatment-seeking cohort.

Intervention and Exposure

The intervention is that of a Web-based cognitive bias modification task. This might include attention bias modification, cognitive bias modification for interpretation, and a visual search or spatial cueing modification task.

Comparator

For randomized trials, we will determine whether participants are compared against individuals who have received placebo training or a sham training intervention.

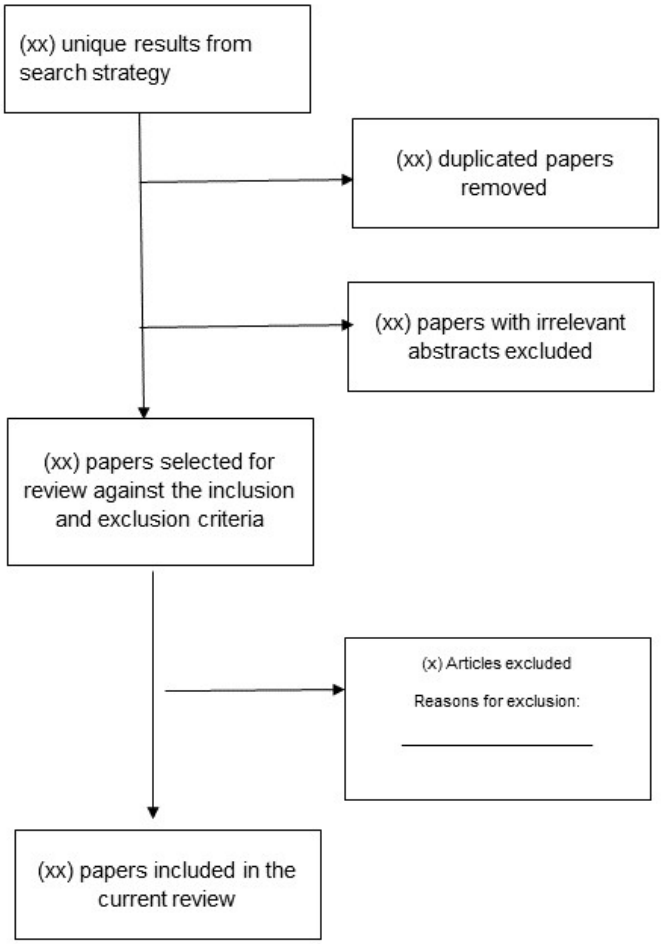
Outcome

For the primary outcome, we will report whether cognitive bias modification has been effective, which is defined as reduction in biases following intervention. For secondary outcomes, we will report whether there are reductions in overall anxiety and depression symptoms, as measured by validated questionnaires, or for addictive disorders, whether there are reductions in overall craving, reductions in total amount of substance consumed, and increases in total duration of abstinence. For secondary outcomes, scores on questionnaires administered pre- and postintervention will be reported.

Data Extraction, Sorting, and Selection

Database searches will be conducted, and abstracts will be obtained and imported in the reference manager Endnote X8. The first author (MWBZ) will review the compiled database and will remove all duplicated articles. Articles will be further independently screened by authors (MWBZ and JY) based on their titles and abstracts. The full text of shortlisted articles will be then be obtained and evaluated against inclusion and exclusion criteria. Any disagreement between the two authors (MWBZ and JY) will be resolved through a discussion with the third author (GS). An electronic form will be used to record reasons for inclusion and exclusion of articles. This systematic review protocol will adhere to reporting guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) [28]. Figure 1 shows a sample of the PRISMA diagram that we will include in the final protocol.

Figure 1. Sample PRISMA flowchart.



The following data and information will be extracted from each article, cross-checked by the second author, and recorded on a standardized electronic data collation form:

1. Publication details: author(s) and study year
2. Study design and methodology: sample size (intervention and control group), characteristics of the sample (mean age and percentage of males and females), method by which participants were recruited; main psychiatric diagnosis for participants; how psychiatric diagnosis was made (clinical versus questionnaire)
3. Cognitive bias task utilized
4. Outcomes of interest: effectiveness of bias modification (effect sizes, either Cohen *d* or Hedge G, if reported) and secondary outcomes reported (for example, scores on questionnaires for anxiety or depressive symptoms, craving scores, mean time to relapse, and total duration of abstinence).

Quality Assessment

For risk of bias assessment, the Cochrane Risk of Bias tool [29] will be used for grading. Studies will be evaluated for risk of selection bias, performance bias, detection bias, attrition bias, and reporting bias. Risk of bias assessment will be conducted by the author (MZ) and then verified by the author (JY). Any disagreements will be resolved through a discussion with the third author (GS).

Strategy for Data Integration and Synthesis

A narrative synthesis of all relevant articles will be conducted. Results will be organized by different types of psychiatric disorders, for example, addictive, depressive, and anxiety. The number of studies reporting effectiveness in each psychiatric condition will be stated. Results about secondary outcomes will be summarized.

Meta-analysis will be considered only if there are sufficient articles in a domain for quantitative statistical analysis. For the meta-analytic study, statistical analysis will be performed using Comprehensive Meta-Analysis Version 2.0 (BioStats, NJ, USA) based on the random effects model. The random effects model will be used because it assumes varying effect size between studies and because of underlying differences in study design and heterogeneity of the sampled population. Statistical analysis aims to compute pooled effect size to determine the clinical efficacy of cognitive bias modification for each different disorder. The analysis also aims to identify potential moderators that could account for heterogeneity in the effect size computed. Between-study heterogeneity will be assessed with the I^2 statistic, which describes the percentage of variability among effect estimates beyond that expected by chance. As a reference, I^2 values of 25% are considered low, 50% moderate, and 75% high in heterogeneity. Meta-regression analysis will be performed to determine if continuous variables such as mean age and proportion of males or females affect heterogeneity in the pooled effect size of cognitive bias modification for a

psychiatric disorder. Subgroup analysis will be undertaken to investigate effects of variables (method of psychiatric diagnosis, cognitive bias task utilized) on the effect size obtained. For meta-analysis, Egger regression test will be conducted to determine if publication bias is present. If there is significant publication bias, the classic fail-safe test will be performed to determine the number of missing studies that will be required for the *P* value of publication bias to be higher than .05.

Ethics and Dissemination

Ethical approval for this protocol and planned systematic review was not required. Results synthesized would be disseminated by means of conference presentation or published works in peer-reviewed journals.

Protocol Registration

The protocol for this planned systematic review has been registered with PROSPERO in 2017 (CRD42017074754).

Results

We have screened 2674 unique articles identified from all the selected databases using the predefined search strategy. We expect that the review will be completed 12 months from the publication of this protocol.

Discussion

Based on our knowledge, there have been systematic reviews as well as meta-analyses published reporting the efficacy of cognitive bias modification for substance use disorders and for other psychiatric disorders. This review is timely because it will expand on findings of prior reviews. In addition, the synthesis of existing evidence will help inform researchers and clinicians as to whether Web-based cognitive bias interventions are effective and if so, for which psychiatric disorder(s). Examining the effectiveness of Web-based interventions is undoubtedly crucial, given that they reduce geographical barriers associated with receiving therapy and reduce the need for a therapist [18] [19]. Web-based cognitive bias modification, if proven effective, could help reduce overall cost associated with receiving psychological interventions.

Acknowledgments

MZ is supported by a grant under the Singapore Ministry of Health's National Medical Research Council (Grant number NMRC/Fellowship/0048/2017) for PhD training. The funding source had no involvement in any part of this project.

Authors' Contributions

MZ and HS jointly conceived, designed, and planned this systematic review protocol. MZ, JY, and GS assisted in writing the initial protocol. HS and DSSF helped in revision of the initial drafted manuscript. All authors have approved the final protocol manuscript prior to submission.

Conflicts of Interest

None declared.

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Review and Meta-analyses

Edited by G Eysenbach; submitted 15.03.18; peer-reviewed by I Choi, M Ferrer; comments to author 11.05.18; revised version received 12.05.18; accepted 20.06.18; published 07.08.18.

Please cite as:
Zhang M, Ying J, Song G, Fung DSS, Smith H
Web-Based Cognitive Bias Intervention for Psychiatric Disorders: Protocol for a Systematic Review
JMIR Res Protoc 2018;7(8):e10427
URL: http://www.researchprotocols.org/2018/8/e10427/
doi:10.2196/10427
PMID:30087091

Protocol

Multifactorial Screening Tool for Determining Fall Risk in Community-Dwelling Adults Aged 50 Years or Over (FallSensing): Protocol for a Prospective Study

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Abstract

Background: Falls are a major health problem among older adults. The risk of falling can be increased by polypharmacy, vision impairment, high blood pressure, environmental home hazards, fear of falling, and changes in the function of musculoskeletal and sensory systems that are associated with aging. Moreover, individuals who experienced previous falls are at higher risk. Nevertheless, falls can be prevented by screening for known risk factors.

Objective: The objective of our study was to develop a multifactorial, instrumented, screening tool for fall risk, according to the key risk factors for falls, among Portuguese community-dwelling adults aged 50 years or over and to prospectively validate a risk prediction model for the risk of falling.

Methods: This prospective study, following a convenience sample method, will recruit community-dwelling adults aged 50 years or over, who stand and walk independently with or without walking aids in parish councils, physical therapy clinics, senior's universities, and other facilities in different regions of continental Portugal. The FallSensing screening tool is a technological solution for fall risk screening that includes software, a pressure platform, and 2 inertial sensors. The screening includes questions about demographic and anthropometric data, health and lifestyle behaviors, a detailed explanation about procedures to accomplish 6 functional tests (grip strength, Timed Up and Go, 30 seconds sit to stand, step test, 4-Stage Balance test "modified," and 10-meter walking speed), 3 questionnaires concerning environmental home hazards, and an activity and participation profile related to mobility and self-efficacy for exercise.

Results: The enrollment began in June 2016 and we anticipate study completion by the end of 2018.

Conclusions: The FallSensing screening tool is a multifactorial and evidence-based assessment which identifies factors that contribute to fall risk. Establishing a risk prediction model will allow preventive strategies to be implemented, potentially decreasing fall rate.

Registered Report Identifier: RR1-10.2196/10304

(JMIR Res Protoc 2018;7(8):e10304) doi:10.2196/10304

KEYWORDS

accidental falls; primary prevention; adults; clinical protocol; pressure platform; inertial sensors

Introduction

Falls and fall-related injuries are major health problems among older adults [1]. About a third of community-dwelling persons aged 65 years or older fall each year [1,2]. Although fall studies are mainly associated with this age group, persons aged 50 years or older often underestimate their risk of suffering a fall [3]. Moreover, fall-related injuries are the most common reason for hospital admission in those who are 50 years or older [4], and screening recommendations were already given to those identified as being at a higher risk of falling because of an underlying condition [1].

Falls are complex and have multifactorial etiologies [5,6]. Different factors can increase the risk of falling, particularly psychotropic medications and polypharmacy, and mitigation of these factors was found to reduce fall rates [7,8]. Vision impairment is also considered a fall risk factor inherent to changes in visual acuity, development of cataracts, macular degeneration, glaucoma, and other conditions related to the aging process [7]. High blood pressure and heart rate and rhythm abnormalities, such as carotid sinus hypersensitivity, vasovagal syndrome, bradyarrhythmias, and tachyarrhythmias, are similarly associated with falls. Environmental hazards at home related to lighting, chair and bed height, floor surfaces, and other factors create opportunities for falls and have been included as essential components of fall prevention programs [7,9]. Additionally, changes in musculoskeletal and sensory system functions that are associated with aging lead to deficits in maintaining postural stability [10]. In turn, fear of falling (FoF) can have a major impact on older adults, raising caution and restricting activities leading to physical fragility [11]. Finally, individuals who experienced previous falls and with multiple risk factors are at a higher risk of falling [12,13].

Falls can lead to minor injuries such as bruises, lacerations, or abrasions, and 10% of cases result in fractures [8,14], thus contributing to significant increases in morbidity and mortality [8,9]. Direct health care costs associated with this phenomenon are high [15], reaching 25 billion euros per year in the European Union [2].

The evidence shows that falls can be prevented by screening for risk factors and by the prescription of tailored interventions [16]. These results allow the professional to identify those in need of more detailed assessments [17]. The assessment of fall risk factors is the focus of a number of different screening methods, such as Morse Fall Scale [18], Berg Balance Scale [19], and Performance - Oriented Assessment of Mobility Problems in Elderly Patients [20].

Recently, in addition to traditional methods, instrumentation has been integrated in some standard assessment tests, adding value to the existing methods because it gives additional quantitative information and eliminates the bias introduced by observation [21].

The aims of this study are to develop a multifactorial, instrumented, screening tool for fall risk based on functional tests, their metrics, and other potential risk factors and to prospectively validate a risk prediction model for the risk of falling among Portuguese community-dwelling adults aged 50 years or older.

Methods

Study Design

This study is a prospective longitudinal study, following a convenience sampling method.

Setting

Individuals are voluntarily recruited from several settings within the community in different regions of continental Portugal, such as parish councils, physical therapy clinics, seniors' universities, and other facilities.

Recruitment started in June 2016 and is ongoing. After the screening, the participants will receive monthly phone calls over a 12-month period to record the rate of falls.

Participants

Inclusion criteria consist of adults aged 50 years or over, able to stand and walk independently with or without walking aids, and who are interested in participating in the study. Individuals will be excluded if they have severe sensorial impairments (deafness or blindness) or cognitive impairments, which preclude the ability to comprehend the questionnaires and functional tests included in the screening protocol.

Ethical Considerations

Ethical approval was obtained from the Research Ethics Committee of Polytechnic Institute of Coimbra (Nº6/2017). All participants will give written informed consent before data collection begins as per the Declaration of Helsinki.

Details of the Screening Protocol

The FallSensing screening tool is a technological solution for fall risk screening, which includes software, a pressure platform, and 2 inertial sensors.

Software

The software consists of a questionnaire that collects information about demographic and anthropometric data (age, sex, height, and weight), history of falls (previous 12 months, HoF), FoF, health conditions (heart attack, stroke, osteoarthritis, diabetes, Parkinson's disease, osteoporosis, high blood pressure, high cholesterol, hearing and vision impairments, and urinary incontinence), medication, sedentary behaviors, upper extremities assistance needed to stand from a chair, living settings, alcohol habits, self-perceived health, and unintentional or involuntary weight lost as well as a detailed explanation about procedures to accomplish every functional test. Finally, 3

questionnaires concerning environmental home hazards, activities and participation profile related to mobility (PAPM), and self-efficacy for exercise are also included.

This app integrates a chronometer used to measure time for the Timed Up and Go (TUG) test, the 30 seconds sit to stand (30s STS) test, the step test, the 4-Stage Balance test "modified," and the 10-meter walking speed test. In the 30s STS, the number of stands is registered manually by the physiotherapist. The same procedure will be used to register the number of steps. Additionally, the software records inertial sensors and pressure platform raw data. All the information will be available in a cloud server designed for the screening tool.

History of Falls

A fall can be defined as "an unexpected event, in which the participant comes to rest on the ground, floor, or lower level" and "excludes coming to rest against furniture, wall, or other structure" [1,8,22].

HoF is considered as a risk factor for falls [23] and the strongest single predictor of future falls [24] because it is associated with reduced lower limbs strength, gait, and balance impairments [12]. According to literature, older adults who have experienced one or more falls have 3 times the risk of falling again within the following year compared with those with no HoF [25]. Although the history and number of previous falls are self-reported, they are often used as golden standards in fall risk assessment studies [26].

HoF within the previous 12 months will be determined by self report, answering the question "Did you fall in the past 12 months? Yes-No." If the participant has fallen, it will be asked if the fall was outdoor or indoor, the reason of the fall (slip, stumble, loss of consciousness, dizziness, lower extremities weakness, no special reason, and other), need of health services assistance, which health service (hospital, primary health care center), hospitalization (how many days), activity limitation and restrictions on participation (how many days), and fracture occurrences (wrist or hand, hip, skull or spine, and others).

History of Falls After 12 Months

Participants will be prospectively followed up for a 12-month period via monthly phone calls to record their fall occurrences. The fall rates will be recorded from the day of inclusion until voluntary dropout, loss of phone contact, or the end of the follow-up period (365 days later).

Fear of Falling

FoF is defined as "a lasting concern about falling that leads to an individual avoiding activities that he or she remains capable of performing" [27]. The literature states that FoF contributes to a loss of independence and disability through the restriction of activities [28,29] because it is associated with an increased risk of functional decline [30], reduced physical activity, lower perceived physical health status, lower quality of life, and increased institutionalization [31]. Despite being more frequent among fallers, FoF and activity restriction are not exclusive of these persons. In addition, FoF was significantly more frequent among women and among people living alone [32].

Considering the negative influence of FoF, its existence will be assessed by self report through the question "Are you afraid of falling? Yes-No."

Health Conditions

There are certain conditions that can have a significant effect on fall rates in older adults, such as bladder incontinence, osteoarthritis, Parkinson's disease, cardiovascular accidents, and conditions associated with cardiovascular disease, such as hypertension. Additionally, deficits in the somatosensory and vestibular systems can also contribute to falls because they are associated with an increase in postural sway, a strong indicator of standing balance [33].

The question "Do you have trouble seeing well or has it been more than 2 years since your eyes were last tested?" assesses changes in visual acuity, development of cataracts, macular degeneration, glaucoma, and other conditions related to the aging process that can contribute to increased risk of falling [7,33].

Medication

It is reported that approximately 20.3% of persons aged 55 years or over take 4 or more medicines [34]. Older adults taking more than 3 or 4 medicines were at an increased risk of recurrent falls [35]. Additionally, a significant association between falls and the use of sedatives and hypnotics, antidepressants, and benzodiazepines was found [34].

The number of medicines taken by each person was assessed by self report through the question "Do you take 4 or more different medicines per day? Yes-No." The names of the medicines were also registered, and they were identified according to their pharmaceutical group (benzodiazepines, antidepressants, antipsychotics, antiinflammatory drugs, antihypertensive drugs, and others drugs).

Sedentary Behavior

Regular physical activity significantly decreases falls in older people; consequently, sedentary behaviors are associated with an increased incidence of falls [36,37]. To understand the community-dwelling adults' sedentary behaviors using a self-reported question, we adopted the estimate measure of sedentariness calculated by Heseltine et al (2015), which is as follows: "Do you spend over 4 hours seated, 5 days or more per week?" This measure resulted from the analyses of sedentary behavior of a sample of 1104 adults aged 65 or more years, who answered the Physical Activity Scale for the Elderly. Additionally, older people underestimate sedentary behavior by self report by up to 50% [38].

Upper Extremities Assistance to Stand From a Chair

Upper extremities assistance to stand from a chair was assessed through the question "Do you need assistance from the upper extremities to stand up from a chair? Yes-No." This action is an indicator of weak lower extremities muscles, a major reason for falling [39].

Living Settings

Because FoF is more frequent among older adults living alone [32], this protocol intends to assess the living settings through the question "Do you live alone? Yes-No."

Alcohol Habits

Regular alcohol consumption among older adults has been linked to impaired balance and postural hypotension, which has been associated with frequent falls [40]. Furthermore, the intake of certain medications, such as benzodiazepines, even with small amounts of alcohol, can increase the risk of falling because of the interactions that can occur [41]. Participants are asked about their daily alcohol habits through the question "Do you drink alcohol every day? Yes-No."

Self-Perceived Health

The self-perceived health (SPH) is considered a valid and reliable indicator of overall health status, a predictor of mortality and health services use. Several studies found an association with sociodemographic characteristics (such as sex, age, or education), chronic diseases, and functional status. Functional status, in particular, is recognized as a powerful determinant of SPH in older adults [42]. Older adults with FoF also demonstrated poor SPH [43]. SPH will be assessed by self report through the question "In general, do you perceive your health as excellent, very good, good, sufficient, or poor?"

Unintentional or Involuntary Weight Loss

Involuntary weight loss is one of the features that, simultaneously with others, can help to define a frailty phenotype [44]. Past literature reveals an association between the frailty phenotype and the number of previous falls in older people [45]. Therefore, participants will be asked if they had experienced a weight loss ≥4.5 kg or ≥5% of their body weight during the previous 12 months.

Functional Tests

Grip Strength

Hand grip strength is significantly correlated with lower limb muscular strength [46] and is a powerful predictor of disability, morbidity, and mortality [47]. This test will be performed with the participant seated on a standard chair without armrests [48], shoulder adducted and neutrally rotated, elbow flexed at 90 degrees, forearm neutral, wrist held between 0-15 degrees of ulnar deviation, and with the arm not supported [49]. A Jamar hydraulic hand dynamometer will be settled at the second handle position held with the dominant hand and during the performance of the test, it will be presented vertically in line with the forearm. The test is performed only once and the participant is encouraged to exert his or her maximal grip strength for 5 seconds [49,50]. The final score is measured in kilograms force (kgf). Normative data for this test are commonly analyzed by gender with males showing higher grip strength at all ages [51]. A score <15 kgf for females and <21 kgf for males identifies those at increased fall risk [52].

Timed Up and Go

The TUG test is used to assess dynamic balance during gait and transfers tasks, mobility, and lower body strength [53,54]. To perform this test, the person, wearing his or her regular footwear, is instructed to sit on a standard chair (chair height between 44 and 47 cm [55]) with his or her back against the chair back [49]. The person then stands up and walks straight for 3 meters as fast as possible, turns around, walks back, and sits down [54,56]. The person must stand up without help (cannot use the upper extremities for support); however, if a walking aid is needed, it should be placed next to the chair and can be used to perform the gait component of the test [54]. The test is performed only one time, the timing begins at the instruction "go" and stops when the patient sits on the chair [49]. A score of >10 seconds indicates which community-dwelling older adults are more likely to fall [53].

30 seconds Sit to Stand

Lower body strength is important for maintaining functional capacity in older adults; therefore, its evaluation is critical [57-59]. The 30s STS test is a simple and effective instrument for assessing lower body strength and identifying muscle weakness in community-dwelling older adults and is one of the most important clinical functional evaluation tests [57,60]. The person is instructed to perform cycles of sit and stand up from a chair as many times as possible over 30 seconds [57,61].

The person starts the test seated in the middle of the chair (chair height between 40 and 43.3 cm), feet approximately shoulder-width apart and placed on the floor, and arms crossed by the wrists placed against the chest. The vocal instruction "go" indicates the test´s beginning and if the participant completes more than halfway up at the end of 30 seconds, it is counted as a full stand. The final score involves recording the number of stands a person can complete in 30 seconds [57,60]. The normative levels for the number of stands depend on age and gender [62].

Step Test

The step test was designed to assess dynamic standing balance and reproduce lower extremity motor control and coordination [63,64]. To perform the test, the person is asked to step on and off a block (7.5 cm height, 55 cm width, and 35 cm depth) placed against a wall as many times as possible for 15 seconds. The person should step onto the block with the whole foot and then return fully to the ground. The total number of completed steps in 15 seconds is recorded. The patient is unsupported and should look straight forward, although the test administrator must stand close by for safety. In cases where patients are overbalanced or need stabilization during the test, the counting of steps stops and the administrator records the complete number of steps prior to overbalancing [64-66]. This test is performed only for the dominant side, as indicated by the person being tested. A performance of <10 steps indicates a higher risk of falling [67].

4-Stage Balance Test "Modified"

Deficits in balance can lead to falls and fall-related injuries, representing one of the most important intrinsic fall risk factors among older adults [68-70] that is commonly assessed in this population.

The 4-Stage Balance test "modified" evaluates balance. To complete this test, the person needs to progressively accomplish the following 4 different feet positions: side by side stance,

semitandem stance (preferred foot forward with the instep of one foot touching the big toe of the other foot), tandem stance (one foot in front of the other, heel touching toe), and one legged stance (preferred leg for support, [71]).

The person is instructed to stand quietly on the pressure platform, arms along the body, with neither shoes nor assistive devices. The positions must be held for 10 seconds each without moving the feet, needing support, losing balance or touching the leg of support with the other leg [68,71] and must be performed with eyes open and then closed (excluding one legged stance position). The sequence will be side by side stance eyes open, side by side stance eyes closed, semitandem stance eyes open, semitandem stance eyes closed, tandem stance eyes open, tandem stance eyes closed, and one leg stand eyes open. If the person fails to accomplish one of the test positions, the test finishes. The final score will be the number of positions that are successfully completed. The inability to complete 10 seconds in the tandem stance position with eyes open has been associated with a higher risk of falling and mobility dysfunction [72,73].

10-Meter Walking Speed

Walking speed is the product of a complex interaction of multiple body structures and functions, such as lower extremity strength, proactive and reactive postural control, motor control, and musculoskeletal condition [74,75]. Accessing gait speed (GS) as a screening tool can be useful for identifying those at risk or in need of intervention [75] because the gait speed results are related to various health outcomes, such as functional decline or FoF. Thus, GS can be a predictor of falls [74].

The performance of this test requires a 20-meter straight path with 5 meters for acceleration, 10 m for steady-state walking, and 5 meters for deceleration. Markers are placed at the 0-, 5-, 15-, and 20-meter positions of the path, and the time to walk along the 5 and 15 meters is registered [76]. The person is instructed to walk at his or her fastest walking speed wearing typical footwear and without running along the 20-meter path; an assistive device can be used if needed.

The range of normal walking speed is between 1.2 and 1.4 m/s because it varies by age, gender, and anthropometrics. A value of <0.4 m/s indicates the likely need for an assistive device at home; 0.4 to 0.8 m/s is correlated with limited mobility; 0.8 to 1.25 m/s indicates ambulation in the community with some risks; those with ≤1 m/s should start a program to reduce the risk of falling; and ≥1.42 m/s indicates a safe speed for crossing streets [74].

Questionnaires

Self-Efficacy for Exercise

Self-efficacy reflects the confidence that a person has to perform a certain behavior [77].

The self-efficacy for exercise is a 5-item scale intended to analyze the confidence that a person has to perform exercise according to 5 different emotional states, such as feeling worried or having problems, feeling depressed, feeling tired, feeling tense, and being busy.

Ratings are done using a 5-point Likert scale from 1 “not at all true” to 4 “completely true.” In between are 2, meaning “slightly true,” and 3, meaning “moderately true” [78].

Activities and Participation Profile Related to Mobility

PAPM is an 18-item scale intended to improve the understanding of the difficulties an individual experiences while performing certain daily activities in their natural environment. These activities can be conditioned by mobility and are related to the interactions and social relations, education, employment, money management, and social and community life and influence a person’s active participation in society [79]. Ratings are done using a 5-point Likert scale from 0, meaning “no limitation or restriction,” to 4, meaning “complete limitation or restriction.” In between, 1 indicates “mild limitation or restriction,” 2 indicates “moderate limitation or restriction,” and 3 indicates “severe limitation or restriction.” Because some activities may not apply, not all activities may be rated. As a result, an individual’s participation profile will be produced [79].

Home Safety Checklist for Fall Prevention

The Home Safety Checklist for Fall Prevention is a 38-item scale intended to identify home hazards in each room of a person’s home, namely the hallways, stairs, living or dining room, kitchen, bathroom, bedroom, and outdoors [80,81].

Ratings are assigned using a 3-point scale from 0 (indicating “no risk”), 1 (indicating “risk”), to 99 (indicating “do not apply”). A risk score is produced both to each room and for the home in general.

Pressure Platform (Universal Serial Bus Cable)

The PhysioSensing platform (Sensing Future Technologies, Lda) measures pressure distribution data, running at a frequency of 50 Hz. It consists of 1600 pressure sensors (10 mm by 10 mm) with a maximum value of 100 N/sensor. Voltage data are converted with an 8-bit A/D converter and is transmitted via Universal Serial Bus. Therefore, it is possible to receive raw data of each pressure sensor as well as the raw center of pressure coordinates (CoP) in cm. To obtain more precision in CoP displacements, an algorithm was employed to obtain CoP positions in millimeters using the matrix of pressure sensors [82]. The pressure platform collects valuable balance information during STS, the step test, and the 4-Stage Balance test “modified.” To collect useful information, participants should be barefoot.

Inertial Sensors (Bluetooth Connection)

Wearable inertial sensors were developed and assembled at Fraunhofer Portugal Research Center for Assistive Information and Communication Solutions, Portugal. Inertial data are collected from the built-in 3-axial accelerometer and 3-axis gyroscope, both sampled at 50 Hz. Raw data from the accelerometer are acquired for all the tests in m/s^2 and raw data from the gyroscope are acquired in $degrees/s^2$.

For the TUG test, 30s STS test, step test, 4-Stage Balance test “modified,” and 10-meter walking speed test, one inertial sensor is placed at the lower back, and one at the ankle. In the case of step test and 4-Stage Balance test “modified,” the ankle inertial

sensor is placed on the dominant leg chose by the participant. Instrumentation with inertial sensors during the execution of standard tests gives additional quantitative information, such as the duration of the standing phase on TUG, contributing to better assessment, and characterizing a person's mobility and balance conditions. Another advantage of using inertial sensors is that they eliminate the bias introduced by observation of movements and subjective assessment and the output extracted are potentially more reliable and reproducible [21].

Statistical Analysis

Statistical analysis will be performed using IBM SPSS version 24 (SPSS Inc, Armonk, NY, USA) software. The sample size was calculated for an infinite population with a 95% confidence interval and a 5% margin of error to assess the number of participants needed to consider a representative sample of Portuguese population (minimum number of participants was 385). To perform the data analysis, the participants will be categorized as "fallers" (with one or more falls) and "nonfallers," according to fall occurrences during the 12 month follow-up period.

The statistical approach will differ according to the level of measurement for the variables. The descriptive analysis will determine the mean and SD for the quantitative variables and frequencies for the qualitative ones. Differences in data between "fallers" and "nonfallers" will be analyzed by Student's *t* test for independent samples or the chi-square test. Binary logistic regression analysis will be performed to determine a model that allows the prediction of falls from the functional tests and other variables. Receiver-operating characteristic (ROC) curve analysis will be used to identify the best cut-off score that distinguishes "fallers" from "nonfallers." Sensitivity (percentage of "fallers" who were correctly identified), specificity (percentage of "nonfallers" that were correctly identified), and area under the receiver characteristic curve of the model will be calculated for prediction of falls. A significance of .05 will be considered for all comparisons, except for the quality of adjustment of the regression models, obtained with the Hosmer and Lemeshow test, whose significance is considered for $P \geq .05$.

Results

This prospective study is in progress. The enrollment has already begun and study completion is anticipated by the end of 2018. Permission letters for data collection were sent to the institutions identified as potential sites in the community to gather data. Authorization was obtained by their representatives and the screening procedures scheduled according to their daily routines. The results will be submitted to a leading journal for publication.

Discussion

To develop a multifactorial screening tool to assess fall risk for community-dwelling persons, key risk factors for falls were identified. The occurrence of previous falls, visual impairment, urinary incontinence, and use of benzodiazepines are strong fall predictors [83]. In this protocol, different questions were included regarding the strongest predictors of falls. However, this screening protocol intended to collect more specific data which allow the characterization of each person. Different functional tests and questionnaires were included in the FallSensing screening protocol to accomplish a detailed evaluation of each case.

The FallSensing screening tool combines multiple validated instruments to identify multiple factors that influence fall risk. By understanding the major factors that increase fall risk, preventive strategies tailored for community-dwelling older adults can help decrease the fall rate and prevent fall-related injuries.

The lengthy screening time will probably represent a limitation of this protocol. However, one of the goals of this project is to prospectively validate a risk prediction model for fall risk by combining metrics collected by the pressure platform and inertial sensors complemented by additional collected data. The risk prediction model, defined according to ROC curve analysis, will allow to identify the most valuable data and consequently, shorten the protocol.

The National Institute for Health and Care Excellence recommends that the interventions to prevent falls should be patient-centered [1]; therefore, the stratification of risk will be a valuable tool for the FallSensing screening protocol, giving more detailed information and guiding the prescribing physiotherapist an intervention protocol toward fall prevention.

This investigation also will determine if the FallSensing screening protocol is feasible, valid, and acceptable in a Portuguese population.

The application of this prospective study protocol will allow us to understand the strengths and limitations of the FallSensing screening tool, leading to adaptations such as a shortened screening protocol.

Acknowledgments

Authors would like to thank COMPETE 2020 (Operational Programme Competitiveness and Internationalization) and European Regional Development Fund from European Union and all participants and centers, clinics, and other entities hosting the screenings performed to date.

Authors' Contributions

ACM and IS developed the study concept and design. JM, CS, and DB were primarily responsible for the literature review. CR and TP will analyze all data. JM and CS were responsible for the drafting and writing of this manuscript. ACM, JS, and CT performed a critical revision. All authors read and approved the final version of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CoP: center of pressure coordinates
FoF: fear of falling
GS: gait speed
HoF: history of falls
PAPM: activities and participation profile related to mobility
ROC: receiver-operating characteristic
SPH: self-perceived health
30STS: 30 seconds sit to stand
TUG: Timed Up and Go test

Edited by G Eysenbach; submitted 28.03.18; peer-reviewed by M Silva, M Nomali; comments to author 18.04.18; revised version received 02.05.18; accepted 05.05.18; published 02.08.18.

Please cite as:
Martins AC, Moreira J, Silva C, Silva J, Tonelo C, Baltazar D, Rocha C, Pereira T, Sousa I
Multifactorial Screening Tool for Determining Fall Risk in Community-Dwelling Adults Aged 50 Years or Over (FallSensing): Protocol for a Prospective Study
JMIR Res Protoc 2018;7(8):e10304
URL: http://www.researchprotocols.org/2018/8/e10304/
doi:10.2196/10304
PMID:30072360

Protocol

Designing and Implementing a Home-Based Couple Management Guide for Couples Where One Partner has Dementia (DemPower): Protocol for a Nonrandomized Feasibility Trial

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Abstract

Background: The increasing rate of dementia and high health and social care costs call for effective measures to improve public health and enhance the wellbeing of people living with dementia and their relational networks. Most postdiagnostic services focus on the condition and the person with dementia with limited attention to the caring spouse or partner. The key focus of the study is to develop a guide for couples where one partner has a diagnosis of dementia. This couple management guide is delivered in the form of an app, DemPower.

Objective: This study aims to investigate the feasibility and acceptability of DemPower and to assess the criteria for a full-integrated clinical and economic randomized control trial. DemPower couple management app will be introduced to couples wherein one partner has dementia.

Methods: The study will recruit 25 couples in the United Kingdom and 25 couples in Sweden. Couples will be given 3 months to engage with the app, and the amount of time taken to complete the guide (can be <3 or >3 months) will be reviewed. A set of outcome measures will be obtained at baseline and postintervention stages.

Results: The proposed study is at the recruitment phase. The DemPower app is being introduced to couples from consultation groups at a pretrial phase for identifying any bugs and exploring if any navigation challenges exist. The feasibility testing will begin in April 2018.

Conclusions: The study will determine how much support couples need to engage with DemPower and whether or not they make use of it in their everyday lives. If there is support for app use, a future study will assess whether it is superior to “usual care.”

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 10122979; http://www.isrctn.com/ISRCTN10122979 (Archived by WebCite at http://www.webcitation.org/70rB1iWYI)

Registered Report Identifier: RR1-10.2196/9087

(JMIR Res Protoc 2018;7(8):e171) doi:10.2196/resprot.9087

KEYWORDS

dementia; couple management guide; dementia self-help; dementia intervention

Introduction

The prevalence of dementia is rising globally with increases in the average age of the world's population and is estimated to reach 131.5 million by 2050 [1]. The evidence base for high-income countries (United States, United Kingdom, Netherlands, and Sweden) suggests a declining trend in age-specific incidence [2,3]. In the United Kingdom and Sweden, two-thirds of all people with dementia are aged over 80 years [4,5] and more than 50% live alone at home or with their care partner [6,7]. In 2013, the total health and social care cost of dementia in the United Kingdom was estimated to be £26.3 billion, of which 44% were unpaid care costs [5,8]. In Sweden, during 2012, the estimate for health and social care costs was SEK 52 billion, of which informal care was 16.7% [2]. The financial costs to health and social care that are attributed to dementia are likely to continue to increase in future years unless effective measures are undertaken to improve public health [4,9]. Accordingly, a well-defined approach needs to be adopted to manage the implications of dementia on societal systems and organizations, including the wellbeing of people living with dementia and their relational networks [1].

The national and international push for early diagnosis and intervention in dementia has incentivized programs and strategies to improve diagnostic rates and quality of life for people living with dementia and their families. In the United Kingdom, some of these strategies involve public awareness campaigns, training health and social care professionals, memory assessment and support services, internet-based forums for caregivers, and creating dementia-friendly infrastructures, spaces and technology [10-15]. However, despite these improvements, some studies indicate that people with a recent diagnosis of dementia are largely left on their own to manage their condition [16,17] and are only (re)visited by statutory services once a crisis at home occurs [7]. This is an interesting paradox as the demographic data suggest that most people with dementia want to live in their own home and neighborhood for as long as possible. It is, therefore, imperative that relevant supports are made available early on during the diagnostic process, and that people living with dementia and their relational networks are made aware of available resources and services. This could prevent the occurrence of crisis situations and reduce health and social care costs.

In the United Kingdom, alongside mainstream health and social care services, some charities such as the Mental Health Foundation, Age UK and the Alzheimer's society have long provided localized support services and opportunities for people with dementia and their families to access community engagement programs. While welcome, there remains a dearth of dyadic, couple-centered approaches [18,19], with most interventions for couples where one partner has a dementia overwhelmingly emphasizing the condition (the dementia), rather than on the needs of partners as a couple [20-24]. In Sweden, most people with dementia live in their homes, in which they require care and support. This has been identified as one of the main challenges facing primary care in Sweden [25]. To address this gap in interventions for couples, an easy to use couple management guide was developed as part of the "Living Life and Doing Things Together" project. This project is one of eight work programs within the Economic and Social Research Council (ESRC)/National Institute for Health Research (NIHR) Neighbourhoods and Dementia mixed methods study [26]. All the eight work programs are underpinned by a neighborhoods' model [27], positioning people living with dementia and their social and relational networks at the center of the overall study aims and objectives. Informed by this approach, the current work program (6) is centered on the lives of couples who live together at home, where one partner has a diagnosis of dementia. The couple management guide developed in this study is delivered in the form of an app, DemPower. In this study, the intervention was tested for feasibility.

The use of mobile apps in health care, especially among people with dementia and their families, has gained prominence due to the ability of these apps to promote quality of life for the person with dementia and their families [28,29]. Some of the apps on the market include global positioning system trackers to enable people with dementia and their families to feel safe in their neighborhoods [30,31], schedule activities of daily living, communicate, and manage appointments and emergency help [32]. The wider research evidence suggests self-management resources in the form of apps, complemented with appropriate training and support, are beneficial for patients in the early to moderate stages of dementia and enhance quality of life [28,33]. This paper reports the protocol to evaluate the acceptability and feasibility of the DemPower intervention.

The overall aim of the study is to investigate the feasibility and acceptability of the app-based couple management guide DemPower among couples living together at home, where one partner has dementia. The key objectives are (1) to explore if the DemPower couple management guide is useful and acceptable to couples, (2) to assess the recruitment capability and how effective and appropriate are the outcome measures and data collection procedures, and (3) to analyze the potential for conducting an economic evaluation in the full trial.

Methods

Study Design

The study uses a prospective, nonrandomized feasibility design to investigate the level of uptake of DemPower among couples where one partner has a diagnosis of dementia. The methodology facilitates an assessment of study processes to explore the criteria for a full trial.

Study Population

The study will involve couples with one partner having a diagnosis of dementia and who live together at home. We will seek to recruit a wide and diverse couple population. This extends to any type of dementia, sexual orientation, age, profession, social, cultural, and religious contexts. Participants

will be enrolled regardless of comorbidities experienced by a partner with dementia and the health status of a supporting partner. We will also include participants enrolled in other research studies. The wide diversity of participants is envisaged to study a better understanding of potential participants for a future full trial. This also provides opportunities to explore population needs, compare outcomes, and inform the areas that need further development. Specific inclusion and exclusion criteria are listed in Textbox 1.

Sample Size

As this is a feasibility study, no formal power calculation is needed. Instead, Lancaster et al [34] recommend including between 30 and 50 participants (in this study, couples) to estimate critical parameters (eg, recruitment rate; standard deviation of primary outcome) with necessary precision. This study does not aim to randomize participants, and therefore, there is no control group in this study. We will aim to recruit 50 couples across North West England and Sweden (Linköping and Norrköping). Figure 1 describes various stages of the study.

Selection and Recruitment

In the United Kingdom

The recruitment of 25 couples in North West England will take place via Clinical Research Network, Joint Dementia Research network, dementia cafes, and third sector organizations. We will also advertise our study in memory clinics and through the wider project's website and social media (Twitter) networks to identify and recruit potential participants who are interested in the study.

Staff members working at National Health Service Trusts and Clinical Research Networks will be involved in identifying people with dementia to the study, and they will use the Trust databases and the Join Dementia Register to identify potential eligible participants.

The researcher will establish contacts with staff from third sector organizations and coordinators of dementia cafes (eg, Age UK, Alzheimer's society, Creative Mind etc). Appropriate permissions will be sought prior to addressing the group. The study poster will be displayed at these meetings, and detailed study information will be available for interested group members. The researcher will ensure that the third sector organizations' contact source or coordinators do not communicate potential participants' details without their prior permission.

For recruiting through advertisements, interested participants are free to contact the researcher. Contacts established in this manner will be followed up through a face-to-face meeting. At this meeting, the researcher will explain the study and hand in the detailed study information pack.

Potential participants who meet the inclusion criteria will be given information about the study and the opportunity to express an interest in taking part in the study. Potential participants will have opportunities to ask any questions they have and to discuss any aspects of the study with the researcher before they make their decision. The interested participants will be given sufficient time to make a decision and be approached again to obtain informed consent (24 hours or more after the first visit).

In Sweden

A total of 25 couples will be recruited from memory clinics and dementia cafes based in county Östergötland (Linköping and Norrköping) of Sweden.

The staff at the memory clinic will identify couples, contact potential participants to discuss the study, and identify couples who are interested in participating. Couples who express interest in participating will have their details passed on to the relevant researcher.

The researcher will contact study staff or coordinators within the third sector organizations (eg, dementia cafes): day care centers and family care centers within the municipalities of Linköping and Norrköping. On obtaining relevant permissions, study posters will be displayed and details of the study will be presented to the members of the group. Researchers will approach interested participants individually to assess for inclusion, discuss the study in detail, and obtain consent.

Textbox 1. Inclusion and exclusion criteria.

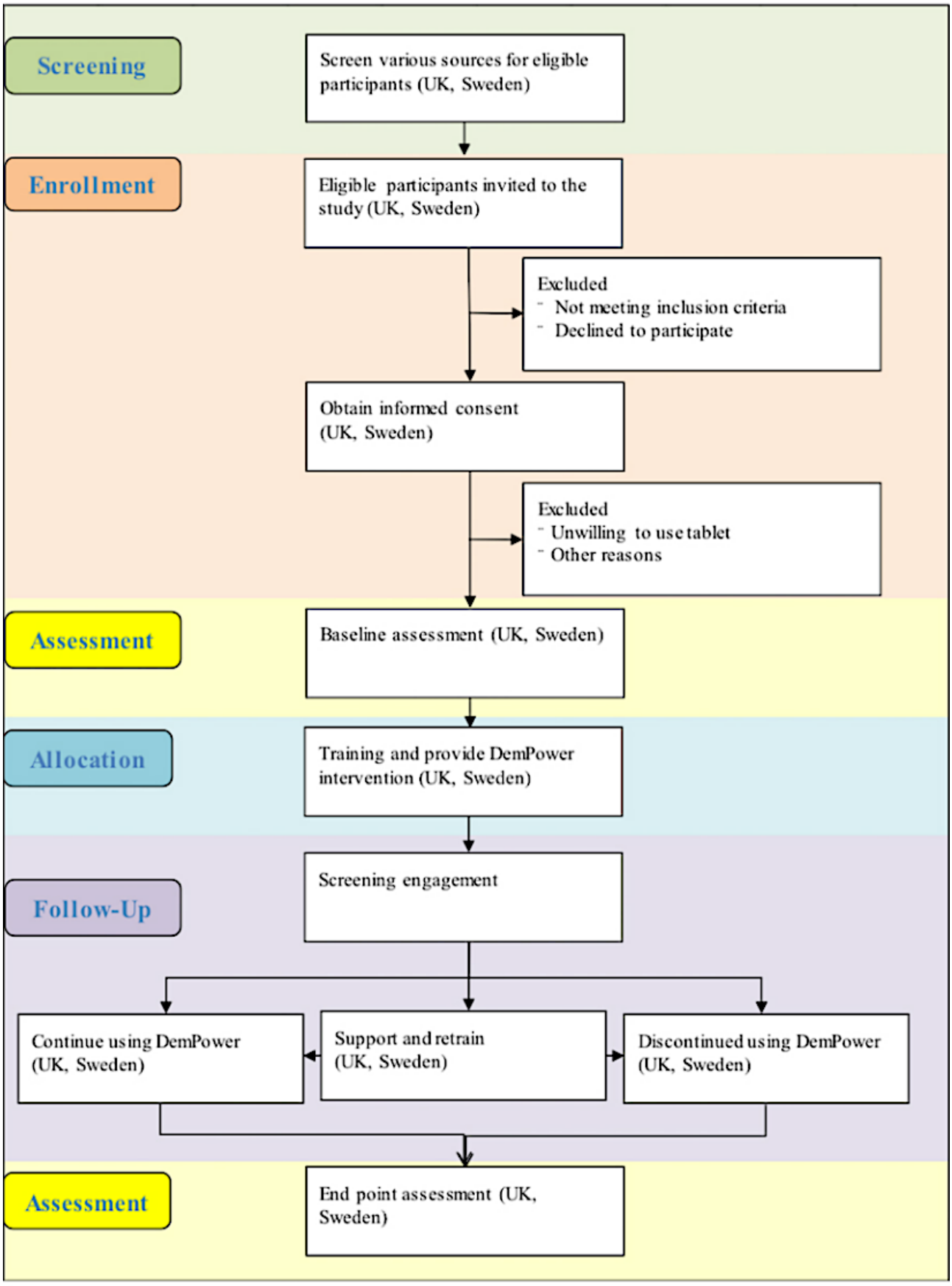
Inclusion criteria

- Couples who have a partner or spouse with a diagnosis of dementia in early to moderate stages. The stage will be identified either via clinical team during referral or through self-report
- Couples who live together in their own homes (not residential care).
- Both partners understand and speak English (in the United Kingdom) or Swedish (in Sweden)
- Couples in a long-term relationship for 2 or more years

Exclusion criteria

- Couples with one or both partners who are blind and might find it difficult to interact with DemPower
- Any partner who has become completely immobile or bed-bound and may not be able to engage with suggested activities
- Both partners having a diagnosis of dementia
- Couples where one or both partners lack capacity or may have fluctuating capacity

Figure 1. Study stages.



DemPower Intervention

Living Life and Doing Things Together is a couple management guide delivered through the platform of an electronic application on a touchscreen device (Android tablet). The guide is aimed at enhancing the wellbeing as well as the relationship of couples where one partner has a diagnosis of dementia. The contents in this guide are based on couples with lived experience, available research, and practice evidence.

The objectives of the DemPower guide are (1) to help couples focus on the activities that they can do rather than what they cannot, (2) to reflect upon the strengths of their relationship, (3) help couple find ways to tackle daily activities together, and (4) to archive reflections, moments, and memories the way they would like them to be remembered.

The guide is structured under 4 primary themes and several sections within each theme, as illustrated in Figure 2. The themes and corresponding sections are introduced using storyboard techniques with a voiceover. Videos clips of couples sharing their experiences demonstrating particular situations follow storyboard illustrations. The guide makes suggestions for activities under each section. Examples of some suggested activities include games (stored on the device), links to useful information, taking pictures, writing reflections, and discussing emotions, needs and required changes to their home and their approach to daily life.

The app design facilitates various forms of user interfaces and provides users the control over font size, color, language, volume etc. The design also focuses on making the interface simple and easy to access. The interaction within the app is multimodal (voice, touch, text to speech). User-centered and participatory approaches inform the overall app design and concept.

The app and all the corresponding resources will be saved onto a portable device (tablet) prior to handing them over to the recruited couples (one tablet per couple). Researchers will provide a tutorial on how to use the device and the app. A detailed help video is inbuilt into the app. Researchers will provide a printed copy on how to use the device and the guide to all the participants. The participants may contact researchers at any time if they require technical support. The researchers will call the participants once a month to check their progress and arrange visits if required. We will recommend the participants to engage with two sections per week. They have the option to engage with a selection of sections or with the entire guide and in any order. Participants are expected to complete the guide within a period of 3 months from the date of device activation.

Feasibility, Acceptability, and Health Outcome Measures

The goal of the study is to explore feasibility, acceptability, and usability of DemPower among couples where one partner has dementia. Using Bowen et al's [35] suggested areas of focus for feasibility studies, Table 1 reports the approaches and measures used to assess the different aspects of the feasibility and acceptability of the DemPower intervention [35-37]. The structure in Table 1 helped to identify relevant outcomes, demonstrate how these address study objectives, and inform the choices of data collection procedures.

Two primary data sets will be generated from the study: evaluation and outcomes data. The study team designed a set of evaluation questionnaires to assess participants' experiences with DemPower and the study processes (Multimedia Appendices 1-5). These questionnaires, DemPower, and chosen outcome measures will be tested with couples from a consultancy group for comprehension errors and bug fixing prior to the feasibility phase. The outcomes used to represent effectiveness include health-related aspects of quality of life, self-efficacy, interconnectedness, and mutuality on the part of both partners.

Figure 2. Guide contents.

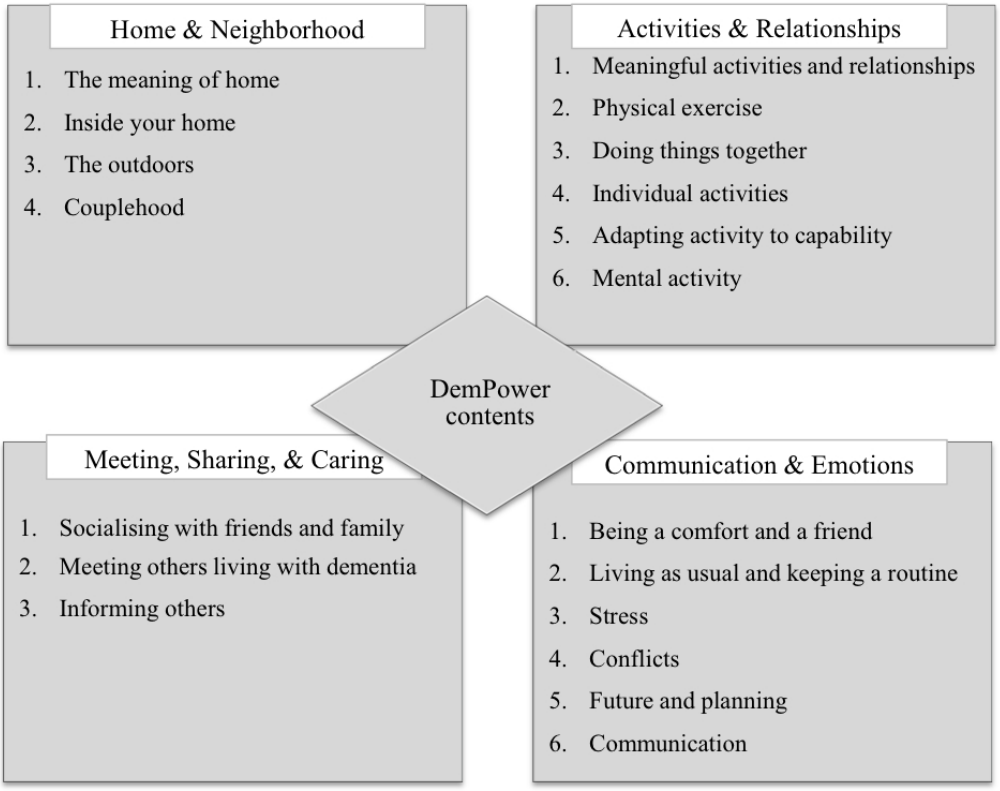


Table 1. Bowen et al's [35] feasibility criteria and study application.

Area of focus	Study application	Outcomes of interest	Data sources
Acceptability and integration	To what extent is DemPower suitable to implement in home-living couples with dementia?	Perceived acceptability and satisfaction	Evaluation Questionnaires, 3-point Likert scale
Demand	To what extent do couples consider the couple management approach and the content of DemPower as desirable support?	Perceived usability	Usage tracking data, self-reported system usability scale [38], 5-point Likert scale
		Perceived benefits of DemPower	Evaluation Questionnaires, 3-point Likert scale
Implementation and practicality	To what extent can DemPower be successfully implemented with couples living with dementia?	Willing and able to complete all the sections of the self-help guide	Dropout rates usage tracking data
		Type of, and amount of support needed by couples	Evaluation questionnaire – custom matrix
		Degree of technical errors, resources, factors influencing implementation	Researcher log
Adaption	To what extent can DemPower be used in its current state?	Degree of errors; levels of support	Researcher log; Evaluation Questionnaires, 3-point Likert scale
Efficacy	To what extent does DemPower show promise of encouraging engagement and positive effects on couples' relationships and beliefs in managing daily life?	Impact on quality of life, relationship quality, mutuality, closeness, sense of couplehood, self-efficacy, and health status	Baseline and post intervention or end point assessments of quality of life—Quality of Life in Alzheimer´s disease [39], Care-related Quality of Life [40]; Relationship Quality and Mutuality – Mutuality Scale [41]; Closeness and interconnection – Inclusion of Other in Self Scale [42]; Empowerment /Self-efficacy – General Self-efficacy Scale [43]; Health status – EQ-5D-5L (EuroQol health measure with 5 levels of severity for 5 dimensions) [44]

Table 2 presents the measures used to assess the potential effectiveness of the DemPower app and provide information for the design of any future randomized controlled trial (RCT), including sample size estimation.

Data Collection

An evaluation questionnaire will explore participants' experiences with the guide, relevance of guide's contents, usability of the app, perceived benefits, relevance of the guide

in everyday living, applicability to various contexts, the volume of contents, and the time required to complete the guide (Multimedia Appendix 1). Responses to questions may vary from rating, multiple choices to descriptive forms.

At the end of each section, written instructions will be provided, guiding participants to use a particular set of questionnaires. Questionnaires are split across 4 themes presented in the guide (Multimedia Appendices 2-5). Researchers will follow up on participants' progress with the questionnaires during regular telephonic conversations or home visits and offer support if required.

The following usage data will be stored on the tablet to measure how the app is used:

- The number of times and timestamp of when each screen was viewed
- The number of times the initial splash or landing screen has opened, in order to tell how many times app was started from scratch
- The contents pages will indicate how users are navigating the app, whether by the contents pages or going through sequentially using next or back buttons.

The outcome measures, questionnaires, and usage tracking data will form primary sources of data for this part of the study. All the questionnaires will be administered using an offline or a paper-based survey tool. The researcher will administer the outcome measures listed in Table 2 at baseline (prior to introducing the guide) and at the end point. Participants who choose to engage with only parts of the intervention will also be assessed at the start and at the time that they declare as completed or at the end of 3 months from the intervention initiation date. The details of participants' progress, telephonic follow-ups, home visits, and variations in follow-up time frames will be recorded in the researchers' logs. Researchers will support the person with dementia as he or she completes the outcome measures at baseline and at the end point during face-to-face meetings. Spouse or partner caregivers will be encouraged to complete the assessments on their own during the researcher's visit.

Feasibility Design Process

The outcome relevant to the design process is to ascertain if a main study is feasible by classifying the study under one of the following categories: (1) Stop – main study not feasible; (2) Continue, but modify protocol – feasible with modifications; (3) Continue without modifications, but monitor closely – feasible with close monitoring, and (4) Continue without modifications – feasible as is.

The evaluation of the study process will be informed by Medical Research Council's guidance on complex interventions [36], and principles and questions specific to feasibility designs discussed by Bowen et al [35] and Osmond and Cohen [46].

Table 2. Outcomes of effectiveness.

Outcomes and tools	Description	Answered by
Quality of Life		
Quality of life in Alzheimer´s disease [39]	• 13-item tool • Addresses mood, cognitive, and functional ability, activities of daily life and quality of relationships with family and friends • Uses a 4-point Likert scale ranging from “poor” (1p) to “excellent” (4p) with a maximum score of 52	Both the spouses or partners individually
Caregiver-Related Quality of Life		
Carer Quality of life [40]	• 7-item tool • Addresses 5 negative and 2 positive dimensions of providing informal care • Uses 3-point Likert scale from “a lot” (0p) to “no” (2p) for the negative dimensions and reversed scale for positive dimensions. The higher the score, the better the care situation	Partner or spouse caregiver
Self-efficacy		
General Self-efficacy Scale [43]	• 10-item tool • Assess coping skills and adaptation to situations • Has a four choice response ranging from “not at all true” (1p) to “exactly true” (4p); Scores are summarized to a total score, and a higher score indicates a higher sense of self-efficacy	Both the spouses or partners individually
Interconnectedness		
The Inclusion of Other in Self Scale [42]	• A single item pictorial measure of closeness • Assess people’s sense of being interconnected to each other	Both the spouses or partners individually
Mutuality		
Mutuality Scale [41]	• 15-item Mutuality Scale • Includes four dimensions—love and affection, shared values, reciprocity and shared pleasurable activities • Rated on a 4-point Likert scale between 0 “not at all” to 4 “a great deal”	Both the spouses or partners individually
Health and social care service use		
Service use questionnaire	• The service use questionnaire was adapted from current service use questionnaires held by the investigators, it will be refined by consultation with the study service user group • Covers key health and social care services • Assesses the range of services used as well as the frequency of use • The measure will be administered by the researcher at the baseline and end of follow-up assessments	Both the spouses or partners individually
Health status		
EQ-5D-5L (EuroQol health measure with 5 levels of severity for 5 dimensions) [44]	• Has a 5-dimensional structure (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) • Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems • Allows estimation of quality-adjusted life years	Both the spouses or partners individually
DEMQOL (Measurement of health-related quality of life for people with dementia) [45]	• A condition-specific measure of health-related quality of life for people with dementia • Can be completed with the person with dementia or a main caregiver • The measures cover 5 domains: daily activities and looking after yourself, health and wellbeing, cognitive functioning, social relationships, and self-concept • Preference weights are available to allow estimation of quality-adjusted life years	Partner or spouse with dementia

The process evaluation plays a key role in assessing the quality of study implementation, recruitment capability, attrition rate, data collection procedures, relevance of outcome measures and evaluation questionnaire, resource capability for implementing the study and acceptability of randomization. The study design does not allow for evaluating the randomization process; therefore, the acceptability of randomization will be explored with participants in the form of open-ended questions administered at the end of the study.

The data relevant to these areas will be obtained from researchers' field notes, process evaluation questionnaires, recruitment and attrition data, contextual data associated with variations in outcomes, evaluating research team's capabilities, researchers' observations of suitability of outcomes, questionnaires, the burden on participants, and support required and will use results from the intervention segment to assess the relevance of chosen methodology.

Data Analysis

All the data obtained from outcome measures and evaluation questionnaires will be entered into an Excel or Stata database for further statistical analysis. The data will be anonymized prior to being uploaded to a database. The qualitative or open-ended responses from evaluation questionnaires will be categorized and analyzed thematically. The data from Sweden will be transferred to the research team at the University of Manchester for statistical analysis.

Given that this is a feasibility study (and that there is no control group), we will not be carrying out hypothesis testing to determine if the intervention is effective. Instead, we will focus on (1) estimating recruitment and attrition rates; (2) determining whether there is sufficient change in potential outcome measures following the intervention, using appropriate descriptive measures of central tendency (mean, median) and spread (standard deviation, inter-quartile range, range); (3) estimating the standard deviation of potential outcome measures to inform or refine a sample size calculation for the Phase III trial; and (4) estimating response rates to participant questionnaires, checking for floor and ceiling effects and in fact whether the intervention is acceptable to participating couples. We will reconsider the use of questionnaires or other items if the amount of missing data exceeds 10%.

Economic Evaluation

This study will not include a formal economic evaluation. Rather, the data collected will be used to inform the design and implementation of a full RCT to assess the (cost) effectiveness of the intervention. We will use the service data to identify the range of services used by participants. The service use data will be costed using published unit costs to estimate the likely health and social care costs. Descriptive statistics and regression analysis will be used to identify key cost drivers. Published utility weights will be applied to the EuroQol health measure with 5 levels of severity for 5 dimensions and the Measurement of health-related quality of life for people with dementia and used to estimate quality-adjusted life years. Descriptive statistics and regression analysis will be used to explore the level of association between the two measures and key domain drivers of overall utility and quality-adjusted life years.

Ethical Considerations

The study is approved by the National Health Service Research Ethics Committee (17/NW/0431) in the United Kingdom and the Regional Ethical Review Board in Sweden (Dnr: 2017 2017/281-31).

The approach to obtaining consent is informed by a "process consent" method [47], whereby a researcher enables participants to make informed decision from the point of initial contact to completion of the study [48]. Guided by the Mental Capacity Act [49] and the process consent approach, the researchers will make every effort to ensure that the participants are provided with all the relevant information that they understand the information and are able to retain the information long enough to make a decision and are willing to participate in the study.

People who have capacity to consent will provide either a written or verbal consent. Participants who find reading or writing challenging will have an option of expressing consent verbally, and it will be audio recorded.

Results

This is an on-going study, currently at the trial phase. The study is currently recruiting participants from both sites. This nonrandomized feasibility study will produce results pertaining recruitment capability, usability, and acceptability of DemPower among couples where one partner has dementia as well as the relevance of chosen outcome measures and evaluation questionnaires. The results will inform a future RCT and fully powered health economic assessment.

Discussion

Principal Findings

A scoping review, conducted earlier on in the study, highlighted the dearth of couple-oriented interventions for couples affected by dementia. Postdiagnostic dementia services and service uptake by people with dementia and their caregivers are quite diverse, depending upon population groups and geographical locations [2,9,50]. The DemPower guide attempts to combine the resources available and act as a single source of information, while providing strategies for managing everyday living. DemPower is particularly aimed at couples who live together at home and where one partner has a diagnosis of dementia. The contents of DemPower have been informed by the experiences of couples who live with dementia and daily life and social situations that include potentially important ways of maintaining a healthy relationship.

Future Work

Through this feasibility study, we will be able to establish participants' interest and engagement with the app, how useful and helpful participants find the sections on "home and neighborhood," "activities and relationships," and "approach and empowerment." We also have the opportunity to explore how this app translates into everyday life. This information is

crucial for exploring how usual care compares with DemPower and sets stage for a full RCT.

In terms of the study methodology, relevant information on recruitment and attrition rate will inform the future power calculation for a full trial. In the current feasibility study, we test the app in two countries (United Kingdom and Sweden); this will provide insights into if any systemic differences influence the uptake of the app. These data will inform the transferability of the app to various contexts, cultures, and countries.

Limitations

The diverse cultural and social contexts in the United Kingdom and Sweden might raise some challenges for comparing data and estimating parameters for a full trial, although it does provide opportunities for identifying key areas for consideration in future multinational trials. The design of DemPower is limited and might require further adaptations to make it applicable to people with visual impairments. Finally, differences in recruitment strategies in the United Kingdom and Sweden might influence the recruitment and retention rate.

Acknowledgments

This work was supported by ESRC and NIHR, grant number R117002. This work forms part of the ESRC/NIHR Neighbourhoods and Dementia mixed-methods study. This paper is taken from Work Program 6.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Process evaluation questionnaire.

[PDF File (Adobe PDF File), 69KB - resprot_v7i8e171_app1.pdf]

Multimedia Appendix 2

App-specific feasibility questionnaire 1.

[PDF File (Adobe PDF File), 61KB - resprot_v7i8e171_app2.pdf]

Multimedia Appendix 3

App-specific feasibility questionnaire 2.

[PDF File (Adobe PDF File), 63KB - resprot_v7i8e171_app3.pdf]

Multimedia Appendix 4

App-specific feasibility questionnaire 3.

[PDF File (Adobe PDF File), 64KB - resprot_v7i8e171_app4.pdf]

Multimedia Appendix 5

App-specific feasibility questionnaire 4.

[PDF File (Adobe PDF File), 67KB - resprot_v7i8e171_app5.pdf]

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Abbreviations

DEMQOL: Measurement of health-related quality of life for people with dementia
ESRC: Economic and Social Research Council
EQ-5D-5L: EuroQol health measure with 5 levels of severity for 5 dimensions
NIHR: National Institute for Health Research
RCT: randomized controlled trial

Edited by G Eysenbach; submitted 26.10.17; peer-reviewed by W Tang, R Maguire; comments to author 14.12.17; revised version received 08.03.18; accepted 03.05.18; published 10.08.18.

Please cite as:
Lasrado R, Bielsten T, Hann M, Davies L, Schumm J, Reilly S, Swarbrick C, Keady J, Hellström I
Designing and Implementing a Home-Based Couple Management Guide for Couples Where One Partner has Dementia (DemPower): Protocol for a Nonrandomized Feasibility Trial
JMIR Res Protoc 2018;7(8):e171
URL: http://www.researchprotocols.org/2018/8/e171/
doi:10.2196/resprot.9087
PMID:30097423

Original Paper

A Remote Intervention to Prevent or Delay Cognitive Impairment in Older Adults: Design, Recruitment, and Baseline Characteristics of the Virtual Cognitive Health (VC Health) Study

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Abstract

Background: A growing body of evidence supports the use of lifestyle interventions for preventing or delaying the onset of Alzheimer disease and other forms of dementia in at-risk individuals. The development of internet-delivered programs would increase the scalability and reach of these interventions, but requires validation to ensure similar effectiveness to brick-and-mortar options.

Objective: We describe the study design, recruitment process, and baseline participant characteristics of the sample in the Virtual Cognitive Health (VC Health) study. Future analyses will assess the impact of the remotely delivered lifestyle intervention on (1) cognitive function, (2) depression and anxiety, and (3) various lifestyle behaviors, including diet, exercise, and sleep, in a cohort of older adults with subjective memory decline. Additional analyses will explore feasibility outcomes, as well as the participants' engagement patterns with the program.

Methods: Older adults (aged 60-75 years) with subjective memory decline as measured by the Subjective Cognitive Decline 9-item (SCD-9) questionnaire, and who reported feeling worried about their memory decline, were eligible to participate in this single-arm pre-post study. All participants enrolled in the yearlong digital intervention, which consists of health coach-guided lifestyle change for improving diet, exercise, sleep, stress, and cognition. All components of this study were conducted remotely, including the collection of data and the administration of the intervention. We assessed participants at baseline, 12 weeks, 24 weeks, and 52 weeks with online surveys and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test. We will conduct intention-to-treat analysis on all outcomes.

Results: A total of 85 participants enrolled in the intervention and 82 are included in the study sample (3 participants withdrew). The study cohort of 82 participants comprises 61 (74%) female, 72 (88%) white, and 64 (78%) overweight or obese participants, and 55 (67%) have at least a college degree. The average baseline RBANS score was 95.9 (SD 11.1), which is within age-adjusted norms. The average SCD-9 score was 6.0 (SD 2.0), indicating minor subjective cognitive impairment at the beginning of the study. The average baseline Generalized Anxiety Disorder 7-item scale score was 6.2 (SD 4.5), and the average Patient Health Questionnaire 9-item score was 8.5 (SD 4.9), indicating mild levels of anxiety and depression at baseline.

Conclusions: Internet-delivered lifestyle interventions are a scalable solution for the prevention or delay of Alzheimer disease. The results of this study will provide the first evidence for the effectiveness of a fully remote intervention and lay the groundwork for future investigations.

Trial Registration: ClinicalTrials.gov NCT02969460; http://clinicaltrials.gov/ct2/show/NCT02969460 (Archived by WebCite at http://www.webcitation.org/71LkYAkSh)

Registered Report Identifier: RR1-10.2196/11368

(JMIR Res Protoc 2018;7(8):e11368) doi:10.2196/11368

KEYWORDS

cognitive impairment; dementia; Alzheimer disease; lifestyle intervention; digital health; health coaching; cognitive dysfunction; risk reduction behavior

Introduction

Lifestyle Interventions for Cognitive Decline

Cognitive impairment is a growing public health epidemic worldwide, and is one of the most prevalent chronic medical conditions in older adults [1]. In 2010, the direct and indirect costs of care associated with dementia totaled US $600 billion globally, amounting to roughly 1% of the world's gross domestic product [2]. The global costs associated with Alzheimer disease, the most common form of dementia, are projected to increase by about 400% from US $186 billion in 2018 to US $750 billion in 2050 [1]. The challenge posed by dementia is amplified by the decades-long failure to develop effective pharmacologic agents for the disease. The success rate of Alzheimer disease drugs is only 0.4%, compared with 19% for oncology compounds [3], leading some major pharmaceutical companies to abandon research efforts in the face of continued failures. The drugs approved for Alzheimer disease treat only the symptoms rather than the underlying causes of the disease, and do not prevent or delay the progression of neurodegeneration involved in Alzheimer disease and other forms of dementia [4].

Conversely, nonpharmacologic lifestyle-based interventions are gaining traction as an effective way to prevent or delay disease progression. Epidemiologic studies estimate that modifiable risk factors, such as diabetes, hypertension, obesity, smoking, depression, physical inactivity, and low educational attainment, account for as many as 30% of dementia cases [5-7]. In the absence of a cure, delay of Alzheimer disease or dementia onset by as little as 1 year is associated with enormous cost savings, with an estimated potential savings of US $219 billion by 2050 in the United States alone [8]. Additionally, a 5-year postponement could almost halve the projected Alzheimer disease prevalence by 2050 [9-11]. Due to the proven ability to decrease some of the modifiable risk factors implicated in Alzheimer disease [12,13], lifestyle-based interventions hold the potential to greatly reduce the burden of dementia as populations continue to age worldwide.

The lifestyle intervention for cognitive decline used in the multidomain Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) [14] has been at the forefront of these Alzheimer disease-related behavioral modification efforts and served as the primary inspiration for the program used in this study. The landmark FINGER study is an ongoing randomized controlled trial (RCT) demonstrating the efficacy of a multidomain intervention as a preventive measure in older adults at risk for cognitive decline and dementia. The lifestyle intervention primarily focuses on exercise, diet, cognitive training, and management of vascular risk factors. The 2-year results [15] clearly showed that (1) individuals can be motivated to make long-term changes in their lifestyle to preserve cognitive function, and (2) a multidomain lifestyle intervention can improve composite cognitive performance at a 2-year follow-up.

The FINGER study, which used a clinic-based lifestyle intervention, was the first RCT to provide proof-of-concept that attending to lifestyle and vascular factors can protect against cognitive decline [15]. The success of the FINGER study has spawned numerous in-clinic replication studies around the globe, including the Singapore Intervention Study to Prevent Cognitive Impairment and Disability (SINGER) [16], Multimodal Intervention to Delay Dementia and Disability in Rural China (MIND-CHINA) [17], and United States Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (US POINTER) [18]. However, face-to-face lifestyle change programs like the ones used in these studies are constrained by geographical and other logistical challenges, therefore warranting the exploration of internet-based programs that are better suited for widespread adoption in a real-world setting. The Maintain Your Brain study is a large-scale clinical trial in Australia aiming to demonstrate the efficacy of a fully digital, multidomain intervention at preventing cognitive decline [19]; however, results will not be available for some years. The Virtual Cognitive Health (VC Health) study described here is the first trial, to our knowledge, that explores the effectiveness of a commercially available digital lifestyle intervention aimed at preventing or delaying cognitive decline in at-risk older adults.

Objective

The primary objective of the VC Health study is to investigate the feasibility and effectiveness of a remotely delivered multidomain intervention for the prevention or delay of cognitive impairment in older adults at increased risk of cognitive decline. Secondary analyses will assess the effectiveness of the program at ameliorating symptoms of depression and anxiety, which are both risk factors for Alzheimer disease [20,21]. Supplemental analyses will examine patterns of user engagement with the program and changes in various lifestyle behaviors. The yearlong intervention consists of 6 months of active multidomain lifestyle change and 6 months of habit reinforcement during the maintenance phase. The main components of the intervention are coach-directed exercise, nutritional guidance, cognitive training, and social engagement. We hypothesize that this digital intervention modeled after the pivotal FINGER study [15] will result in (1) significant improvements in composite cognitive performance and (2) positive changes in depression and anxiety levels. Here we report the study design and analysis plan, as well as baseline characteristics of the study population for the VC Health study.

Methods

Study Design

The VC Health study is a 52-week-long, prospective intention-to-treat, single-arm, pre-post, virtual nationwide clinical trial to evaluate the impact of the VC Health program on cognitive function and mental health in older adults in the United States.

While conventional clinical trials rely on in-person interactions for recruitment, screening, enrollment, data collection, and data monitoring, virtual clinical trials are enabled by advances in technology and digital health, allowing for fully remote participation in clinical trials [22]. For the VC Health study, we used an online study platform (Achievement Studies; Evidation Health Inc.; San Mateo, CA, USA) to screen, obtain consent from, and enroll participants into the study, as well as to collect and monitor study data and guide participants through the trial. The study was approved by the Solutions Institutional Review Board (Little Rock, AR, USA) and is registered with clinicaltrials.gov (NCT02969460). The study protocol was designed and written by investigators at Evidation Health, with input and review from the VC Health intervention team.

Participant Selection and Recruitment

We recruited study participants through various digital platforms, including online patient communities, social media, and targeted advertisements across all 50 US states. Potential participants learned about the trial through a Web portal explaining the study details. Those who were interested in participating then completed an online screener that assessed their eligibility for the study.

Eligible participants were aged 60 to 75 years; endorsed subjective cognitive decline with worry as assessed by the validated Subjective Cognitive Decline 9-item (SCD-9) questionnaire [23] and the 1-item subjective cognitive decline with worry item ("Do you feel like your memory is becoming worse?" Possible responses were "No," "Yes, but this does not worry me," or "Yes, this worries me") [24], which have been shown to have early predictive value for progression to mild cognitive impairment and Alzheimer disease [24,25]; had reliable access to a phone, text messaging, and the internet; and were interested in using a coaching program for cognitive health (Textbox 1). Study candidates were considered ineligible if they had a history of mental illness, substance abuse, learning disability, neurologic conditions, or dementia; had ophthalmologic or visual problems that would interfere with computer use; were already using a cognitive-training coaching program; or were currently pregnant.

Enrollment and Study Procedures

Study candidates who met the eligibility criteria and who were interested in participating provided electronic informed consent on the online study platform, and then completed an online baseline assessment, which consisted of questions about demographic characteristics, lifestyle and overall health behaviors, Patient Health Questionnaire 9-item (PHQ-9), Generalized Anxiety Disorder 7-item (GAD-7) scale, and self-reported sleep, diet, and activity levels. Next, we asked study candidates to schedule a baseline Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test. The RBANS was remotely administered via video-teleconference by a licensed psychologist (Echelon Group; Woodstock, GA, USA). Once participants completed the RBANS test, we asked them to complete their first VC Health coaching session. This session lasted approximately 60 minutes and was conducted over the phone. We considered study candidates to be enrolled once they completed their first coaching session.

Once enrolled, participants completed online assessments and RBANS tests at 12 weeks, 24 weeks, and 52 weeks. Since there are four alternative forms of the RBANS test, designed to reduce practice effects during repeated testing over time, we gave participants in this study a different form for each of the 4 testing periods [26]. Participants were able to engage with the VC Health program throughout the 12-month study period.

Textbox 1. Inclusion and exclusion criteria for the VC Health study.

Inclusion criteria

- Aged ≥60 but ≤75 years
- Show signs of subjective cognitive decline (assessed by scoring ≥1 on the Subjective Cognitive Decline 9-item (SCD-9) questionnaire and endorsing "Yes, this worries me" on the subjective cognitive decline with worry item)
- Have the ability to make and receive phone calls
- Have the ability to send and receive text messages
- Have access to a desktop computer, video-teleconferencing and reliable internet connection
- Motivated to use a daily coaching program

Exclusion criteria

- Have a significant history of mental illness, substance abuse, learning disability, or neurologic conditions
- Have a history of dementia
- Have ophthalmologic or visual problems that prevent viewing a computer screen at a normal distance (eg, legal blindness, detached retinas, occlusive cataracts)
- Currently participating in a formal cognitive-training coaching program
- Currently pregnant

Virtual Cognitive Health Program

The VC Health program comprises two phases: a 6-month active phase of lifestyle change and a 6-month maintenance phase of habit reinforcement. The individually tailored intervention encourages a healthy diet, physical exercise, cognitive training, and social engagement, all of which are supported by a coach who is reachable via telephone, email, and text messaging. To supplement all coaching interactions, we provided participants with Web-based psychoeducational material to help guide and pace individual learning.

Health Coaching

We assigned each participant a health coach for the duration of the intervention. All coaches were certified as personal trainers through nationally accredited programs, where the basic level of certification requires mastery of exercise physiology safety and nutritional health practices. To further ensure safety, a VC Health program nurse was available to assist coaches with the more complex behavioral health needs of participants.

After participants completed baseline testing, they were assigned a coach and completed an initial 1-hour phone call to discuss more detailed information about their current exercise and dietary habits. During the first 6 months of the intervention, participants had the option of scheduling weekly phone calls with their coach to discuss questions, difficulties, or adjustments to lifestyle behaviors. After the first 6 months, we gave participants the option to maintain the weekly cadence of coaching calls or to reduce the cadence to biweekly or monthly calls. We offered the option to adjust the call frequency to accommodate the varying levels of self-efficacy that the participants developed throughout the intervention.

Physical Exercise

All participants received psychoeducation regarding the benefits of physical exercise, such as aerobic and bodyweight training, on cognitive health. As part of the intervention, we also provided participants with Fitbit Flex 2 wearable devices (Fitbit, Inc, San Francisco, CA, USA) to help track and monitor activity levels. Participants were encouraged to log all exercise data in electronic trackers on the VC Health program platform. In an effort to prevent overwhelming participants with too much educational content at once, we prioritized exercise for the first month, prior to coaching for diet or cognitive training.

Health coaches assisted participants with creating individually tailored physical activity programs that incorporated aerobic exercise and progressive muscle strength training. Individual aerobic exercise plans prioritized activities preferred by each participant, such as swimming, biking, and walking. The exercise training program is a modified version of the FINGER study [15] physical activity intervention, including bodyweight strength training and aerobic exercise. The bodyweight strength training program included exercises for all primary muscle groups.

Coaches assessed each participant's level of fitness at the beginning of the program and used the information to individually tailor exercise recommendations. Based on coach evaluations of self-reported exercise levels at baseline, participants were placed into low, moderate, and high categories. Low exercisers were those who completed aerobic exercise fewer than 3 times per week (minimum of 30 minutes per session) or no body resistance exercise (minimum 30 minutes). Moderate exercisers were those who completed aerobic exercise 3 times per week (minimum 30 minutes per session) or body resistance exercise fewer than 2 times per week (minimum 30 minutes per session). High exercisers were those who completed aerobic exercise 4 or more times per week (minimum 45 minutes per session) and body resistance exercise 2 or more times per week (minimum 45 minutes per session). Participants were encouraged to set a goal of reaching the next exercise threshold throughout the program or sustaining current levels if they were categorized as high exercisers at baseline.

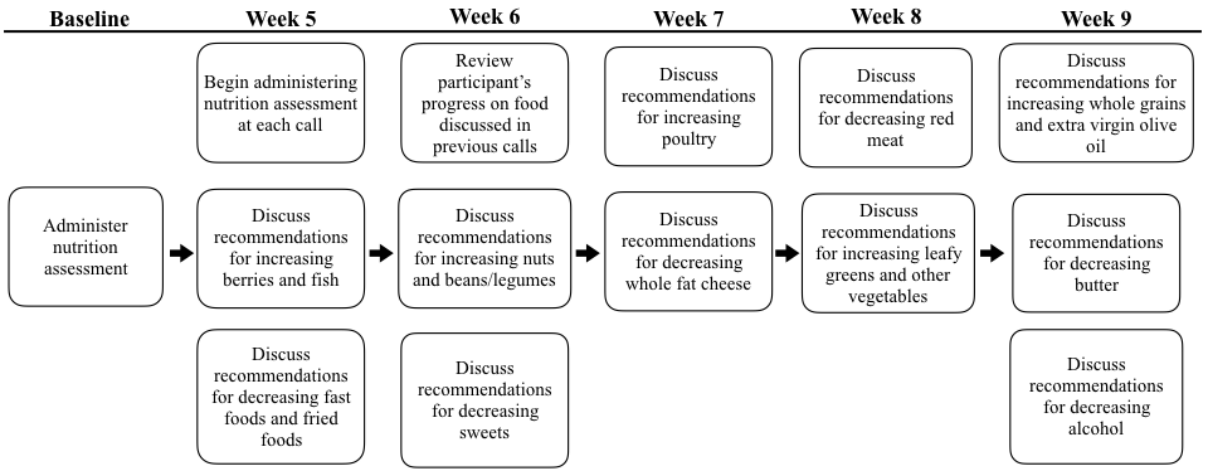
Diet and Nutrition

All participants received psychoeducation on the benefits of the Mediterranean-Dietary Approach to Systolic Hypertension (DASH) Intervention for Neurodegenerative Delay (MIND) diet for cognitive health. The MIND diet emphasizes the consumption of foods that have been shown to have positive effects on cognitive health [27]. Combining pieces of the Mediterranean and DASH diets, the MIND diet recommends regular consumption of berries (≥5 servings per week), fish (≥1 servings per week), nuts (≥5 servings per week), beans or legumes (≥4 servings per week), poultry (≥2 servings per week), green leafy vegetables (≥1 servings per day), other vegetables (≥1 servings per day), grains (≥3 servings per day), and extra virgin olive oil (≥3 servings per day) [28]. The MIND diet recommends limited consumption of fried and fast foods (≤1 servings per week), sweets (≤5 servings per week), whole fat cheese (≤1 servings per week), red meat (≤4 servings per week), butter (≤1 servings per day), and alcohol (≤2 servings per day) [28]. During the initial coaching call, participants were assessed on their current fidelity to the MIND diet and were categorized as either high adherers (meets >7 MIND recommendations) or low adherers (meets ≤7 MIND recommendations). Coaches used these categories as a baseline for guiding participants through increasing MIND diet adherence (Figure 1), helping each participant create an individually tailored diet plan.

Cognitive Training

We provided participants with a curriculum on the benefits of cognitive training for cognitive health, including a library of curated content on the topic. VC Health program coaches helped participants create an individually tailored cognitive training program. The training program was provided by a Web-based service (MindAgilis, London, England) and included several tasks adapted from protocols previously shown to be effective in shorter-term RCTs, focusing on processing speed, executive function, working memory, episodic memory, and mental speed [29,30].

Figure 1. Flow for assessing and improving participant dietary habits.



Social Engagement

All participants received access to an internal, private social network where they could engage in communal support and directed life review. Participants in the study were given the opportunity to connect with one another and were also able to invite one family member and one friend to join the social network. Participants were asked to respond to a variety of discussion prompts, including structured life review questions based on an evidence-based protocol [31,32], and participate in discussions about other study participants' life review reflections. The social network was moderated by a clinical psychologist.

Neurotrack Imprint Eye-Tracking Test

As part of the intervention, we asked participants to complete the Neurotrack Imprint eye-tracking test as an additional measure of cognition [33]. The test consists of a 5-minute visual paired-comparison task developed by Neurotrack Technologies, Inc. (Redwood City, CA, USA). Visual paired-comparison tasks quantify how the test participant splits attention between familiar and novel visual stimuli, with a familiarization phase preceding a testing phase. During the familiarization phase, participants are presented with pairs of identical visual stimuli for a fixed period of time (5 seconds). During the test phase, which follows a delay of either 2 seconds or 2 minutes to assess immediate and delayed recognition memory, participants are presented with additional pairs of visual stimuli, including one from the familiarization phase and one novel stimulus. The ratio of time participants spend gazing at the novel stimulus relative to the total viewing time produces a novelty preference score, with higher scores representing better declarative memory function [34]. Test-retest reliability (r range .88-.92) and interrater scoring agreement (κ range .81-.88) for the Imprint test have both been documented as high based on previous literature [33].

Outcome Measurements

With cognition as the primary focus of this investigation, the RBANS was remotely administered [35] to all participants by qualified clinicians with experience in digital delivery at baseline (week 0), week 12, week 24, and week 52. The RBANS has demonstrated strong efficacy as a dementia assessment tool in community-dwelling normal individuals [36,37] and can also detect cognitive impairment associated with Alzheimer disease

[38]. The primary outcome in this study was change in RBANS total score from study baseline to week 24 and week 52.

We assessed secondary risk factors for Alzheimer disease (depression and anxiety) through the PHQ-9 and GAD-7 scale at baseline, week 12, week 24, and week 52. We chose these items because depression [39-41] and anxiety [42,43] are predictive of future cognitive decline, with symptoms of both tending to manifest before direct evidence of cognitive decline is present. The PHQ-9 is a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) diagnostic instrument for common mental disorders [44]. The PHQ-9 comprises the depression module, which scores each of the 9 *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for depression from 0 (not at all) to 3 (nearly every day) and has been validated for use in primary care [45]. The GAD-7 is a self-report anxiety questionnaire designed to assess anxiety status during the previous 2 weeks. The items in the questionnaire assess the degree to which an individual has been bothered by nervous, anxious, or on-edge feelings; lack of ability to stop or control worrying; worrying too frequently about various things; inability to relax or sit still; ease of becoming annoyed or irritable; and feeling afraid [46]. The secondary outcome of this study was change in PHQ-9 and GAD-7 scores from study baseline to week 24 and week 52.

In addition to depression and anxiety symptoms, we asked participants about their sleep (hours per night) and exercise (days per week) habits during the previous 3 months. We collected these data at the same time points as the PHQ-9 and GAD-7 results. At 24 and at 52 weeks, we asked all participants to provide subjective data on their perceived improvements in cognitive ability, physical activity levels, eating habits, sleep patterns, and stress levels. Exploratory analyses will examine changes in self-reported behaviors and how engagement with the VC Health program is associated with change in RBANS performance.

Lastly, we will assess a number of feasibility outcomes to inform future study designs and program iterations. For one, we will analyze the ease of recruitment and the study retention rate. These results will provide rough estimates of what we can expect in future trials on the VC Health intervention. We will also analyze qualitative data about the participant experience in the intervention that we collected through online surveys at 12, 24, and 52 weeks. The feedback from participants will shape future program features and help to optimize the participant experience.

Sample Size and Statistical Analysis

Given the preliminary nature of this study, we did not power the study to detect any specific difference in RBANS score, and we determined the sample size based on intervention capacity. Ultimately, 85 participants enrolled into the study.

Analyses will be conducted on deidentified aggregate data from the intention-to-treat population. The primary analysis will explore mean and median change in RBANS score from study baseline to the 24-week and 52-week primary end points. For both the RBANS and online assessments, we included the 12-week time point to allow for an interim nonprimary analysis early on in the study. We will also examine the mean and median changes stratified by key participant characteristics, such as sex, age, and education. Secondary analyses will examine the mean and median change in PHQ-9 and GAD-7 scores from study baseline to 24 and 52 weeks. Potential supplemental analyses will examine various measures of user engagement, the relationship between engagement and changes in RBANS scores and secondary outcome measures, and changes in various lifestyle behaviors, such as sleep and exercise habits.

Results

Study recruitment, screening, and enrollment took place between November 2016 and March 2017. A total of 4255 participants were identified as potentially eligible from recruitment strategies and initiated the screening process. Of these, we determined 2655 to be ineligible based on factors including baseline cognitive function, history of mental illness, vision issues, and current pregnancy. Out of the final 405 individuals deemed eligible, 85 individuals provided informed consent, completed baseline surveys, finished all baseline assessments, were assigned a health coach, and started the VC Health program. Of these, 3 individuals withdrew from the study due to personal reasons, leaving 82 individuals eligible for data analysis (Figure 2).

Table 1 displays the baseline demographic characteristics of study participants. Overall, 61 of the 82 participants (74%) were female, and the mean age was 64 years (range 60-74.9). Of the 82 participants, 72 (88%) identified as white, 5 (6%) as African American, 3 (4%) as Hispanic, 1 (1%) as Asian, and 1 (1%) as other. Of the 82 participants, 55 (67%) had a college degree or higher. Average baseline body mass index was 30.7 (SD 7.0) kg/m^2, with an average weight of 87.5 (SD 20.8) kg. Enrolled participants represented a geographically diverse population (Figure 3).

At baseline, the average total RBANS score was 95.9 (SD 11.1), which is within normal age-adjusted ranges. The average SCD-9 score was 6.0 (SD 2.0), indicating minor subjective cognitive decline and, as previously mentioned, all participants endorsed worry about cognitive decline. The average GAD-7 score was 6.2 (SD 4.5) and the average PHQ-9 score was 8.5 (SD 4.9), respectively indicating mild levels of anxiety and depression at baseline (Table 2).

Figure 2. Enrollment cascade and study timeline. RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

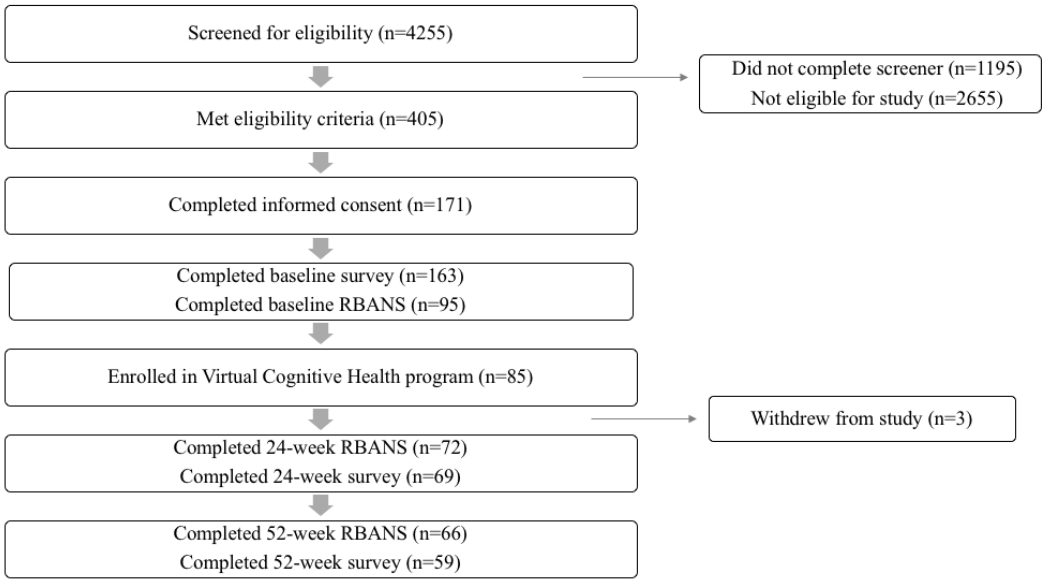


Table 1. Baseline demographics of enrolled participants (N=82).

Characteristics	Value
Age (years), mean (SD)	64 (4)
Sex, n (%)	
Male	20 (24)
Female	61 (74)
Other	1 (1)
Education, n (%)	
High school graduate or GED[a]	3 (4)
Trade, technical, or vocational training	2 (2)
Some college, no degree	22 (27)
College graduate, associate's or bachelor's degree	29 (35)
Graduate degree	19 (23)
Doctorate	7 (9)
Race/ethnicity, n (%)	
African American	5 (6)
Asian	1 (1)
White	72 (88)
Hispanic	3 (4)
Other	1 (1)
BMI[b] (kg/m^2), n (%)	
<18.5 (underweight)	0 (0)
18.5-24.9 (healthy weight)	16 (20)
25.0-29.9 (overweight)	24 (29)
30-34.9 (obese)	25 (30)
≥35 (very obese)	15 (18)
Average nightly sleep duration (hours), n (%)	
<3	1 (1)
4-5	4 (5)
5-6	18 (22)
6-7	35 (43)
7-8	16 (20)
8-9	6 (7)
9-10	0 (0)
>10	6 (2)

[a]GED: General Education Development.

[b]BMI: body mass index; 2 participants were excluded due to BMI >60 kg/m^2.

Figure 3. Geographic distribution of study participants. Each dot on the map corresponds to a study participant's zip code. Larger dots represent multiple individuals from that zip code.

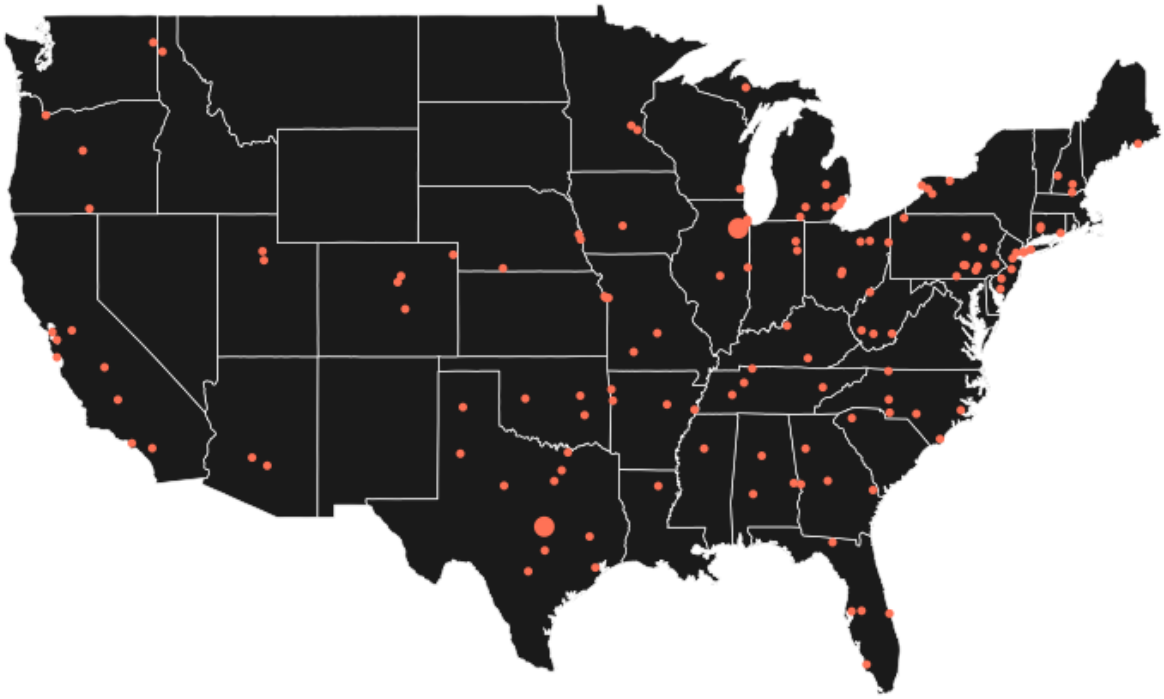


Table 2. Baseline assessment scores of enrolled participants (N=82).

Assessment instruments	Mean (SD)
Repeatable Battery for the Assessment of Neuropsychological Status	
Immediate Memory	99.4 (12.5)
Delayed Memory	96.6 (12.5)
Visuospatial/Constructional	90.4 (14.3)
Language	97.2 (10.2)
Attention/Processing Speed	102.8 (14.8)
Total	95.9 (11.1)
Subjective Cognitive Decline 9-item questionnaire	6.0 (2.0)
Patient Health Questionnaire 9-item	8.5 (4.9)
Generalized Anxiety Disorder 7-item scale	6.2 (4.5)

Discussion

Principal Findings

The VC Health study will investigate the feasibility and effectiveness of a remotely delivered multidomain lifestyle intervention for the prevention or delay of cognitive impairment in older adults with subjective cognitive decline. As the digital delivery of these interventions is a new area of study, validation of this format is needed to ensure similar effectiveness to in-person options. The results of this pilot study will provide preliminary insights into the translation of a traditionally in-person multidomain lifestyle intervention to a fully digital format and will help shape future program iterations. While face-to-face interventions like the one used in the FINGER study have shown promise for decreasing risk of cognitive decline [12], participation in these types of programs is constrained by geographical and logistical complications, such as scheduling conflicts and access to transportation. The only requirement for participation in a digital lifestyle intervention like VC Health is access to an internet-connected device, such as a mobile phone, tablet, or computer. For those who do not own such devices, the program may still be accessible by using technology that is available at local libraries and community centers, which further expands the potential reach of the program. The successful translation and adoption of digitally delivered lifestyle interventions has the potential to reduce the incidence of Alzheimer disease and medical spending on the disease as the search for effective pharmaceutical agents continues.

Digital lifestyle interventions have been developed for a variety of health-related conditions. These multipronged interventions have shown efficacy for diabetes prevention [47,48], diabetes

management [49-52], cardiovascular risk reduction [53-55], pain management [56], and smoking cessation [57]. Many of the core components of lifestyle interventions are similar, independent of the health condition they address. These components generally include psychoeducational material, social support from a peer group, access to a health coach, and tracking tools to facilitate the adoption of new health behaviors. The VC Health program contains all of these features, with adjustments tailored to individuals at risk for cognitive decline. Some of the unique aspects of the VC Health program are the addition of cognitive training exercises [58-60], specific dietary recommendations for following the MIND diet [27,28,61,62], and validated physical activity recommendations specific for enhancing cognitive function [63-65]. Based on the successful translation of other lifestyle programs into a digital format, the VC Health intervention should lend itself well to online delivery.

While the adoption of Web-based lifestyle change programs has increased over the years, one of the main barriers to the widespread adoption of remote cognitive tests is the concern about data integrity. The remote delivery of cognitive tests makes it difficult to accurately monitor patients for effort, focus, and test understanding, which is normally completed by an in-person test administrator. However, previous literature has demonstrated the efficacy and effectiveness of remote RBANS delivery via videoconference [35], supporting its use in our investigation. The Imprint test, which is embedded in the VC Health program, uses webcam-based eye-tracking data, with recorded video from the test providing analysts with “eyes on the patient.” This allows the analysts to assess various elements of data quality and fidelity to test-taking procedures [33]. Remote administration of the RBANS and Imprint tests allows for the feasible and scalable collection of data at multiple time points and for the longitudinal monitoring of cognitive health. This investigation is, to our knowledge, the first of its kind in the cognitive health space, and is structured to demonstrate that a digital intervention can be delivered from baseline to completion while measuring primary, secondary, and exploratory outcomes with entirely remote mechanisms.

Strengths and Limitations

The design of the VC Health study has both strengths and limitations. One strength is the digital administration of the intervention and collection of data in a real-world setting, which provides more ecologically valid results than studies completed in traditional research settings [22]. This is important, as it enhances the generalizability of the results and provides more powerful estimates of how the intervention is likely to perform in broader populations and settings. Another strength is the 52-week study duration, as this allows the results to reflect the long-term impact of the intervention. Examining the long-term outcomes of lifestyle change programs is essential to demonstrate the true impact of participation after the program tapers off or ends.

Limitations of this study include the small sample size and lack of a control group, which were both a result of the pilot nature of this investigation. However, it should be noted that intervention studies evaluating digital lifestyle programs commonly employ single-arm designs, and this design is well accepted in the field for early studies [47,48,52,66,67]. Lastly, the study sample was primarily white and well educated, so the results may not be generalizable to other populations. Future studies require the exploration of similar interventions in a more diverse group of individuals.

Conclusion

This single-arm pre-post pilot study will provide initial evidence of the feasibility and effectiveness of a remotely delivered multidomain intervention to prevent or delay cognitive decline in older adults at risk for dementia. We will collect qualitative information on specific intervention components and use it to inform the ongoing design iterations of the Web-based intervention, as well as the design of larger studies investigating the effect of the intervention. The 24- and 52-week longitudinal follow-up periods used in this fully remote study will be the first to evaluate the effectiveness of a digital intervention to prevent or delay cognitive decline in older adults. In addition to composite cognitive performance, assessment of symptoms of anxiety and depression will allow us to explore the effects of the intervention on other aspects of mental health. We expect the results of this trial to provide crucial insights into the promise of remotely delivered cognitive health interventions, which could have a substantial impact on dementia incidence over the coming decades.

Acknowledgments

The authors thank all participants in the VC Health study and all of the study collaborators for their cooperation and hard work. This study was funded by Neurotrack and completed by Evidation Health.

Authors' Contributions

NB, CK, SK, and JLJ conceived the study and participated in its design. SK and JLJ drafted the study protocol with review and input from NB and CK. NB, JMG, and ENM drafted the manuscript. JLJ and SK provided data and reviewed and edited the manuscript.

Conflicts of Interest

Neurotrack makes and owns the eye-tracking assessment and behavior change program used in this study. NB, CK, JMG, and ENM are employed by Neurotrack and receive a salary and stock options. Evidation Health collected and analyzed all study data. JLJ and SK are employed by Evidation Health and have no financial interest in Neurotrack.

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Abbreviations

DASH: Dietary Approach to Systolic Hypertension
FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
GAD-7: Generalized Anxiety Disorder 7-item
MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay
MIND-CHINA: Multimodal Intervention to Delay Dementia and Disability in Rural China
PHQ-9: Patient Health Questionnaire 9-item
PRIME-MD: Primary Care Evaluation of Mental Disorders
RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
RCT: randomized controlled trial
SCD-9: Subjective Cognitive Decline 9-item
SINGER: Singapore Intervention Study to Prevent Cognitive Impairment and Disability
US POINTER: United States Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk
VC Health: Virtual Cognitive Health

Edited by N Kuter; submitted 21.06.18; peer-reviewed by J Ploeg, C Bailey; comments to author 16.07.18; accepted 23.07.18; published 13.08.18.

Please cite as:
Bott N, Kumar S, Krebs C, Glenn JM, Madero EN, Juusola JL
A Remote Intervention to Prevent or Delay Cognitive Impairment in Older Adults: Design, Recruitment, and Baseline Characteristics of the Virtual Cognitive Health (VC Health) Study
JMIR Res Protoc 2018;7(8):e11368
URL: http://www.researchprotocols.org/2018/8/e11368/
doi:10.2196/11368
PMID:30104186

Protocol

Virtual Medical Modality Implementation Strategies for Patient-Aligned Care Teams to Promote Veteran-Centered Care: Protocol for a Mixed-Methods Study

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Abstract

Background: The Veterans Health Administration (VHA) is making system-wide efforts to increase integrated use of health information technology (HIT), including My Health*e*Vet (MHV), the Veterans Affairs (VA) electronic patient portal, Vet Link kiosks, telehealth, and mobile apps. Integrated use of HIT can increase individual and system efficiency, maximize resources, and enhance patient outcomes. Prior research indicates that provider endorsement and reinforcement are key determinants of patient adoption of HIT. HIT implementation strategies need to reflect providers' perspectives to promote adoption and endorsement of these tools; however, providers often lack awareness or are unmotivated to incorporate HIT into clinical care with their patients. When these modalities are used by patients, the approach is often fragmented rather than integrated within and across care settings. Research is needed to identify effective implementation strategies for increasing patient-aligned care team (PACT) member (ie, the VHA's Patient Centered Medical Home) awareness and motivation to use HIT in a proactive and integrated approach with patients.

Objective: This paper describes the rationale, design, and methods of the PACT protocol to promote proactive integrated use of HIT.

Methods: In Aim 1, focus groups (n=21) were conducted with PACT members (n=65) along with questionnaires and follow-up individual interviews (n=16). In Aim 2, the team collaborated with VA clinicians, electronic health researchers and operational partners to conduct individual expert interviews (n=13), and an environmental scan to collect current and emerging provider-focused implementation tools and resources. Based on Aim 1 findings, a gap analysis was conducted to determine what implementation strategies and content needed to be adapted or developed. Following the adaptation or development of resources, a PACT expert panel was convened to evaluate the resultant content. In Aim 3, a local implementation of PACT-focused strategies to promote integrated use of HIT was evaluated using pre- and postquestionnaire surveys, brief structured interviews, and secondary data analysis with PACT members (n=63).

Results: Study enrollment for Aim 1 has been completed. Aims 1 and 2 data collection and analysis are underway. Aim 3 activities are scheduled for year 3.

Conclusions: This work highlights the practical, technological, and participatory factors involved in facilitating implementation research designed to engage PACT clinical members in the proactive integrated use of HIT. These efforts are designed to support the integrated and proactive use of VA HIT to support clinical care coordination in ways that are directly aligned with PACT member preferences. This study evaluated integrated VA HIT use employing mixed-methods and multiple data sources. Deliverables included PACT-focused strategies to support integrated use of HIT in the ambulatory care setting that will also inform strategy development in other systems of care and support subsequent implementation efforts at regional and national levels.

Registered Report Identifier: RR1-10.2196/11262

(JMIR Res Protoc 2018;7(8):e11262) doi:10.2196/11262

KEYWORDS

ambulatory care; health information technology; implementation; medical informatics; veteran; virtual medical modality

Introduction

Background

The Department of Veterans Affairs (VA) MyVA Initiative articulates a vision for personalized, proactive, and patient-driven care leveraging information technologies, analytics, and new models of health care delivery [1,2]. To operationalize this vision, the Veterans Health Administration (VHA) is making system-wide efforts to increase the integrated use of health information technology (HIT), including My Health*e*Vet (MHV), VetLink kiosks, telehealth, and mobile apps. Integrated use of HIT can increase individual and system efficiency, maximize resources, and enhance patient outcomes [3]. Prior research indicates that provider endorsement and reinforcement are key determinants of patient adoption of HIT [4,5]. HIT implementation strategies need to reflect providers' perspectives to promote adoption and endorsement of these tools [6]. Providers often lack awareness or are unmotivated to incorporate HIT into clinical care with their patients [3]. Current use of these modalities is often fragmented rather than integrated within and across care settings [3]. Therefore, research is needed to identify effective implementation strategies for increasing the proactive and integrated use of HIT among patient-aligned care teams (PACTs; VHA's primary care Patient-Centered Medical Home model).

Research Aims

This research was responsive to the vision of the VA's MyVA Initiative and strategic plan for veterans to receive timely and integrated care through enhanced use of HIT. Our short-term goal was to locally develop, deliver, and evaluate implementation strategies with both core PACT members (ie, clerical associates, clinical associates, nurses, providers) and extended PACT members (ie, mental health, nutrition, pharmacy, social work) to increase use of HIT. This research sets the foundation for subsequent implementation efforts at regional and national levels. Long term, this research has potential to inform sustained HIT use by PACTs in a nationwide integrated health care system. We used a community-based participatory research approach [7] and theoretical constructs from the Consolidated Framework for Implementation Research [8] including elements from the Diffusion of Innovations theory [9,10] and the Promoting Action on Research Implementation in Health Services (PARiHS) framework [11] to inform this 3-year concurrent mixed-method [12] implementation study. The research aims were to (1) identify characteristics of PACT members that impact HIT use among high- and low-volume users, (2) develop implementation strategies to promote PACT adoption of HIT, and (3) evaluate local implementation of PACT-focused strategies to promote HIT adoption.

The first aim addressed three research questions: (1) What are the characteristics of high- and low-volume clinical team users? (2) What factors influence use (ie, compatibility, observability, complexity, relative advantage)? and (3) What are PACT member experiences and preferences for using HIT (ie, evidence, context, facilitation)?

The second aim addressed two research questions: (1) What implementation strategies currently exist to support HIT adoption? and (2) What implementation strategies promote HIT adoption?

Finally, the third research aim addressed three research questions: (1) Do implementation strategies reflect PACT member needs and preferences? (2) How can the implementation strategies be refined and improved to support adoption of HIT? and (3) Does exposure to implementation strategies increase PACT use of HIT? The third research aim also addressed two hypotheses: (1) Exposure to implementation strategies will increase PACT members' self-reported value, intention, and use of HIT, and (2) Exposure to implementation strategies will significantly increase PACT use of HIT.

Intended outcomes of this study were to develop novel PACT-focused strategies to advance implementation science, implement a pioneering protocol to objectively evaluate integrated HIT use employing secondary data sources, and support operational efforts in the expansion of HIT within VHA.

Background on the VA's Health Information Technology

The VA's HIT are central components for delivering personalized, proactive, and patient-driven care. My Health*e*Vet, mobile apps, VetLink kiosks, and telehealth are core virtual resource technologies designed to increase patient access, participation in care, and self-care management. The VA is vested in supporting veteran and provider use of virtual resources to improve patient outcomes [13,14] and promote

efficient system utilization. In alignment with the strategic plan for Digital Services put forth by the VA Secretary's Office, HIT provides an integrated approach to delivering virtual care throughout the VHA system of care. This integrated HIT system is an important interface to support increased veteran access to the VHA, Veterans Benefits Administration, and National Cemetery Administration.

Patients value virtual health care delivery [15-19]. More than 4 million veterans are registered MHV users (Veterans and Consumers Health Informatics Office, US VA, unpublished data 2017), and this number continues to increase. VA's multiple HIT platforms (eg, mobile, Web, kiosks) are likely to become the primary interface for patients and providers. Virtual communication between patients and providers facilitate information sharing, patient-centered communication, and coordination of care [11,20]. Use of HIT extends the focus of care beyond the acute care setting to support the ongoing health maintenance, medical treatment, prevention of secondary complications and comorbidities, and psychosocial and community reintegration support of veterans [12,21]. Despite the benefits of HIT, limited information exists about team user preferences for integrating multiple HIT in their clinical practice. The benefits of proactive integrated use have important unexplored potential.

Although veterans drive HIT use based on their preferences and needs, VHA provider engagement is critical for the promotion of sustained and integrated use [4,5,22-24]. Providers can increase HIT use by encouraging patients to enroll and use these resources [3,15,16,25]. Providers may impede use by actively discouraging or passively failing to address patient needs [16,17,26]. The value of exploring the needs and preferences of PACT members was to effectively promote their integrated use of HIT to meet the health care delivery needs of veterans.

Patient-Aligned Care Team Care Delivery Model and Virtual Medical Modality Use

The VHA PACT initiative was implemented between 2010-2014 to achieve team-based care, improve access, and provide comprehensive care management for more than 5 million veterans for primary care needs [19]. The PACT model emphasizes care delivery by a "team" typically comprising a physician, nurse, clinical associate, and clerical associate. Extended PACT members represent specialty service areas. Since implementation of PACT, the use of HIT has increased. Even with increased use, HIT is still not used to its full potential as a tool to improve veteran access to care. From 2009 (pre-PACT) to September 2012, the following trends have been observed: (1) phone encounter rates increased more than 10-fold for patients assigned to a primary care provider ($P \leq .01$ each) [27], (2) the number of patients using telehealth increased from 38,747 (0.8% patients) to 70,486 (1.4% patients; $P \leq .01$), and (3) the number of authenticated VA patients with enhanced access to all MHV features increased from 3% of 4,759,668 primary care patients to 13% of 5,163,531 primary care patients ($P \leq .01$). Primary care patients using secure messaging (SM) increased from 0.07 per 1000 in 2009 to 22.8 per 1000 in 2012 ($P \leq .01$) [19]. It is critical that use of these resources is maximized to realize their potential in delivering patient-driven care.

This study focused on PACT members to understand the personal, contextual, and other factors that impact use of HIT. Based on clinical partner feedback, we originally focused on data collection from PACT because they are the driving force of HIT use among extended PACT members (eg, SM). However, snowball sampling was used to identify noncore PACT members who drive HIT use, to create a holistic dataset from all PACT members.

Adoption of Health Information Technology as an Integrated System

This study leveraged previous efforts by VHA researchers to support the implementation of individual HIT (eg, Blue Button, SM). As part of this research, we synthesized individual evidence-based strategies to create a more holistic approach to support the use of HIT as an integrated system. We conducted a preliminary review to develop and refine our proposed aims informed by our previous work in this area. While much of the work in this area is recent and not yet published, our review clearly identified the need for additional research to better understand providers' perspectives in implementing HIT and created a starting point for leveraging existing materials to develop PACT-focused implementation strategies.

Implementation of HIT often focuses on a single HIT [18,28-31]. Few strategies have focused on supporting implementation of multiple HIT platforms, and few are specific to the needs of PACT, both of which represent a limitation in these approaches. If strategies are focused on single HIT, siloed use of HIT is perpetuated. Furthermore, if strategies are not specific to PACT, there is a gap between HIT capacity and specific use for PACT in clinical settings. To maximize impact, HIT needs to be used as an integrated system in ways that are most appropriate for PACT, for example, a clinical team can receive a secure message (ie, email) from a patient reporting an increase in blood pressure. The team's licensed practical nurse reviews the message and determines that the patient needs additional monitoring. She or he then alerts the team's registered nurse (RN) who uses telehealth technology to remotely collect the patient's vitals over the next several days. The patient's blood pressure remains high so the RN schedules a remote appointment using televideo technology to follow up. During this appointment the patient asks for blood pressure medication to be refilled and anxiety medication renewed. The RN alerts the physician to authorize the prescription refill and alerts the team's clerk to schedule an in-person appointment to address the renewal. At the appointment, the physician prescribes use of a relevant mobile app to help the patient manage their health conditions. The provider can then document the education in the Veteran's electronic health record for other providers to access and then renew the patient's prescription using the electronic system. This example is only one example of proactive integrated use; it is critical to develop and disseminate a comprehensive set of these best practices. Though generic HIT implementation strategies exist for delivering education to clinical care team members to increase awareness and support sustained use, they

are not comprehensive, do not promote integrated use, and are not PACT specific.

Methods

Design and Overview

This 3-year concurrent mixed-method implementation study employed a community-based participatory research perspective [7] using concurrent mixed-methods [12]. Table 1 provides an overview of implementation activities and deliverables/outcomes. The study flow chart documents study progress over each of the three aims (Figure 1). We engaged PACT clinical partners in all aspects of this research. In Aim 1, we used qualitative semistructured focus groups and follow-up interviews to describe PACT members' HIT experiences, needs, and suggestions for integrated use. In Aim 2, we conducted expert interviews and an environmental scan to identify existing implementation resources, develop, and formatively evaluate implementation strategies that reflect needs identified in Aim 1. In Aim 3, we proposed formative and summative methods to evaluate implementation outcomes. This study was approved by the University of South Florida Institutional Review Board. Participants did not receive incentives in alignment with VHA Office of Research Oversight regulation.

Aim 1 Methods

We conducted focus groups and follow-up interviews with PACT members and extended PACT members. At each focus group, participants completed a questionnaire describing implementation strategies.

Sampling

We used a registry of all PACT members within Tampa VA (Florida) facilities, including one large hospital and 4 community-based outpatient clinics of varying size and geographic location, to develop a database. We compared the database with data from the VHA Support Service Center (VSSC) Transformation Initiative to identify individual PACT utilization level of SM. While our study targeted the full range of HIT resources, we used SM as a proxy indicator for HIT use because it is a valid direct measure for assessing HIT adoption among providers.

Our clinical partners indicated that monthly meetings are held with all PACTs. We held in-service presentations to engage PACT members during one of the meetings and introduced the study to all PACT members. An information sheet was provided to potential PACT participants during formal and informal meetings, posted in break rooms and other common areas, and shared through email. These information sheets provided an overview and purpose of the study and included study team contact information. This boosted PACT members' awareness of the project; allowed introduction of clinical co-investigators, consultants, and champions; and promoted participant engagement as invested community members. We then sent individual email invitations to specific PACT members to participate in the study to include high- (top 25th percentile) and low-volume users (bottom 25th percentile) as measured by frequency of inbound and outbound SM and the ratio of patients assigned to SM with the PACT. Consultation with our clinical partners suggested some PACT members as high- or low-volume users who may not be readily identified by the secondary data sampling method (eg, patients may opt not to use SM). As such, we also overlapped the secondary data with their recommendations of perceived high- and low-volume HIT using PACT members to validate our sampling strategy and ensure recruitment of true high- and low-volume users.

The PACT members who were contacted were provided the choice of opting out of the study. Those who expressed interest were invited to participate in a focus group interview at their convenience. A subsample of those who participated was also contacted by telephone for an individual follow-up interview in person or by telephone. PACT members who were high- and low-volume HIT users expressed their desire to share their experiences and reasons for use/nonuse to create individual and organizational change to meet their personal and professional needs. We started with the core PACT members; however, during initial focus groups, we also solicited information about extended PACT members (eg, pharmacy, social work) and used snowball sampling to identify a subsample of extended PACT members.

Sample Size

Using purposive sampling, 65 PACT members (eg, physician, nurse, clinical associate, clerical associate, social work, pharmacy) in the Tampa VA hospital and community-based outpatient clinics, serving five counties, were recruited to participate in this study for a total of 21 focus groups. These focus groups included 10 high-volume, 9 low-volume, and 2 extended PACTs. In qualitative research, sample size relies on the quality and richness of information obtained [32,33]. Achieving conceptual saturation is the goal of qualitative research and is not dependent on sample size but rather the ability of the data to support interpretations [32,33]. Previous research by this team in this topical area reached thematic saturation between 20-30 interviews. We recruited to represent the facility type (hospital clinic vs community-based outpatient clinics). Based on emergent themes, we conducted 16 follow-up individual interviews with team members. We recruited the minimum sample necessary to represent the types of team member roles (ie, professional discipline) to compare experiences.

Measures

Participant data were collected using a participant demographic questionnaire and interview guides (see Table 2).

Data Collection Procedures

We used focus group interviews and follow-up individual interviews to complete data collection for Aim 1. Focus groups were used to collect data with PACT members (grouped by HIT volume status). Participants were scheduled to participate in groups at their facility for approximately 1 hour. Clinical partners recommended using the time that PACTs are given, one hour weekly, to do free-style staff activities. This promoted participation while not interfering in work and care delivery. Participants received an email before the focus group that included interview questions and some provider-focused HIT implementation content for review.

Table 1. Implementation plan activities and associated deliverables/outcomes.

Aim and activity	Deliverable/outcome
Preimplementation	
Aims 1-3	
Communicate the plan and begin process with PACT[a] members	• Investment across PACT/stakeholder groups • Shared norms and expectations
Include all representative groups in the planning process to get input	• Investment across stakeholder groups • Input from PACT/stakeholder groups
Ensure strategies/goals are aligned with organizational & stakeholder goals	• Investment across stakeholder groups • Aligned strategies reflecting Diffusion of Innovations/PARiHS[b] constructs
Engage PACT leadership, consultants, and champions	• Investment across stakeholder groups • Setting expectation of organizational investment
Aim 1	
Conduct focus groups, follow-up interviews, and analysis	• Data synthesis to inform implementation strategy development
Set goal and strategy planning on timeline with PACT clinical partners	• Implementation timeline aligned with expectations • Matrix product that illustrates each audience, targeted strategies, with start date and duration
Identify and train facilitators to identify champions to support strategy delivery	• Points of contact designated • Complete facilitator training for implementation
Reiterate key measures and clear expectations	• Planned outcomes data elements with stakeholders • Align outcomes that reflect constructs and HIT[c] use
Plan visibility, integrated into regular activities	• Integrate strategies with PACT activities (eg, staff meetings/professional development time)
Address implementation program management needs with PACT	• Action plan for activities, identify points of contact, deadlines, intermediate accomplishments, etc
Aim 2	
Conduct expert interviews and environmental scan	• Collection of expert informant data and existing HIT implementation content and determination of need
Implementation strategy development	• Adaptation/development of strategies and content based on identified needs
PACT member panel evaluation	• Evaluation and revision of strategies and materials needed for implementation
Implementation	
Aims 1-3	
Prepare PACT members/stakeholders for implementation	• Awareness of implementation activities • Readiness across PACT/stakeholder groups
Aim 3	
Schedule implementation activities that align with PACT needs	• Confirmed awareness of forthcoming implementation activities and readiness across PACT/stakeholders
Conduct implementation activities that represent PACT needs	• Primary pretest data collection to measure use of HIT and reflect implementation strategies
Collect primary qualitative and secondary quantitative data	• Implementation strategy feedback summary • HIT use dataset

Aim and activity	Deliverable/outcome
Conduct follow-up with PACT members, other stakeholders (operational partners)	• Primary posttest and secondary data collection • Follow-up communication with PACT members, other stakeholders
	Postimplementation
Aim 3	
Track implementation activities and outcomes and summarize progression of HIT use	• Continue efforts on implementing initiatives • Progress documented for continued efforts • Continued use of community-based participatory research with PACT
Recognize interim accomplishments and progress with PACT	• Document and recognize accomplishments and milestones during implementation
Conduct data analysis with invested PACT and stakeholders	• Complete analysis of data with partnered input with PACT consultants and members
Monitor & document lessons learned in efforts to increase HIT use with PACT members	• Document lessons learned, approaches that work, those that need refinement, and adapt for future implementation in efforts
Share study findings to PACT and stakeholder as recommended by feedback	• Dissemination efforts supported by PACT member input to key audiences • Reporting reflects pre-post measure changes

[a]PACT: Patient-Aligned Care Team.

[b]PARiHS: Promoting Action on Research Implementation in Health Services.

[c]HIT: health information technology.

Figure 1. Study flow chart. PACT: Patient-Aligned Care Team.

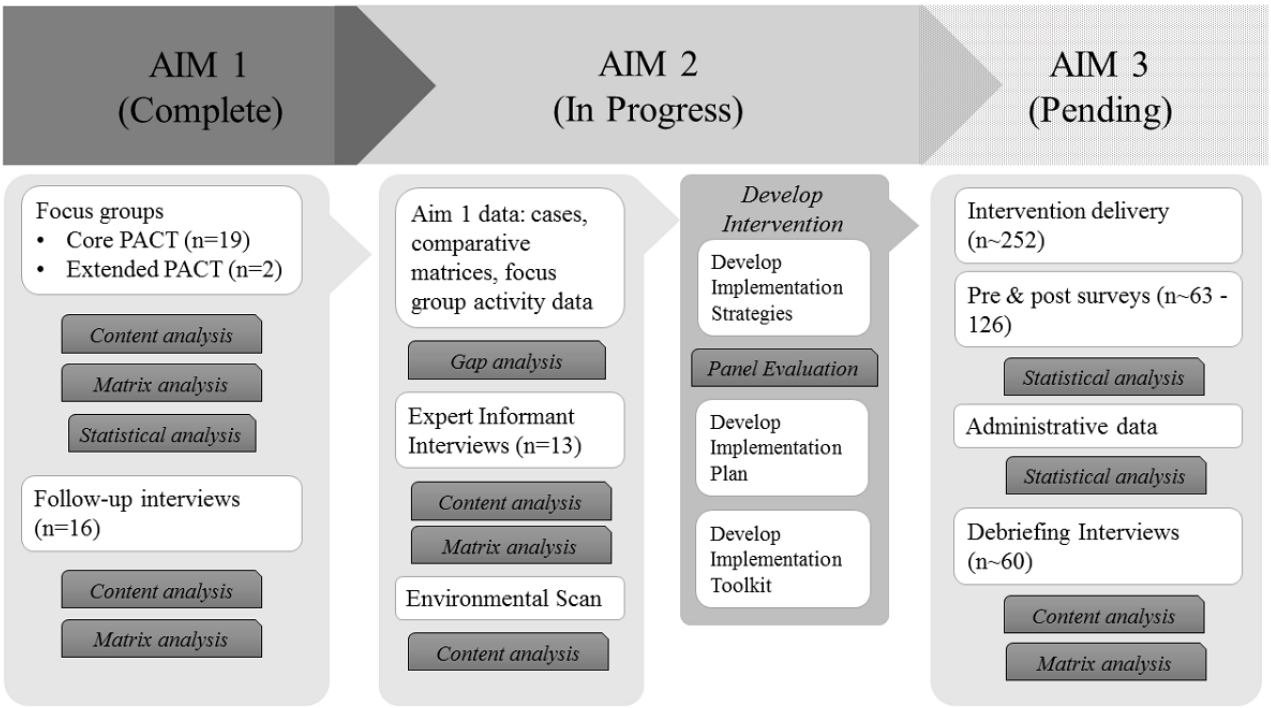

Table 2. Aim 1 participant self-reported measures and characteristics.

Concept and measure	Psychometric properties
Demographics	
Participant survey	16 self-report items to assess facility & unit; PACT[a] role; length of time at facility, unit, in VHA[b], in health care; age; gender; race; ethnicity; professional degree; licenses; computer/internet use; My Health*e*Vet status
Virtual medical modality use	
Participant survey	18 self-report items for each HIT[c] including use count; HIT use; patient HIT use count, and relative advantage, compatibility, complexity, observability, context, facilitation constructs
Focus group script	Items to elicit information about concepts including clinical experience/evidence, personal and team factors and best practices; context, team, organizational, and environmental factors; and external/internal facilitation factors such as readiness for use, audit, feedback & reinforcement, leadership; advantages/ usefulness, compatibility, complexity/ease of use, observability of HIT. Items addressed PACT member perceptions of patients' preferred communication methods, attempts to engage patients, and alternative resources for using HIT
Follow-up interview script	Items were driven by data collected in PACT focus groups to follow up on emergent themes and preferred dissemination methods

[a]PACT: Patient-Aligned Care Team.

[b]VHA: Veterans Health Administration.

[c]HIT: health information technology.

Consent and data collection were conducted in a designated room at Tampa facilities to ensure confidentiality. Before beginning the focus group, each participant was asked to complete the demographic survey, and the focus group facilitator asked and received permission to audio record the discussion using VHA-approved equipment. The facilitator used the interview script to ensure that all topics were covered. Standard communication techniques were used to stimulate discussion, such as prompts, summarizing statements, silence, and eye contact. The facilitator also took written observational notes.

After completion of the focus groups, follow-up individual interviews were conducted with a purposeful subsample by phone or in person at the PACT member's convenience. These interviews served multiple purposes. Though we addressed group dynamics in the focus groups, we needed to account for power differentials. We used individual interviews to ensure team members had an opportunity to communicate personal needs and experiences, discuss issues that may not have been fully addressed in the focus groups, explore themes that emerged in focus groups, discuss relevant issues based on the respondent's PACT role, and explore the dynamic of using HIT within the context of the team. Methods like those used in focus groups were used to solicit information. Follow-up interviews allowed PACT members to review data cases and focus group summaries. The participants verified findings and provided additional input and/or clarification to ensure validity of Aim 1 findings from the PACT member perspective.

Data Analysis

Qualitative data collection and analysis progressed concurrently. In this way, insights from data analysis were used to iteratively guide subsequent data collection. The unit of analysis of the case study focused on the lived experiences of PACT members using HIT. These "cases" were analyzed using content analysis to identify patterns of similarities and differences that resulted in descriptions of relationships and recurring patterns of experience, behavior, and beliefs so that the phenomena could be understood within its cultural context. Analysis methods were used to identify domains and taxonomies related to provider data for focus groups and follow-up interviews [32]. This method involved inductive data reduction to distill the essential domains of participant experiences. Participant comments for case studies were organized to develop codes and merged to develop categories. Categories were compared and relationships were identified. Categories were grouped into a taxonomic structure. As coding schemas were developed to create domains and taxonomies, data samples were extracted and coded by two research team members and evaluated for interrater reliability and credibility. The datasets collected for each PACT member type were compared to one another to determine commonalities and differences. The research team conducted a complex matrix analysis to analyze across-group domains and taxonomies [34]. Descriptive and comparative matrices, which identify the patterns of regularities and inconsistencies were constructed. Comparative matrices provided an opportunity to identify the most relevant and representative components by HIT users. Representative cases were extracted from the dataset and analyzed for domains and themes, which were used to support strategy development. Focus group activities were entered into a Research Electronic Data Capture database and exported into a Microsoft Excel file. Response frequencies were analyzed statistically to determine which implementation strategies PACT members considered most and least useful for increasing uptake of technology. Once cases and comparative matrices were developed, follow-up interviews allowed PACT members and consultants to review these data to verify findings and provide additional input and/or clarification. Quantitative data including demographic survey data were summarized with descriptive statistics to describe sample characteristics.

Aim 2 Methods

After conducting Aim 1, we developed PACT-focused implementation strategies using expert informant interviews, environmental scan, strategy development and evaluation, and

the development of an implementation plan to address the PACT member needs identified in Aim 1. Our team, and identified champions, facilitated forums to (1) deliver core HIT information, (2) facilitate open group discussion of HIT specific implementation tools and best practices, and (3) identify champions and team members for follow-up contact and support. After the first forum, forums focused on trouble shooting barriers and discussing work-arounds relevant to HIT. Research team members met between forums with clinical investigators and champions to prepare and anticipate potential barriers and trouble shooting. Feedback received during these forums were documented as supplemental qualitative data memos in the qualitative Aim 3 dataset. We also developed a toolkit that was reviewed and distributed to all PACTs using multimedia. Other activities (eg, emails, presentations) were used.

Sampling

A subsample of participants from Aim 1 were invited to participate as panelists for a PACT Member Panel Evaluation. We approximated a subsample of minimum of 10 and a maximum of 15 PACT members to participate in this panel. These participants were selected based on study team members' assessment of their enthusiasm to participate and their thoughtful responses during their focus group. Due to our observation of the limited ability of PACT members to visualize and articulate a vision of integrated proactive use of HIT across systems, the study protocol was amended to add a series of expert interviews with 13 clinical, operational, and administrative expert informants to assist the team in collecting more robust data that would contribute to the vision of integrated proactive use of HIT to deliver care within the VA.

Expert Informant Interviews

Expert informant interviews (n=13) were conducted by phone or in person. Aim 2 participants were recruited via email using the expert informant invitation email. In addition, a snowball technique was used in which the study team provided current participants with our PACT HIT study recruitment materials and contact information that they could pass on to other expert individuals who were also interested in participating. Expert informant interviews were conducted to answer the Aim 2 research questions. All interviews were recorded with permission. The interviewer used methods like those described in the focus group data collection procedures described above. Audio recordings were transcribed and analyzed using content analysis.

Environmental Scan

An environmental scan was conducted to answer Aim 2 research questions. Our team had ongoing partnerships with several electronic health (eHealth) researchers within the VA and had worked with several of these stakeholders during previous projects. We leveraged these existing relationships to complete Aim 2. We contacted these researchers and stakeholders to identify existing materials, as reviewed previously. To complete this aim, we distributed an initial email and made follow-up calls as needed to identify any new or emerging provider focused implementation strategies/tools to support HIT adoption. Though, some materials already existed for individual HIT, we identified the need to either adapt these or develop new materials and strategies to specifically address integrated use.

Patient-Aligned Care Team–Focused Implementation Strategies Development and Evaluation

We collaborated with operational, research, and PACT partners to collect resources to support PACT-focused HIT implementation strategy development and PACT member evaluation. We conducted a gap analysis based on Aim 1 findings and reviewed collected resources to determine what implementation strategies needed to be created or further developed. We drew from the bank of evidence-based implementation strategies [35], which supported adoption of an innovation that aligned with participant reports from Aim 1. Once strategy content and an implementation plan were developed, a PACT member panel provided a formative evaluation of content and finalized the implementation plan.

PACT Member Panel Evaluation was conducted with invested PACT consultants and team members who expressed willingness to participate on the panel to provide feedback on the implementation content and plan. As part of completing Aim 1, we identified key informants and invited them to participate on a panel to evaluate the implementation content. Once all materials were developed, panel members electronically received access to the content and evaluation form(s) to conduct a formal review of implementation content. To avoid reviewer burden, the number of products reviewed by each reviewer was minimized. Each panel member used the Implementation Content Evaluation Measure to evaluate their assigned implementation content. This measure consisted of three sections to facilitate evaluation: (1) relevance to virtual medical modalities, (2) relevance to implementation constructs, and (3) evaluation of content design and format. Scoring ranged from not applicable to strongly disagree. Once completed, evaluation forms were collected and collated, and a panel reviewer call/in-person meeting was scheduled to allow panel member discussion, collective review, and final synthesis of feedback and recommended revisions. Panel meeting type was determined by the member preference. Panel member participation took 3-5 hours total time.

Implementation Strategy Development

Implementation strategy development was conducted on receipt of all content. We conducted a gap analysis based on the needs identified in Aim 1. We developed a content review matrix to evaluate the materials to facilitate the gap analysis. The content review matrix addressed three primary sections of interest: (1) the degree to which the content addressed each HIT and their integrated use, (2) the degree to which the content addressed issues identified in Aim 1 relevant to implementation constructs including external environment, health care organization, site factors (ie, context) facilitation (eg, role clarity, supportive activities), patient factors, individual factors (eg, high- vs low-volume users, relative advantage, compatibility, complexity, observability), and (3) evaluation of the content design and format. Each evaluation item solicited feedback on how content could be improved to address evaluation elements. This tool was also used by the expert panel reviewers.

Guided by PACT clinical partner input, we adapted and developed content in collaboration with operational partners. We synthesized evidence-based strategies to create a more holistic approach to support HIT use as an integrated system. We employed a comprehensive set of strategies that were identified as evidence-based approaches to implementing change using core constructs from Diffusion of Innovation and PARiHS. We employed strategies including (1) audit and feedback (eg, HIT data elements were collected for PACTs to monitor, evaluate, and provide feedback), (2) dynamic virtual training/support (eg, HIT templates, virtual PACT telehealth materials, standalone videos, experiential learning test accounts), (3) educational meetings (eg, training/in-services at regularly scheduled bimonthly staff development meetings), (4) incentive structures (eg, increasing awareness about workload credit), and (5) tailored strategies (eg, PACT-driven development and evaluation of strategies and content as recommended by Powell et al [35]. We also employed emerging innovative strategies. As appropriate, these approaches were synthesized within a peer-to-peer story-telling context. We collaborated with PACT members to identify best practices focusing on how high-volume users leverage HIT within their workflow. Data have been previously collected related to use of SM in an ongoing collaborative operational project. We used this existing project as a road map for collecting best practices from high-volume users. We included these best practices in "forum" in-service trainings, story-telling videos, and other strategy content.

Aim 3 Methods

After developing PACT-focused products to promote HIT adoption (intervention), we will conduct an evaluation using formative and summative methods in a pre-post single group design.

Sampling

All PACT members will be exposed to the intervention as part of monthly training and staff development meetings. We will conduct open recruitment with all 252 PACT members from the participating Tampa facilities (ie, hospital, 4 community-based outpatient clinics). Participants in Aim 2 will not participate in data collection for Aim 3.

Sample Size/Power Analysis

To answer the Aim 3 hypothesis, of the 252 PACT members, we anticipate a minimum participation rate of 50% in the pretest and posttest surveys (n=126). Because it is difficult to get clinicians with competing demands to complete questionnaires, we have calculated our expected sample size based on a worst-case scenario of a 25% response rate (n=63). We tested change scores on 8 separate subscales on the pretest/posttest measure. To control for hypothesis-wide error, we employed the Bonferroni adjustment and divided the nominal error rate of 5% by 8. A review of the literature did not identify a prior study to provide information about effect size, therefore we used the convention suggested by Cohen to compute the effect size [36]. Since a single group for each change score was measured before and after intervention, the effect size (Cohen d=0.50, medium effect size) was the mean difference between the pretest and posttest scores divided by the sample standard deviation of the change score [37]. A sample size of 63 achieves an 86% power to detect a difference in pre- and postintervention using a one-sample paired t test. We will use the rate of response for each strategy presented in Table 3 of each PACT member as outcome. We will have six timepoints preintervention and six timepoints postintervention for each implementation strategy. We expect separate slopes before and after the intervention. We will employ the simulation methods, to fit a piece-wise random effect model that includes separate pre- and postintervention slopes with an assumed effect size of 0.5 standard deviations from the mean [38,39]. A sample size of 63 (with 12 repeated values) with a type 1 error rate of 0.01, after Bonferroni adjustment, will give greater than 80% power for the analysis.

Measures

Participant data will be collected using a participant demographic survey and interview guides. Measure characteristics are presented in Table 3.

Data Collection Procedures

To answer Aim 3 research questions, participants will be asked to complete the questionnaire used in Aim 1 before and after the intervention followed by a brief debriefing interview. For Aim 3, secondary administrative data of HIT use from all PACTs in the Tampa hospital system 6 months pre- and postintervention will be obtained.

Links to electronic self-administered surveys via research electronic data capture will be emailed to each participant pre- (on consent) and postexposure (6 months post consent) to the implementation strategies as self-reported measures. Paper-pencil surveys will be provided as an option.

Debriefing interviews will be conducted in a group setting or as individual interviews, based on PACT member need. If the respondent is unable to stay, they will be given the option to conduct the debriefing by phone at another time of their convenience. All interviews will be recorded with permission.

Table 3. Aim 3 self-reported measure characteristics.

Concept and measure	Characteristics
Demographic	
Participant survey	Described in Table 2
Strategy effectiveness	
Participant survey	Described in Table 2
Interview script	To elicit perceptions about strategies and materials, respondents were prompted to provide recommendations for improvement, and additional materials, formats, etc

The interviewer will use methods like those described in the focus group data collection procedure described above. The brief interview script will solicit respondents' perceptions about the implementation strategies and materials and as well as recommendations on ways to improve and increase engagement, for example, "Did you think the intervention/strategy was useful to you for providing care to patients/daily workflow?" and "Did your participation/exposure impact your intention to use virtual care tools?"

We will collect administrative data to examine HIT use from local (ie, VetLink) and national administrative data sources (ie, VSSC, Corporate Data Warehouse [CDW]). Data will be collected for all PACTs in the Tampa VA hospital system 6 months pre- and postintervention. Secondary data collection will allow examination of changes in rates of HIT use (Table 4). We have identified multiple data sources to ensure we have options if data availability changes. We will also collaborate with operational partners to collect data elements from CDW. When data are received at the patient level, crosswalks will be used to connect patient level data to PACTs for team level analysis. If any data elements are housed for only 30-day increments, such as the MHV prescription refill data, we will collect data as often as needed, such as 30-day increments. Additionally, the study team has access to local VetLink Kiosk administrative data.

Data Analysis

Qualitative data analysis methods described in Aim 1 will be used to analyze debriefing interviews [32]. Quantitative data will be analyzed using the individual PACT member as the unit of analysis. We will use a one sample paired *t* test to compare pre- versus postintervention. To determine the association between the change scores across MHV implementation strategies, we will use Pearson correlation coefficient. If the response rate is higher than our conservative estimate, we will compare results for low- and high-use groups. We will use administrative data to calculate the rate of response for each implementation strategy of each PACT member (Table 4). For example, the number of patients per time interval within a PACT that opt to use SM divided by the number of PACT patients in the teams' panel will represent the outcome. We will first conduct an exploratory analysis to evaluate the rate of responses separately for the pre- and postintervention and calculate summary statistics for differences in PACT pre- and post-averages.

Table 4. Aim 3 secondary data elements and data collection plan (data collected 6 months pre- and postexposure to implementation intervention).

Construct and variables	Measure	Data source
Secure messaging use		
Registration	Number of patients registered	VSSC[a] Compass PACT[b] data cubes or VSSC Transformation Initiative data cube or Veteran and Consumer Health Informatics Office CDW[c] data request
Authentication	Number of patients authenticated	
Opted-in	Number of patients opted in	
Inbound SM[d]	Number of inbound messages	
Outbound SM	Number of outbound messages	
MHV[e] Rx refills use		
Prescription refill orders	Number of prescription refill orders	VSSC Transformation Initiative data cube or Veteran and Consumer Health Informatics Office data request
Telephone use		
Encounters	Number of encounters	VSSC Compass PACT data cubes
Home telehealth use		
Encounters	Number of encounters	CDW Telehealth Visits Report, including secondary codes for Home Telehealth, Clinical Video, Store & Forward
Visits	Number of visits	
Unique patients	Number of unique patients	
VetLink kiosk use		
Check-in	Number of patients checked in	Local VetLink Kiosk administrative data report
Demographic update	Number of patients who updated demographic data	
Assistance required	Number of patients requiring help at kiosk	

[a]VSSC: VHA Support Service Center

[b]PACT: Patient-Aligned Care Team.

[c]CDW: Corporate Data Warehouse.

[d]SM: secure messaging.

[e]MHV: My Health*e*Vet.

We will use standard statistical tests to check for the departures of normality pre- and postintervention. As we expect to see separate slopes before and after the intervention, we will define a model that accommodates the two slopes and their difference using a piece-wise random effect model and separate pre- and postintervention slope in one model for each implementation strategy [40]. The results of the fitted model will consist of two main parts: a set of individual intercepts and two slopes (each representing pre- and postintervention). We will compare the pre- and postintervention slopes and if the difference is significantly different from zero, we will conclude that the pre- and postimplementation strategy was different. We will investigate effects of baseline covariates (eg, community-based outpatient clinics vs noncommunity-based outpatient clinics) that may influence changes in response rate over time.

Results

Study enrollment for Aim 1 has been completed. Aims 1 and 2 data collection and analysis are underway. Aim 3 activities are scheduled for year 3.

Discussion

Principal Considerations

The goal of this study protocol was to identify effective implementation strategies for increasing PACT member awareness and motivation to use HIT proactively and in an integrated approach to better serve their patients and increase workflow efficiency. This protocol illustrates a community-based (ie, PACT) participatory approach to support clinical team members' adoption and sustained integrated proactive use of HIT. To our knowledge, this protocol is unique in that it informs PACT-focused implementation strategies to support HIT use within a large health care system.

The proactive integrated use of HIT is a direct pathway to optimizing health care delivery to support patients' ongoing health care needs. Participatory methods are a human-centered approach to engage clinical team members to identify focused implementation strategies that support their proactive integrated use of HIT to support health care delivery. The use of mixed-methods with critical stakeholders supports the development of targeted implementation approaches that will drive adoption and sustained use of HIT. From the end user perspective, proactive integrated use of HIT will increase individual proficiency and efficiency and ultimately optimize HIT value.

Strengths and Limitations

This protocol contributes to the field in three distinct ways: (1) use of a community-based participatory approach, with primary care teams as the unit of analysis, (2) identification of primary care–focused implementation strategies to increase uptake and proactive integrated use of electronic health resources, and (3) use of secondary data to assess utilization of an enterprise-wide suite of electronic health resources. Primary care teams such as VA PACTs and community Patient-Centered Medical Homes are relatively new to US health care systems. Using them as a unit of analysis highlights the influence of team philosophy on behavior. Implementation strategies are varied. Focusing on primary care strategies tailors our findings to this unique segment of health care. Secondary data analysis of individual electronic health resource utilization uses a new data source to inform findings of this research as well as future eHealth-related research efforts.

This protocol also had limitations. First, the sample size was comparable to other qualitative studies [41], based on a representative sample of participants but may not be generalizable to other clinical groups. We purposively recruited PACT members as a base of community members representing primary care, as they can provide salient in-depth feedback; however, we may have missed valuable data that may represent other clinical groups. To address this limitation in part, we expanded recruitment to extended PACT members to include pharmacy, nutrition, mental health, and social work providers. Furthermore, the third aim was designed to develop a blueprint for secondary data collection to measure HIT use pre- and poststrategy implementation. Although the sample size was powered to determine intervention effects, findings will not be conclusive, as such a subsequent larger multisite study is warranted, with a more rigorous implementation study design, such as a step wedge design.

Second, this protocol was designed to develop implementation strategies designed to promote proactive integrated use of HIT. Because this is not common practice in delivering clinical care, PACT members recruited in Aim 1 had limited ability to visualize and articulate a vision of integrated proactive use of HIT across systems. As such, the study protocol was amended to add a series of expert interviews with clinical, operational, and administrative expert informants to assist the team in collecting data that would contribute to the vision of integrated proactive use of HIT to deliver care within the VA.

Future research should inform the continued support of clinical team member's proactive integrated use of HIT resources, including both clinical team member user experiences and outcomes, representing diverse clinical groups. Clinical and organizational processes, including workflow should be explored and clearly identified. These continued efforts can guide the development and dissemination of best practices. In alignment with VA goals and the mission of VA's Office of Connected Health, these data will support the adoption and sustained use of HIT to support clinical team delivery of personalized, proactive, and patient-driven health care [42].

Conclusions

This protocol employed community-based participatory mixed-methods and multiple data sources to identify effective implementation strategies for increasing PACT member awareness and motivation to use HIT in a proactive integrated approach with patients. This protocol highlights the practical, technological, and participatory factors involved in facilitating implementation research designed to engage PACT clinical members in the proactive integrated use of HIT. Using this protocol, best practices can be identified and disseminated, leveraging PACT-focused strategies that reflect team member preferences to support subsequent implementation efforts at regional and national levels.

Acknowledgments

The Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development Service (IIR 15-443 - Virtual Medical Modality Implementation Strategies for Patient-Aligned Care Teams to Promote Veteran-Centered Care), and National eHealth Quality Enhancement Research Initiative Coordinating Center (RRP 12-495) supported the development of this manuscript. This manuscript was supported in part by the Center of Innovation for Disability and Rehabilitation Research at the James A Haley Veterans Hospital. The contents of this manuscript do not represent the views of the Department of Veterans Affairs or the US Government.

The authors would like to acknowledge the efforts of Robert M "Goose" Gosline, Communications Specialist and My Health*e*Vet Coordinator at James A Haley Veterans Hospital for his significant contribution to the recruitment for and success of this project. We would also like to thank Timothy Hogan, PhD, for his generosity of time and consultation throughout the conceptualization and implementation of this project.

Conflicts of Interest

KA was affiliated with the Department of Veterans Affairs during the time of this study.

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Abbreviations

CDW: Corporate Data Warehouse
eHealth: electronic health
HIT: health information technology
MHV: My HealtheVet
PACT: Patient-Aligned Care Team
PARiHS: Promoting Action on Research Implementation in Health Services
RN: registered nurse
SM: secure messaging
VA: Department of Veterans Affairs
VHA: Veterans Health Administration
VSSC: VHA Support Service Center

Edited by G Eysenbach, N Kuter; submitted 14.06.18; peer-reviewed by C Turvey, L Richardson, T Waltz; comments to author 10.07.18; revised version received 23.07.18; accepted 23.07.18; published 15.08.18.

Please cite as:
Haun J, Chavez M, Hathaway W, Antinori N, Melillo C, Cotner BA, McMahon-Grenz J, Zilka B, Patel-Teague S, Messina W, Nazi K Virtual Medical Modality Implementation Strategies for Patient-Aligned Care Teams to Promote Veteran-Centered Care: Protocol for a Mixed-Methods Study
JMIR Res Protoc 2018;7(8):e11262
URL: http://www.researchprotocols.org/2018/8/e11262/
doi:10.2196/11262
PMID:30111531

Protocol

A Personalized Physical Activity Program With Activity Trackers and a Mobile Phone App for Patients With Metastatic Breast Cancer: Protocol for a Single-Arm Feasibility Trial

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Abstract

Background: About 5% of breast cancer cases are metastatic at diagnosis, and 20%-30% of localized breast cancer cases become secondarily metastatic. Patients frequently report many detrimental symptoms related to metastasis and treatments. The physical, biological, psychological, and clinical benefits of physical activity during treatment in patients with localized breast cancer have been demonstrated; however, limited literature exists regarding physical activity and physical activity behavior change in patients with metastatic breast cancer.

Objective: The primary objective of this study is to assess the feasibility of a 6-month physical activity intervention with activity trackers in patients with metastatic breast cancer (the Advanced stage Breast cancer and Lifestyle Exercise, ABLE Trial). Secondary objectives are to examine the effects of physical activity on physical, psychological, anthropometrics, clinical, and biological parameters.

Methods: We plan to conduct a single-center, single-arm trial with 60 patients who are newly diagnosed with metastatic breast cancer. Patients will receive an unsupervised and personalized 6-month physical activity program that includes an activity tracker Nokia Go and is based on the physical activity recommendation. Patients will be encouraged to accumulate at least 150 minutes per week of moderate-to-vigorous intensity physical activity. Baseline and 6-month assessments will include anthropometric measures, functional tests (eg, 6-minute walk test and upper and lower limb strength), blood draws, patient-reported surveys (eg, quality of life and fatigue), and clinical markers of tumor progression (eg, Response Evaluation Criteria In Solid Tumors criteria).

Results: Data collection occurred between October 2016 and January 2018, and the results are expected in August 2018.

Conclusions: The ABLE Trial will be the first study to assess the feasibility and effectiveness of an unsupervised and personalized physical activity intervention performed under real-life conditions with activity trackers in patients with metastatic breast cancer.

Trial Registration: ClinicalTrials.gov NCT03148886; https://clinicaltrials.gov/ct2/show/NCT03148886 (Accessed by WebCite at http://www.webcitation.org/71yabi0la)

Registered Report Identifier: RR1-10.2196/10487

(JMIR Res Protoc 2018;7(8):e10487) doi:10.2196/10487

KEYWORDS

metastatic breast cancer; physical activity; oxidative stress; activity trackers; feasibility

Introduction

Breast cancer is the most common cancer among women worldwide with >1.6 million new cases diagnosed annually and 54,062 incident cases in France in 2015 [1]. About 5% of breast cancer cases are metastatic at diagnosis, and 20%-30% of localized breast cancer cases become secondarily metastatic [2-4]. Metastatic breast cancer is considered incurable, and treatments are proposed to improve the quality of life and overall survival.

Fatigue and reduced quality of life are frequent in patients with metastatic breast cancer related to the site of metastasis and cancer treatment [5,6]. Evidence from meta-analyses and systematic reviews in patients with localized breast cancer has demonstrated the benefits of physical activity on multiple health outcomes [7-12]. However, only five studies have focused on the investigation of physical activity interventions in patients with metastatic breast cancer [13-17] despite the need, desire, and ability of these patients to engage in physical activity [14,15,18]. Some studies have already investigated the association among metastatic cancer, fatigue, and physical activity; however, the results are mixed and warrant confirmation, specifically in patients with metastatic breast cancer [13-16].

In the cancer context, activity trackers with step pedometers are increasingly being used to measure physical activity and promote physical activity behaviors [19-21]. The benefits of mobile eHealth apps and pedometers on physical fitness, physical activity, and quality of life of patients with breast cancer have been reported [22]. These devices might motivate people to remain active and facilitate reaching a personal or recommended goal because of the feedback received in real time (eg, steps) [23-25]. In addition, activity trackers are often linked to a mobile app with a personal interface that provides a summary of the physical activity (ie, light, moderate, and vigorous intensity), sedentary time, and the number of steps accumulated per day, week, and month.

Reportedly, regular physical activity and fatigue can affect blood biomarker levels, including inflammatory markers [26] and oxidative stress [27]. Evidence from randomized controlled trials (RCTs) has indicated an effect of physical activity in patients with cancer on the levels of circulating growth factors and cytokines (eg, interleukin 6 and tumor necrosis factor alpha) [28,29] and suggests that physical activity might markedly alter the frequency and functional competence of immune cell subsets of the innate immune system (eg, neutrophils, monocytes, and natural killer cells) [30,31]. Concerning the oxidative stress, an excessive accumulation of oxidative stress in cells has been shown to induce marked cellular and molecular damages and likely plays an important role in carcinogenesis, tumor promotion, and breast cancer recurrence and metastasis [32-34]. Moreover, plasma antioxidant defenses seem to be lower in women with breast cancer [34]. On the contrary, physical activity programs have shown to decrease the oxidative stress in patients with chronic diseases other than cancer, in particular through the improvement of enzymatic antioxidant defenses [27,35].

The Advanced stage Breast cancer and Lifestyle Exercise (ABLE) Trial was designed to address the gaps in the current literature. The primary aim is to determine the feasibility of an unsupervised and personalized physical activity intervention in patients with metastatic breast cancer. The secondary aims are to investigate (1) how the physical activity intervention changes the total global physical activity, sedentary time, and physical fitness; (2) how the physical activity intervention changes patient-reported outcomes, including the quality of life and fatigue; (3) how the physical activity intervention changes patients' anthropometric measurements and body composition; (4) the barriers and facilitators of the adherence to a physical activity program; and (5) whether the physical activity intervention affects the oxidative stress and inflammation as biomarkers of the tumor progression.

Methods

Study Design

The ABLE Trial is a single-arm trial that is being conducted in the Léon Bérard Comprehensive Cancer Center (Lyon, France). The study protocol was approved by the French ethics committee (*Comité de protection des personnes Sud-Est IV*), and the study database was reported to the National Commission for Data Protection and Liberties (CNIL; reference number: 1994192). The study is registered on ClinicalTrials.gov (NCT number: NCT03148886).

Study Population

The inclusion criteria for this study are as follows: (1) female; (2) aged 18-78 years; (3) newly diagnosed with primary or secondary metastatic breast cancer histologically confirmed (ie, within the last 3 months) and treated in a cancer center by chemotherapy or radiotherapy or hormonal therapy or targeted

therapy; (4) Eastern Cooperative Oncology Group Performance status <2; (5) able to speak and understand French and able to complete questionnaires and follow instructions in French; and (6) valid health insurance affiliation. For patients willing to participate in the study, confirmation from their treating oncologist of no contraindications to physical activity is required.

The exclusion criteria for this study are as follows: untreated brain metastases; pregnancy; and contraindications to physical activity (eg, uncontrolled hypertension, cardiac disease). All patients must sign an informed consent form.

Recruitment

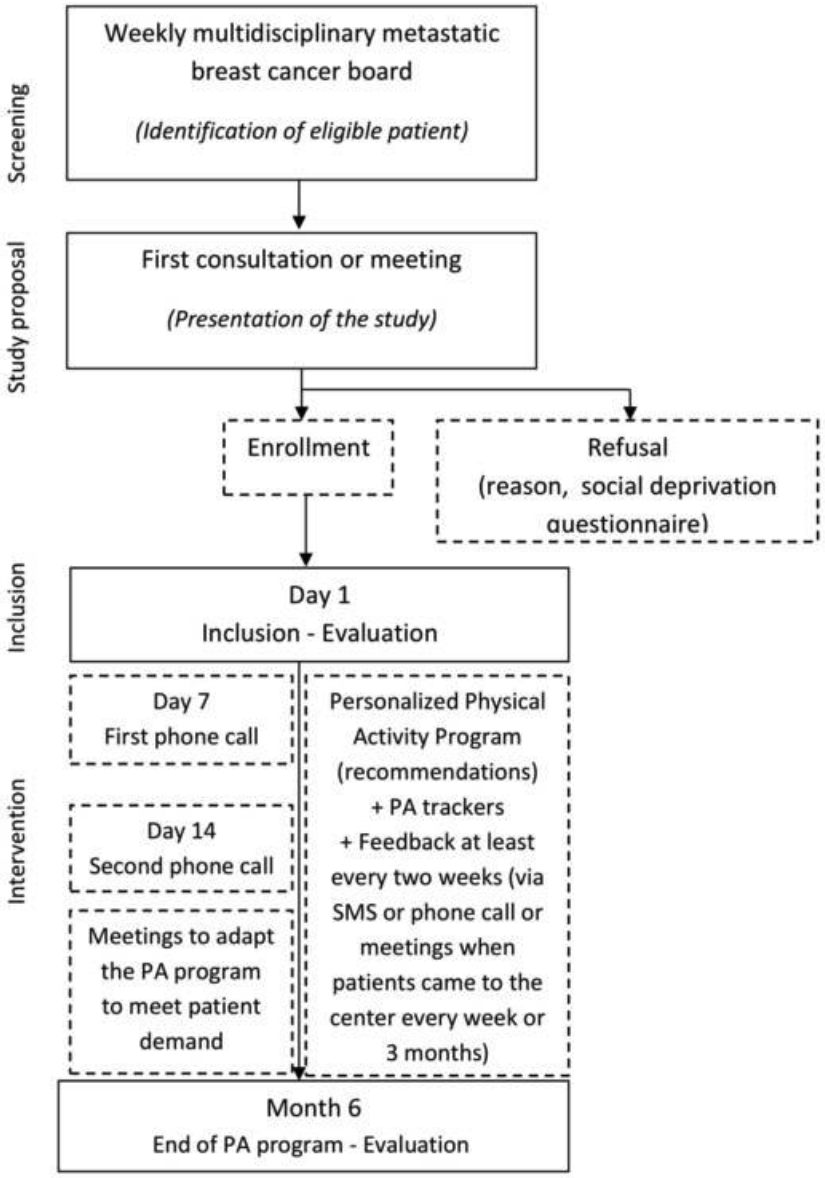
Women are screened weekly during the center's multidisciplinary metastatic breast cancer board meetings, as seen in Figure 1. After checking the inclusion and exclusion criteria, the study is directly proposed by an oncologist or radiotherapist to patients treated by chemotherapy or radiotherapy. As patients treated by hormonal therapy do not come to the center, they receive an information letter and study brochure through post and are contacted by telephone 1 week later to know whether they intend to participate. For all enrolled patients, a physician provides a certificate indicating no contraindications to physical activity, and an appointment is subsequently planned to sign an informed consent and proceed to the baseline evaluation (day one, D1).

Intervention

Adapted Physical Activity Program

The evaluated intervention is a home-based, personalized physical activity program. The frequency, duration, and intensity of physical activity sessions are modulated depending on patients' capacities.

Figure 1. Participant flow chart for the Advanced stage Breast cancer Lifestyle and Exercise study, Lyon, France (PA: Physical activity).



Patients are encouraged to accumulate at least 150 minutes per week of moderate-to-vigorous intensity physical activity to maintain and improve health benefits. In addition, patients are asked to walk at least 30 minutes per day, increase their activities in their daily routine, and reduce their sedentary time. Several individual strategies are established with patients to attain their objectives (eg, using stairs whenever possible and walking for groceries or shopping). Moreover, meetings at the center with physical activity instructors are proposed depending on patients' needs. Patients receive feedback at least monthly from their instructor. For patients undergoing chemotherapy, meetings take place during their day care visits at the cancer center. For patients with hormonal therapy treatment, meetings occur by phone or during a consultation with a physician in the center.

Activity Trackers

Activity trackers (Nokia Go wristband, Nokia France, Issy-les-Moulineaux, France) are given to all study participants. Patients are instructed to wear the device every day for the duration of the 6-month intervention. In addition, patients receive real-time feedback on their number of steps per day. Recommendations are to achieve 5000-10,000 steps a day depending on patients' ability and comorbidities. For a patient who reaches 10,000 steps per day, we will advise her to maintain her goal. For a patient who is not able to achieve 5000 steps a day, we will gradually increase her objective. The goal is adjusted regularly throughout the 6-month intervention period. The instructor has access to the data pertaining to the number of steps per day and can modify the daily steps goal directly in the app or by a phone call to the patients during meetings.

Data are collected by regular transfer to the wearable activity tracker mobile phone app (Nokia Health Mate) available on a mobile phone or Tablet PC. Patients can use the mobile phone app to follow their number of steps per day represented by a graph. After receiving the wearable activity tracker, patients are called on days 7 and 14 to ensure the proper use of the device and answer any questions. Personalized objectives might be redefined to increase their daily physical activity. For patients without a mobile phone, data are collected during the 6-month intervention when visiting the hospital for a consultation every week or 2 weeks. Instructors might use the activity tracker interface to monitor change over time and to adapt to physical activity recommendations. At the end of the 6-month intervention, patients can keep the activity tracker to continue their efforts.

Data Collection

Table 1 provides the complete data collection schedule in this study.

All assessments are recorded at the baseline and the end of the 6-month physical activity program (M6) by the instructor, as seen in Figure 1.

Demographic and Clinical Data

Demographic and clinical data, including date of birth, age at diagnosis, living situation, employment status, hormonal status, tumor histology, personal history of breast cancer, sites of metastases, and current treatment, are collected at the baseline. The Response Evaluation Criteria In Solid Tumors (RECIST) is used to assess the tumor progression between the diagnosis and the end of the physical activity program [36]. All clinical data are extracted from patients' electronic medical records.

Body Composition and Anthropometrics

The standing height (cm), body weight (kg), waist (cm), and hip (cm) circumferences are measured using standardized procedures. The waist circumference is measured midway between the last floating rib and the iliac crest. The hip circumference is measured at the tip of the pubis. The body mass index is calculated as the body weight in kilograms divided by the square of the height in meters.

Physical Activity Fitness and Sedentary Behavior

Cardiorespiratory fitness is measured by evaluating the peak oxygen consumption during the 6-minute walk test (6MWT) [37,38]. Patients are asked to perform the maximum walk shuttle distance on 30-meter-long flat corridors in 6 minutes. During this test, the oxygen consumption, carbon dioxide production, heart rate, and oxygen arterial saturation are continuously recorded using a portable respiratory gas analyzer (MetaMax 3b; Cortex Biophysik, Leipzig, Germany). In addition, the perception of the difficulty during 6MWT is evaluated at the end of the test using the Borg Rating of Perceived Exertion questionnaire [39].

Then, prehensile and grip strength is measured using a hand dynamometry (Jamar Plus Digital Hand Dynamometer; Patterson Medical, Huthwaite, United Kingdom), which is a validated index of the elbow extension strength [40]. Moreover, patients are asked to squeeze the handgrip as strongly as possible for 5 seconds to obtain the maximal force. Of note, two measures are performed on each hand, and the best performance is registered.

The maximum isometric strength of quadriceps extension is measured using a back-leg dynamometer (DFS II Series Digital; Force Gauges Chatillon, Largo, FL, USA). Patients are asked to sit on a chair with the knee articulation at 90°, arms crossed on the chest, and the dynamometer attached to the ankle. At the signal of the instructor, patients must try to extend the leg as strongly as possible in 3 seconds. Only the dominant leg is tested twice, and the best performance is obtained.

The International Physical Activity Questionnaire (IPAQ) [41] is used to measure the self-reported physical activity. IPAQ (long form) is a validated self-administered physical activity questionnaire with 31 items and covers 4 activity domains, work-related physical activity, transportation physical activity, domestic physical activity, and recreational physical activity [41]. IPAQ gives specific scores in the metabolic equivalent of task (MET)-minutes/week for walking, moderate-intensity, and vigorous-intensity activity within each of the work, transportation, domestic chores and gardening (yard), and leisure-time domains. Questions are coded and converted in MET per minute and per week according to the Compendium of Physical Activities [42] by multiplying the number of METs by the duration and frequency of the activity. Then, the total physical activity score for each intensity is obtained by adding

the score for this intensity in each domain and by adding the number of MET-minutes per week at each intensity.

Table 1. The data collection schedule for the Advanced stage Breast cancer Lifestyle and Exercise Trial.

Assessments	Time		
	Patients' recruitment	Day 1: Baseline	Month 6: End of the study
Clinical data (patient record)			
Date of birth		✓	
Age at diagnosis		✓	
Employment status		✓	✓
Hormonal receptor status		✓	
Personal history of breast cancer		✓	
Metastasis localization		✓	✓
Current treatment		✓	✓
Tumor histology		✓	
Disease progression (Response Evaluation Criteria In Solid Tumors)		✓	✓
Demographic data		✓	✓
Anthropometrics[a]		✓	✓
Physical fitness			
6-minute Walk Test with oxygen consumption		✓	✓
Upper limb strength: handgrip		✓	✓
Maximum isometric strength of quadriceps extension		✓	✓
International Physical Activity Questionnaire (long form)		✓	✓
Sedentary behavior: Marshall Questionnaire		✓	✓
Steps per day: Activity tracker[b]			✓
Psychological questionnaires			
Quality of life: Cancer Quality Of Life Questionnaire, breast cancer module		✓	✓
Fatigue: Piper Fatigue Scale		✓	✓
Physical activity preferences, facilitators, and barriers	✓	✓	✓
Incentive effect of activity tracker			✓
Social deprivation: EPICES (Evaluation of Deprivation and Inequalities in Health Examination Centres) score	✓	✓	✓
Other			
Reason for refusal	✓		

[a]Height, weight, waist-to-hip circumference, and body mass index.

[b]During 6 months.

Next, the global score of physical activity is divided into 3 categories commonly used by physical activity guidelines (<600 MET-minutes/week is equivalent to low physical activity; between 600 and 3000 MET-minutes/week is equivalent to moderate physical activity; and >3000 corresponds to high physical activity [43]). Furthermore, the sedentary time in minutes per week is obtained by adding the weekday sitting time in minutes for 5 weekdays, and the weekend sitting time in minutes for 2 days.

Patient-Reported Outcomes

The quality of life is measured with the European Organization for Research and Treatment of Cancer Quality Of Life Questionnaire (QLQ-C30) and its specific module for breast cancer (BR-23) [44]. QLQ-C30 is a 30-item self-administered questionnaire that evaluates 5 functioning domains (physical, role, emotional, cognitive, and social), a global quality of life domain, 3 symptom domains (pain, fatigue, and nausea), and 6 single items (dyspnea, insomnia, anorexia, diarrhea, constipation, and financial impact). Each item is associated with a score ranging from 0 to 100. For the functioning and global

scales, a higher score corresponds to a better functioning level. The specific module for breast cancer (BR-23) gathers data about perceived body image, sexual functioning, sex enjoyment, arm symptoms, breast symptoms, and systemic therapy side effects.

Fatigue is assessed with the revised Piper Fatigue Scale [45,46], which is a 22-item self-reported questionnaire with 4 subscales, behavioral and severity, affective, sensory, and cognitive and mood. All these items together produce a score for total fatigue defining categories as follows: no fatigue (score=0), mild fatigue (score 1-3), moderate fatigue (score 4-6), and severe fatigue (score 7-10).

The social deprivation is assessed using the EPICES (Evaluation of Deprivation and Inequalities in Health Examination Centres) score [47,48]. The score is computed by adding each question coefficient to intercept whenever the answer is "yes." The score ranges from 0 to 100 with the threshold for deprivation at 30, and higher scores indicate greater deprivation levels.

Determinants of Physical Activity

Preferences, facilitators, and barriers are evaluated with the translated version of a specific questionnaire developed by Vallance et al [49]; this questionnaire includes questions regarding the interest and willingness of patients with metastatic breast cancer to participate in a physical activity program designed for patients with metastatic breast cancer. In addition, it includes questions on their interest and preferences for physical activity counseling and specific aspects of these programs, including how, where, and when they would be interested in these physical activity programs as well as the type of intervention that would be most amenable for them.

Biological Data

A 7-mL blood sample is collected at the baseline (D1) and at the end of the study after 6 months (M6). The sample is centrifuged within half an hour after drawing and kept at 4°C before and during centrifugation. The plasma is distributed into cryotube aliquots of 1 mL and buffy coat in a single 1-mL cryotube; these cryotubes are frozen and stored at −80°C at the center and used for the analyses of oxidative stress and antioxidant biomarkers. Superoxide dismutase, catalase, glutathione peroxidase enzymatic activities, and markers of DNA oxidation (8-hydroxy-2'-deoxyguanosine), prostaglandins oxidation (8-Iso Prostaglandin $F_{2\alpha}$) are measured in the plasma [50]. Furthermore, levels of circulating growth factors, cytokines, neutrophils, monocytes, and natural killer cells are assessed as previously described [51].

Statistical Analysis

Sample Size

The sample size was defined empirically to explore the feasibility of the program according to the enrollment potential in the study center. Because the main objective of the ABLE Trial was to assess the feasibility of a physical activity intervention in women with metastatic breast cancer, without major regard for the efficiency, no formal calculation was performed. Given that 200 patients are treated annually for metastatic breast cancer in the Center Léon Bérard and that 60% of patients are expected to survive for at least 6 months, with a projected acceptance rate of 50%, the pilot study will aim to recruit 60 patients within 9 months.

Statistical Methods

Patients' characteristics will be described at D1 and M6 using the mean and SD for quantitative data, frequency, and percentage for qualitative data.

The primary outcome to assess the feasibility of the study will be the proportion of patients achieving the physical activity recommendations corresponding to 150 minutes per week of moderate physical activity evaluated by the IPAQ score during the last week of the study. In addition, we will estimate the proportion of patients who agreed to participate in the ABLE Trial among eligible patients. The reasons for refusal will be documented and described as well.

The secondary outcomes to assess will be the evolution of physical activity, anthropometric, physical fitness, psychological, and biological variables between the initiation (D1) and the completion (M6) of the physical activity intervention using Wilcoxon signed-rank tests. In addition, the level of physical activity according to biological, psychological, and clinical outcomes adjusted on potential confounders, including age, treatment, and number of visits, will be explored using multiple linear regressions. Moreover, the level of oxidative stress will be correlated to the RECIST criteria. Data on barriers and facilitators of the adherence to a physical activity program from D1 to M6 will be compared by Mac Nemar tests. All statistical analyses will be performed using SAS software (version 9.4. SAS Institute Inc, Cary, NC, USA).

Results

The recruitment and enrollment in this single-arm feasibility trial started in October 2016. A follow-up was completed in January 2018. Data analyses began in February 2018 and will be completed in October 2018. All results are expected to be available by the end of 2018.

Discussion

Principal Findings

Given the beneficial effects of physical activity in localized breast cancer, the ABLE Trial is the first European study to propose a physical activity intervention for patients with metastatic cancer that will obtain preliminary data on biological, functional, psychological, and clinical outcomes and identify the determinants of physical activity. In addition, the use of wearable activity trackers in the ABLE Trial strengthens its novelty. Although wearable activity trackers are comparable to pedometers in some aspects, they are more effective for behavioral modification [52] because the Health Mate app and the wearable activity tracker provide more detailed data on the physical activity performed over time. These types of devices are emerging in the health care field and are being shown to help motivate people to increase their physical activity level and facilitate them to reach a personal or recommended goal because of the feedback received in real time (eg, steps) [23-25].

International recommendations for patients with cancer are to practice 30 minutes of moderate physical activity per day at least 5 times a week [53]. The number of steps per day is more easily comprehensible for individuals to achieve these physical activity recommendations. For adults with health impairment, 5000-7000 steps per day might be a more appropriate target than the target of 10,000 steps per day recommended for healthy people [54]. Indeed, walking is feasible at no charge and practiced by the majority of people. In the ABLE Trial, the recommended number of steps is individualized to each patient because research has suggested that a small goal is more effective and easier to achieve than a higher activity goal. In addition, it is important to increase these physical activity targets gradually [24].

The links between the level of physical activity and the biological mechanisms involved in the tumor progression have never been studied in patients with metastatic breast cancer. A study of the oxidative stress in this population might help identify potential new biomarkers associated with physical activity and tumor progression.

Of note, some limitations are acknowledged in the ABLE Trial. First, the sample size is limited but is sufficient to test the feasibility of the intervention. Second, the device used in the study has not been validated but uses the same algorithm as Nokia Pulse that has been validated by comparing this tracker with the OptoGait system for laboratory and ActivPAL for free-living conditions [20]. Finally, the test-retest reliability for Nokia Pulse was excellent with an intraclass correlation coefficient >0.90.

The results of this trial will provide quantitative and qualitative outcomes that will help design a future multicenter RCT on a physical training intervention in patients with metastatic breast cancer. Given the paucity of data in this population of patients and the potential for measurable health benefits to them, in many domains, this trial will provide new data that will be relevant in assessing the feasibility and acceptability of a larger-scale trial for this previously underinvestigated population.

Ethics and Dissemination

The study protocol was approved by the French ethics committee (Comité de protection des personnes Sud-Est IV), and the study database was declared to the National Commission for Data Protection and Liberties (CNIL; reference number: 1994192).

Acknowledgments

The authors would like to thank the French League against Cancer, especially the League of Landes, the Cancéropôle Lyon Auvergne Rhône-Alpes, the associations Odyssea and Activ'RA for their financial support and Nokia for providing wearable activity trackers for patients. Furthermore, the authors would like to acknowledge the contribution and support of Nicole Falette for her help on the methodological design.

Conflicts of Interest

None declared.

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Abbreviations

6MWT: 6-minute walk test
ABLE: Advanced stage Breast cancer Lifestyle and Exercise
D1: day one
IPAQ: International Physical Activity Questionnaire
M6: end of 6 months
MET: metabolic equivalent of task
RCT: randomized controlled trial
SMS: Short Message Service

Edited by G Eysenbach; submitted 23.03.18; peer-reviewed by M Nomali, M Ainsworth, E Bantum; comments to author 22.05.18; revised version received 02.06.18; accepted 04.06.18; published 30.08.18.

Please cite as:
Delrieu L, Pérol O, Fervers B, Friedenreich C, Vallance J, Febvey-Combes O, Pérol D, Canada B, Roitmann E, Dufresne A, Bachelot T, Heudel PE, Trédan O, Touillaud M, Pialoux V
A Personalized Physical Activity Program With Activity Trackers and a Mobile Phone App for Patients With Metastatic Breast Cancer: Protocol for a Single-Arm Feasibility Trial
JMIR Res Protoc 2018;7(8):e10487
URL: http://www.researchprotocols.org/2018/8/e10487/
doi:10.2196/10487
PMID:30166274

Original Paper

A Mobile App (iBeni) With a Neuropsychological Basis for Cognitive Stimulation for Elderly Adults: Pilot and Validation Study

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Abstract

Background: Cognitive impairment is considered one of the most feared chronic conditions among the older adult population since its incidence is approximately twice more frequent than that of dementia. In Mexico, no studies or reports of older adults using technology for cognitive interventions have been published, given that institutions usually frame cognitive stimulation tasks in paper and pencil (ie, in the traditional manner).

Objective: The objective of this study was to create and analyze the effect, viability, and impact of a mobile app for cognitive stimulation implemented among a group of elderly adults (over 60 years of age) from the state of Hidalgo in Mexico.

Methods: This study was a nonprobabilistic pilot trial using convenience sampling. An intervention was implemented among a group of 22 older adults between 60 and 80 years of age over 12 weeks. Half of the older adults were stimulated with the mobile app (experimental group) and the other half followed the traditional paper and pencil training (control group). Assessments with the Mini-Mental State Examination (MMSE) and the Neuropsi, a neuropsychological test validated in Mexico, were done before and after both cognitive stimulations.

Results: According to the analyzed data, 6/11 (55%) participants from the experimental group obtained better results in their cognitive skills, and 5 (45%) of the adults maintained their score, given that the participants were able to execute the exercises repetitively. Meanwhile, for the control group, only 3/11 (27%) participants obtained better results in the postevaluation. Significant values for results of the MMSE were obtained in the postevaluation for the experimental group compared to the control group, while results did not show significant differences in the Neuropsi. Regarding the validation of the app, all the participants evaluated its pertinence positively.

Conclusions: The intervention data show that the experimental group obtained better results in the postevaluation given that the participants were able to execute the exercises repetitively. The control group could not accomplish this since they had to respond on the manual and no further attempts were provided. However, both groups increased their score in the neuropsychological evaluations. This suggests that a longer and more frequent intervention is required.

Registered Report Identifier: RR1-10.2196/9603

(JMIR Res Protoc 2018;7(8):e172) doi:10.2196/resprot.9603

KEYWORDS

mobile application; cognitive stimulation; cognitive impairment; older adults; neuropsychological evaluation.

Introduction

The prevalence of chronic diseases related to aging is becoming a significant public health issue as the rate of the elderly population increases worldwide [1-3], particularly in Mexico [4]. Cognitive impairment is a chronic condition that is considered one of the most feared by the older adult population since its incidence is approximately twice as frequent compared to dementia [5]. According to projections, it is estimated that by 2050 the number of adults over the age of 60 will be around two billion and it will represent 22% of the world population. Similarly, four-fifths of this older adult population will live in developing countries (ie, Africa, Asia, and Latin America) [6-8].

Consequently, several studies have evaluated the effectiveness of different cognitive interventions on cognitively preserved older adults and populations with mild cognitive impairment (MCI) [9-13]. One of the key findings of these studies is that cognitive ability is significantly preserved with the use of these interventions, which are mainly focused on memory and function. As a result, institutions are recommending their implementation as a preventive step.

The terms *cognitive stimulation* and *cognitive training* have been used interchangeably. However, these terms do not necessarily mean the same thing, so it is crucial to describe, define, and clarify these 2 intervention methods. Bigand and Tillman [14] mention that cognitive stimulation involves actions directed to maintaining or improving cognitive skills and is based on the pyschopedagogical planning of activities aimed at activating and maintaining mental skills. For their part, Li et al [15] define cognitive training as the teaching of strategies and theoretical abilities that allow the enhancement of cognitive functions, particularly with the intention of improving specific domains.

Thus, it is possible to establish that cognitive stimulation aims at maintaining and preserving cognitive functions in individuals that are relatively healthy or have a MCI, boosting their preserved cognitive capacity and skills, and decelerating cognitive decline process. Moreover, this intervention can be applied to any individual since anyone can improve his or her cognitive capacities to be more cognitively skillful.

Information and Communication Technologies (ICT) have assisted cognitive stimulation. These tools have increased and expanded recently due to greater availability of mobile devices (ie, mobile phones and tablets) in everyday life [16]. Health professionals and researchers have adopted these devices as an alternative intervention when dementia is presented or when the intention is to preserve the patient's cognitive capacity, even in patients with mild cognitive decline [17-20].

Studies have affirmed that one of the strengths of this type of intervention is that they offer instant feedback. By using ICTs, they can adapt the tasks dynamically to the particular needs of the patient, even about their progress in the completion of tasks [21-22]. Also, Martinez-Alcala et al [23] indicate that technologically assisted interventions involve structured task practice and cognitively challenging exercises and that they offer several advantages over traditional methods, including visually attractive interfaces, efficient result delivery and the ability to adapt to the patient's progress.

Likewise, some studies have demonstrated that cognitive improvement does not transfer easily to the realization of new tasks and that these yield better results when established repetitively with increasing levels of difficulty [24]. Similarly, other studies have shown that cognitive stimulation interventions can be administered not only through therapist instruction but also through computerized technology [25-26].

Recently, interest has thus been focused on interventions based on computerized cognitive stimulation or technologically-assisted cognitive stimulation. Regarding cognitive impact, this is justified because interventions supported by ICT can have a positive impact on attention measures, executive functions, and memory [11,17,20-22,24-26].

Based on a review of 226 cognitive interventions of ICT in healthy older adults and people with MCI between January 2015 and January 2018 in Pubmed, a total of 9 studies were included. Articles that did not match the corresponding period were excluded, as were the research studies that did not include people over 60 years of age. Those included had to be either healthy individuals or experiencing MCI, aimed at cognitive aspects, and written in English. From the 9 studies, 5 (56%) were about cognitive training, 2 (22%) used cognitive stimulation, and 2 were cognitive assessment studies (see Multimedia Appendix 1).

The findings from the recent research studies indicate that mobile phone apps can help healthy elderly people and with MCI in the enhancement of their quality of life by targeting these apps at their cognitive deficiencies such as memory loss [27-31]. Also, as the evidence shows, mobile phone apps can uniquely contribute to early diagnosis and assessment of dementia [27,32]. Generally, when people present subjective memory complaints and MCI, mobile phone apps can help them to be more independent and socially engaged.

Lu et al [33] argue that apps must involve end-users in the co-design of new technologies to develop tailored devices, as well as testing them in a real-world context. The results showed that the cognitive training game developed in this study was accepted by the nine participants included in the study, and a high degree of satisfaction was noted. Yasini and Marchand [28] indicate that the use of tablets and the development of serious games in close cooperation with health professionals and elderly patients (ie, the end user) are likely to provide satisfactory results to improve health care for those patients suffering from cognitive disorders.

Furthermore, Zygouris et al [32] and Zorluoglu et al [27] show evidence that mobile phone apps are effective in cognitive screening and the assessment and diagnosis of MCI. One advantage of apps is that they are more accurate than traditional manual testing. They are easily administered and understood by the elderly. They also save time, minimize the examiner's biases, can provide an early diagnosis enabling patients to stay independent on their tasks of daily living, they may cut hospitalization and treatment costs, they can improve the overall quality of life of the elderly, and they are ecological [27-35].

Considering the studies mentioned above, the cognitive interventions based on ICT can provide support for healthy seniors and MCI in the early diagnosis of this cognitive disorder to improve their cognitive functions. Also, they can reduce both the mental and economic burden of subjects and their caregivers.

It is important to point out that in Mexico only a few institutions aimed at the elderly are endowed with cognitive stimulation programs, and even these interventions lack pre- and postneuropsychological studies. Also, exercises in the training lack a neuropsychological basis, are extracted from books in an unsystematized way and are not entirely validated. In the same vein, no studies or reports on seniors using technology for these interventions have been published since institutions usually frame cognitive stimulation tasks in a traditional manner. Also, digital literacy levels among elderly Mexicans is very low. The population lacks access to technology and many feel incapable of learning how to use computers and the internet. According to the National Institute of Statistics and Geography at the Instituto Nacional de Estadistica y Geografia [36], only 2% (1/10) of Mexican seniors have access to technological devices. Due to the progressive nature of cognitive impairment, and the need for this type of intervention, a cognitive stimulation app aimed at the senior Mexican population was designed and implemented. The creation of this app reduces the need for human resources after a short period of training and adds efficiency.

This study describes a pilot nonrandomized study seeking to examine the effect, viability, and impact of the app. For this, an intervention was carried out with 22 adults 60-80 years of age. This population was divided into a control group, which executed cognitive stimulation exercises in a traditional manner (ie, paper and pencil), and an experimental group (EG), which used the app. Assessments with the Mini-Mental State Examination (MMSE) and the Neuropsi (a neuropsychological test validated in Mexico) were done before and after both cognitive stimulations. This study also shows that this technology and its benefits over traditional methods were validated.

Methods

Participants

This was a pilot nonrandomized and unblinded study where the participants self-allocated. For the recruitment of participants, a talk was held at the Centro Gerontológico Integral (CGI) at Punta Azul, Pachuca de Soto, where the objectives of the intervention were presented. Subsequently, all subjects were summoned through an advertisement offline. Those who accepted to attend the digital workshop at the Instituto de Ciencias de la Salud (ICSa), Universidad Autónoma del Estado de Hidalgo (UAEH) who had access to the app (explained below) represented the EG.

The study involved 22 seniors between 60-80 years of age. The EG participants underwent cognitive stimulation through an app. This group included 11 older adults (7 women and 4 men) with a mean of 64 years of age and had 6 years of academic study. It is important to point out that these adults attended a digital literacy course before implementation of the cognitive stimulation to develop the necessary technical competencies that enabled them to use the app more efficiently.

The control group (CG) included 11 older adults (8 women and 3 men) with a mean of 69 years of age and with 12 years of academic study. These adults did not have digital skills and did not participate in the digital workshop. They underwent cognitive stimulation in a traditional manner (ie, paper and pencil). It is important to note that both groups carried out the same exercises, with a difference only in the methods used. None of the participants discontinued the intervention.

Similarly, during the intervention, both groups were assisted by 2 students of gerontology and a project leader (CIMA). Even though the exercises for the EG were fully automated (ie, the app automatically increased the level according to the adult's progress) the study authors indicated the type of exercise they should perform and provided support to the participants at all times. For example, they provided encouragement so that any doubts of discontinuation would not arise during the use of the app. For their part in the CG, the authors followed each participant to complete the exercises in the manual.

The exclusion criterion adopted in the study for both groups was that no participant presented any untreated visual or hearing impairment. Table 1 shows the characteristics of both groups who participated in the study. As it can be seen, there were no significant differences between groups in age and education.

All participants were actively involved in the cultural and social activities at their nearest gerontology center. Also, it is important to mention that this study was reviewed and approved by the Research and Ethics Committee at the ICSa, UAEH. At the start of the intervention, participants provided written informed consent (see Multimedia Appendix 2). In the case of the EG, informed consent was provided electronically, and upon acceptance, registration was then carried out.

Measures and Evaluations: Cognitive Evaluation

Before admittance to the program, participants undertook a neuropsychological evaluation through standardized tests called the Mini-Mental State Examination (MMSE) and the Neuropsi. The average time of administration was 40-60 minutes. The aim was to characterize the different aspects of the groups' cognitive functions. The Neuropsi is a validated test in Mexico with norms according to age and educational level [37]. The maximum score on the test is 130. Neuropsi measures several neuropsychological functions: orientation, attention and concentration, verbal and visual-spatial memory, language, writing, reading, comprehension, conceptual executive functions, and motor executive functions. The evaluation also included other exploration tests based on the level of autonomy and ability to carry out basic Activities of Daily Living (ADL) or Barthel Scale. Furthermore, information on personal relative variables was gathered to know whether participants had a predisposition to cognitive impairment or any dementia. The variables included gender, academic level, and family background. Likewise, 2 questions of self-perception of their cognitive state were included. For both groups, face-to-face interventions were performed to ask about their name, age, and

level of education. Also, both groups had face-to-face assessments of their neuropsychological level. Only the cognitive stimulation exercises for the EG were Web-based assessed. Finally, prepilot tests were carried out before compiling the final release of the app in which the seniors interacted with the app to know if the cognitive stimulation exercises had been correctly presented (eg, design and functionality) and the records from each participant were saved in the database. It should be mentioned that prepilot tests were performed on a group of 50 seniors from the IGC, but none participated in this study. These pretests provided some technical considerations for the app development and are described elsewhere in this manuscript.

Description of the Mobile Application iBeni

The objective of this study was to create an app with a neuropsychological basis for elderly adults. This app was developed given the need for this type of intervention in Mexican communities. Likewise, this research was conducted as part of a CONACyT Commission at the UAEH through the Cátedras Program where the researchers (CIMA and ARL) are assigned.

The cognitive stimulation app primarily aims to improve cognitive functions and to decelerate the impairment process in healthy older adults or older adults with mild indicators of decline. The cognitive areas stimulated in the app were memory, attention, comprehension, perception, and visual-spatial processes. As previously mentioned, the exercises included in the app were specially designed for the elderly population. Moreover, each of the exercises were comprised of 3 levels of difficulty (low, medium, and high), which were selectively enabled as the users progressed.

The app had the advantage of cognitively stimulating seniors not only in memory but in other neuropsychological functions not found in other apps. It is important to notice that the exercises were based on items that appear on the MMSE and the Neuropsi tests. However, the app followed a graded level of difficulty based on the progress of the user. For example, in the first level of attention exercises, the user clicks (or selects) 1 image that does not coincide with the other. In subsequent levels, the app shows more objects but the user must select more images in less time. As previously mentioned, before compiling the final version of the app, prepilot tests were carried out to find out if the cognitive stimulation exercises were working correctly. These tests also confirmed that no change would be applied to both the content and the organization of the exercises included in the app.

Technical Considerations

Since the elderly population presents other age-related changes apart from cognitive decline, additional aspects were considered. These were (1) visual deterioration including a decrease in close focusing ability, contrast sensitivity decline and color differentiation alterations, (2) hearing loss, especially loss of the ability to detect high-pitched sounds, to decipher fast language and to understand speech in noisy environments; and (3) psychomotor deficiencies, including delayed responses in complex psychomotor tasks, a decrease in the ability to track moving targets, and low accuracy in fine movements. Consequently, the authors considered the following guidelines for the design of the app (Textbox 1).

A clear, simple, and attractive design was chosen, in which the user was able to access all the exercises and levels directly from the main menu (Figure 1). Additional considerations were taken to simplify the tasks (Textbox 2).

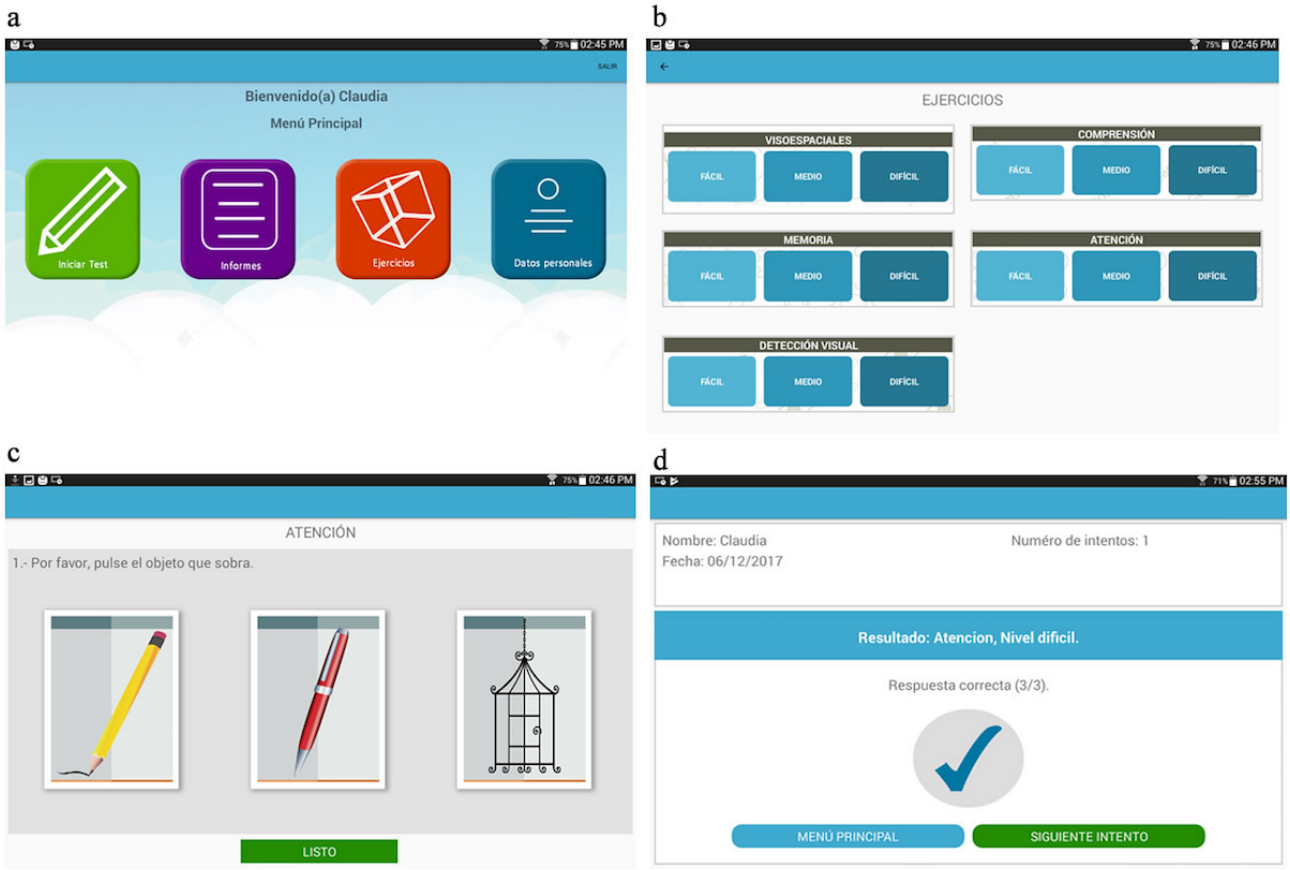
Table 1. A comparison between the characteristics of the experimental and control groups in this study.

Characteristic	Experimental group, mean (SD)	Control group, mean (SD)	*t* test	*P* value
Age (years)	67 (7)	71 (5)	1.53	.14
Education level (years)	8 (4)	11 (4)	1.45	.16

Textbox 1. Guidelines used in the design of the iBeni mobile app.

- The app interfaces presented large-sized elements such as text, icons, images, and buttons.
- The color palette selected for the interface keeps conservative colors and maintains contrast in the foreground and background, especially in text messages.
- The structure on each screen keeps a well-organized distribution of its elements.
- Too complex interface designs should be avoided; hence irrelevant information is minimized on general screens, as well as on screens containing exercises.
- The number of clicks within the app is optimized to keep track of the user's location in the app.
- Simple tasks that do not require long attention spans are implemented.

Figure 1. Mobile app screens: (a) main menu, (b) exercise menu, (c) memory exercise level 1, attempt 1, (d) results screen.



Textbox 2. Optimizations considered to simplify participant use of the iBeni mobile app.

- The main menu is simplified so that the user can define the level of the exercise with just two clicks.
- The display of the exercises shows simple directions that indicate the user what to do.
- Each result screen displays the name of the user, number of attempts, type of exercise, level, date, and number of right answers.
- The use of scrollbars was avoided since this movement seemed challenging for the users.
- All the actions in the app are carried out at just 1 click.

Database

The app was programmed based on the Android operating system, and contains several screens with forms. These include registration, desertion, modifications, and consultations, which are sent to databases located in a MySQL server in the cloud. This database is comprised of 4 tables containing information from the app (Textbox 3).

A hypertext preprocessor (PHP) code was used to store and access the information. The code operates as a Web-based service allowing access and response requests between the mobile device and the database. It works as a bridge so that the Android code generated is capable of interpreting and displaying the information from the database. It also carries out different operations according to the screen on which the user is working (Figure 2).

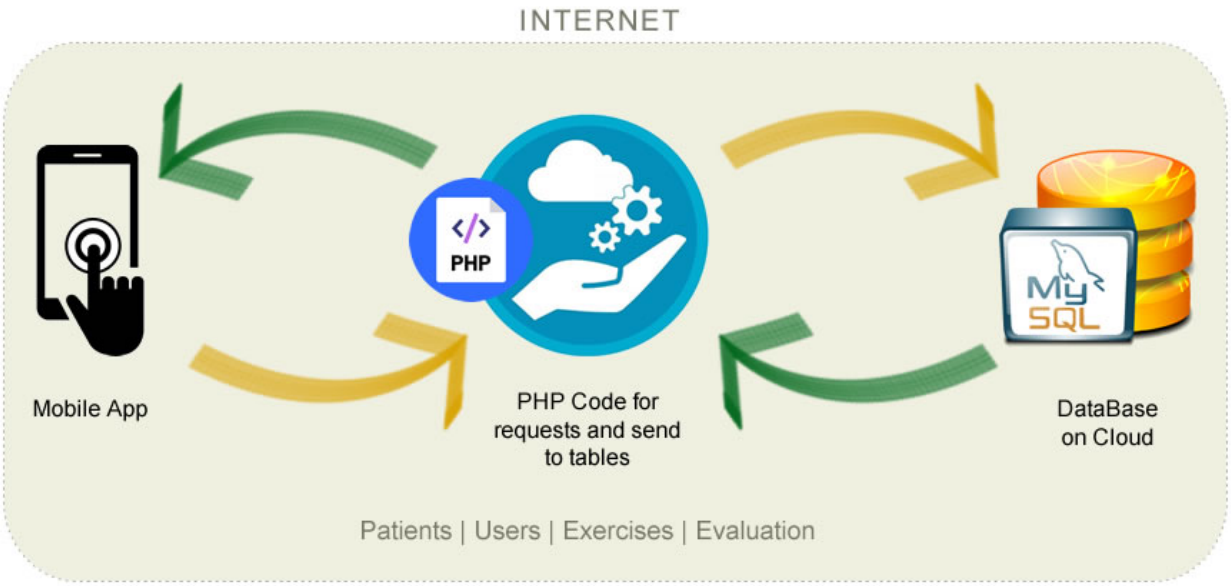
The mechanism for sending the data entered by the participant from the app to the database occurs in 2 ways. First, for alphanumeric texts, PHP services were adopted, using standardization of characters to ensure the total sending of data. These services have an encrypted connection and security features to safeguard the integrity of the app. Second, for some visual-spatial items, users were due to generate copies of figures and thus these images were protected by a file transfer protocol to guarantee their protection.

The decision to choose the database provider was based on the range of services offered and the low costs involved. However, data integrity was also critical. Recognized companies such as TechRadar and TrustPilot are the best for ease of use, integration of solutions, and security of information. Also, they provide enough storage and database space along with excellent bandwidth.

Textbox 3. The 4 categories that comprise the app database.

1. Patients: information corresponding to the name, email address, age, sex, marital status, academic level, city and state, and social security affiliation.
2. Users: this information registers the accounts and passwords of patients for their logging into the app.
3. Exercises: it stores dates and times at which an exercise started and concluded, the type of evaluation currently taking place, the level in which it was executed, scores and attempts, the image corresponding to a test and finally the ID and name of the patient.
4. Evaluation: it concentrates the evaluation results corresponding to each type of evaluation executed, the total scores, as well as the date and time at which they were carried out.

Figure 2. Conceptual representation of the mobile app database.



Intervention Sequencing

This was a parallel study. As a nonrandomized trial of a pilot study, the allocation ratio was based on self-allocation. All subjects were summoned to attend the digital workshop, and those who accepted to go to ICSa became the EG with access to the app. In contrast, the CG remained at the IGC facilities. Therefore, no interaction took place between the 2 groups. Nevertheless, care was taken to evaluate how the cognitive performance was before beginning the intervention. This assured that the groups did not statistically differ in age, education, MMSE or Neuropsi assessments. Also, prepilot studies had taken place before the trail began to create and evaluate the design of the app.

Cognitive stimulation among the 2 groups was implemented in 3 months (May-July 2017), from which 12 weeks were devoted to direct intervention. The neuropsychological evaluation was conducted 2 weeks before the start of the program (ie, preevaluation). After the neuropsychological evaluation, the EG received 10-minute training to get familiarized with the interface of the app. It is important to note that both groups carried out the same activities, with the only difference being the methods used. Likewise, the schedule in which they did the activities was identical (ie, 10:00 am-12:00 pm) to ensure that they were conscious and alert during the sessions.

The cognitive stimulation program consisted of 24 sessions. Participants carried out the exercises assigned according to their progress. At the end of the intervention, all participants were re-evaluated with the neuropsychological and supplementary tests. Figure 3 shows the structure and sequencing of the sessions.

Session Procedures

Sessions with the EG group were conducted in the facilities of the computer center at the ICSa. Each participant was provided with a 10.1-inch Samsung Galaxy Tab 4 tablet, in which the app (Version 2017-03-08) was installed and configured. Sessions for the CG group were carried out in a classroom of the IGC de Punta Azul. The materials used consisted of 2 manuals. One was for the examiner, in which answers, partial and total scores, attempts, level and date of the session were registered. The other manual was for the participants, in which the exercises they had to work on were provided. Every week, the stimuli, number of exercises, levels and attempts were made as equal as possible. In the first week, both groups were assigned memory, attention, and perception exercises at a low level of difficulty. As participants progressed, more exercises were added and the level of difficulty gradually increased (Multimedia Appendix 3). Table 2 describes the exercises programmed for the 24 sessions.

Figure 3. Structure and sequencing of the sessions undertaken by each group.

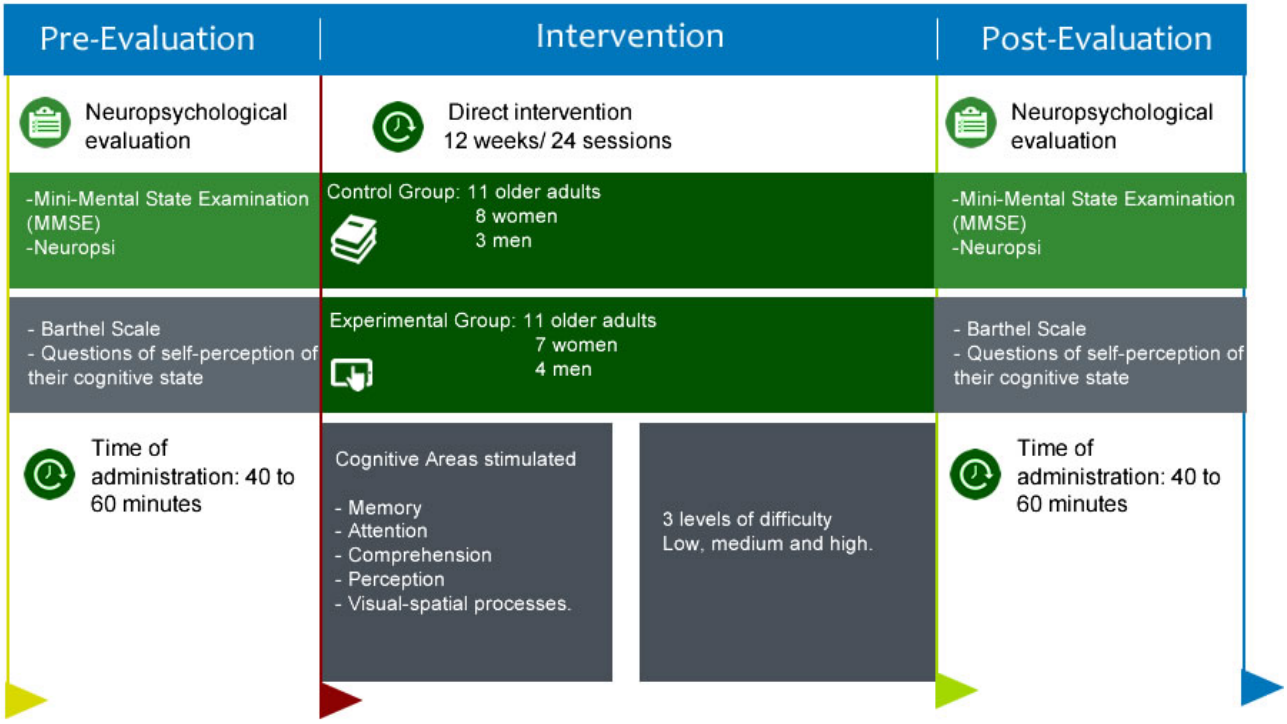


Table 2. A description of the cognitive stimulation exercises included in the intervention.

Cognitive function	Exercise description	Exercise materials	Number of levels
Memory	These exercises allowed the senior to test information retention capacity in each period. The participants had to observe an image, and then had to respond to related questions. The number of questions increased as the participants progressed from one level to the next.	12 images depicting places, people, and landscapes. Open-ended questions related to the image.	3 levels with 4 attempts
Attention	These exercises aimed to preserve the level of intellectual and association skills in older adults. They consisted of showing a series of similar images, in which they had to point out which was different or was not related to the rest.	68 images	3 levels with 4 attempts
Comprehension	These exercises were aimed at preserving the degree of interpretation and perception in the senior. Each was presented as a series of directions for the participant, and they had to execute them by pointing to and marking the corresponding images. As levels were reached the number and type of geometrical figures were increased.	Series of directions and 72 geometrical figures	3 levels with 4 attempts
Visual detection	The objective of these exercises was to understand whether the older adult discriminates visual stimuli. It consisted of presenting a series of images in which participants must find one or several letters.	768 images of letters	3 levels with 4 attempts
Visual-spatial	They allowed the older adult to mentally represent, transform, and manipulate an object or image. In these exercises, participants had to visualize the image for 40 seconds and then replicate it.	12 abstract images, classified from the number of lines in the figure or from angles. In levels 2 and 3 the participant was given 60 seconds to replicate the image.	3 levels with 4 attempts

Results

Overview

All adults lacked experience using ICTs. Only those from the EG attended a digital literacy course before the intervention to develop the necessary technological competencies for efficient app use [38]. Although the purpose of this study was not to promote the level of digital literacy of seniors, it is important to mention that before joining the course the adults had no digital skills. They did not know how to use the computer or the internet. However, after attending the digital literacy course for 4 months at the ICSa facilities, they increased their level so they could carry out the necessary activities on a computer and other electronic devices such as tablets. They also learned to surf the internet and use email.

Pilot Study

According to the postevaluation in the MMSE, 55% (6/11) of participants from the EG obtained better results in their cognitive skills, and 45% (5/11) maintained their score. The cognitive areas where the results improved were: attention, comprehension, and short-term memory. In the CG, 27% (3/11) of participants obtained better results in the postevaluation, and 64% (7/11) were able to maintain their score. However, 9% (1/11) of seniors obtained a lower score.

Significant values for results obtained from the MMSE in the EG versus the CG are shown in Table 3. A mixed analysis of variance (ANOVA) (2X2) was used to compare the effects of the interventions. Only the repeated measures effect in both groups was significant ($F_{1,22}$=4.59, P=.04), while there were not differences between groups ($F_{1,20}$=0.18, P=.67), neither an interaction between them ($F_{1,22}$=2.04, P=.16). The Cohen d=0.45 indicated a minimal effect. The Neuropsi results did not show significant differences. The repeated measures effect in both groups did not differ ($F_{1,22}$=1.98, P=.17). Also, there were no differences between groups ($F_{1,20}$=0.10, P=.75), and no interaction between them ($F_{1,22}$=1.44, P=.24).

Based on the ANOVA, the repeated measure factor was significant for the MMSE, and two 90% CI levels were computed considering the MMSE preevaluation mean of both groups and another 90% CI for the postevaluation mean of both groups. For the preevaluation mean, the CI=(28.17≤mu≤29.10) and for the mean belonging to the postevaluation, 90 % CI=(28.84≤mu≤29.51; see Figure 4).

Figure 4. Results of the pre and post evaluation obtained from the Mini-Mental State Examination (MMSE). EG: experimental group; CG: control group.

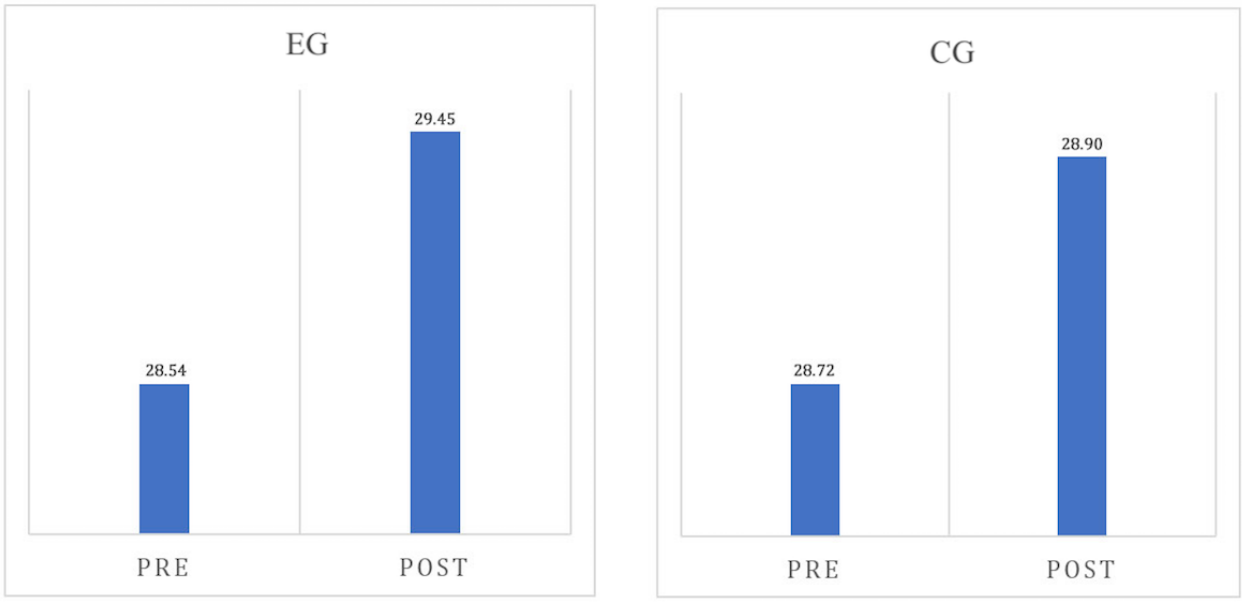


Table 3. Means and standard deviations of the Mini-Mental State Examination and the Neuropsi test in the pre- and postevaluations in the experimental group compared to the control group.

Neuropsychological test	Experimental group, mean (SD)		Control group, mean (SD)	
	Preevaluation	Postevaluation	Preevaluation	Postevaluation
MMSE[a]	29 (1)	29 (1)	29 (1)	29 (1)
Neuropsi	102 (6)	103 (6)	97 (11)	97 (11)

[a]MMSE: Mini-Mental State Examination.

Concerning autonomy and capacity to perform basic ADL, 100% of the adults maintained their levels of autonomy in the postevaluation according to the Barthel Scale. Regarding questions about cognitive state perception, 73% (8/11) of seniors from the EG reported improved cognitive capacity after the intervention, while 27% (3/11) revealed that they maintained their cognitive state. In the CG, 45% (5/11) of older adults perceived an improvement in their cognitive capacity, while 55% (6/11) indicated that their memory and cognitive functions remained unchanged after the intervention.

Validation of the Mobile Application

With the aim of adequately evaluating the relevance of the app, it was essential that users analyzed its usefulness, performance, and design by providing feedback on existing failures, any concrete benefits, and areas for improvement. After the intervention in both groups, the EG was invited to evaluate the acceptability and viability of the app. For this validation, a technology acceptance test with 17 closed questions was performed based on the technology acceptance model (TAM). This test has been widely used to predict the acceptance of new technologies. Also, TAM has been built on collective findings suggesting that the desired technology was substantially dependent on user acceptance [39,40].

To understand the benefits from the use of this kind of medium, interviews were conducted to explore any concerns, reasons, and contexts related to the decision of using or not using this type of app. The interviews with the seniors also allowed for obtaining detailed answers. The tests, as well as the interviews, were performed between July and August 2017. The parameters used for the validation of the app were: (1) ease of use, (2) functionality, (3) design, (4) usefulness, and (5) satisfaction. In this study, the ease of use of the app was defined as the degree to which the user believes that using the app will be effortless. Meanwhile, the usefulness of the app is defined as the degree to which the user believes that using the app would enhance his or her cognitive state. The TAM posits that the usefulness and ease of use perceived have a direct effect on attitudes and satisfaction using new technology. The parameters of the functionality and design are the degree to which the user believes that the functionality and design quality of the app is correct. The measurement used in the questionnaire corresponds to a 5-point Likert scale. The options in the scale appeared as follows: strongly agree (5), agree (4), neutral (3), disagree (2), and strongly disagree (1).

Concerning the analysis of the first parameter, *ease of use*, 91% (10/11) of EG participants agreed to a positive evaluation, confirming that the app is easy to use in both the evaluation and the exercise sections. Thus, interaction with the interface is clear and intuitive. Regarding *perceived usefulness*, all the participants had a favorable agreement, suggesting that the app allowed them to keep their mind active and that this kind of app is helpful to this type of population. Moreover, when the possibility of using an app for cognitive stimulation was presented to the older adults, they showed a positive attitude towards the idea. During the evaluation of the third parameter, *Attitude towards the Use of Technology*, all the participants maintained a positive attitude, which suggests that the use of apps for cognitive stimulation is a valuable project. Similarly, participants indicated that this type of technology allows cognitive stimulation to be efficient, it is easy to perform, and, above all, it has an attractive design. In the parameter *Intention of Use*, 82% (9/11) of the participants indicated that they would use the app and other cognitive activation technologies as much as they can. This shows that there is a need to create similar apps that are more accessible for this population. Only 9% (1/11) of participants was neutral regarding the use of technological methods for cognitive activation. Lastly, the parameter *Satisfaction* received a favorable evaluation from all the participants, meaning that the app provides an attractive interface to improve cognitive performance in older adults and to decelerate cognitive impairment processes. Table 4 shows the raw marks obtained for each parameter.

Regarding the participant interviews, the responses obtained suggested that this type of app offers several opportunities. During an interview, the older adults were asked in an open question format what benefits they perceived when using the app. Some of the benefits highlighted were: visualization of results in real time, customizable interface, automatic registration, more active cognitive stimulation, and time-saving. Visualization of the results was the most commonly mentioned benefit. As one senior explained:

> *For me it is important to visualize the results that I got in the exercises I did, because many times these data are not provided to us.* [EG participant, female]

The participants also observed that the app allowed them to have a more active and personalized stimulation. Additionally, the seniors noticed that during intervention many tasks were not adequate for traditional paper execution because they required the presence of various stimuli or the inhibition or delayed presentation of specific elements. Consequently, the app allowed broader interaction, which was fundamental for the accomplishment of some tasks.

Table 4. The technology acceptance model validation results for the iBeni mobile app.

Parameter	Mean (SD)
Participant ease of use	7 (1)
Perceived usefulness	7 (0)
Attitude towards using of technology	7 (1)
Intention of use	7 (1)
Satisfaction	7 (1)

Also, about the perceived benefits, participants were asked whether they would be willing to use the app in the future. Every participant stated that they would be willing to use the app for cognitive stimulation exercises. Finally, it was clear that while the seniors recognized the app's benefits, it should be used as a supplement in health care. However, it must not be used to replace the human contact. As one older adult said:

> *Well, I think people contact is very important, and I wouldn't want the app to be used excessively.* [EG participant, female]

In other words, health care systems should supplement, but not replace, health care professionals or the attention given by family members.

Discussion

Principal Results

It is a fact that adults over 60 years of age express their concern regarding the decline in their mental skills. Several studies assert that change in cognitive skills and mental processes is related to the aging process and the person's quality of life. However, there are very few studies of older Mexicans adults that have discussed whether the improvement of cognitive functions can have short or long-term effects with the use of technology. The studies mentioned above have found that cognitive interventions based on ICT can result in improvements in many perceptual and cognitive abilities [27-35]. Thus, these types of interventions are potentially an ideal solution to address the many perceptual and cognitive declines associated with aging. The study by Pereira-Morales et al [35] suggested that cognitive training of moderate intensity, supported by a web platform, could lead to significant improvements in cognitive and psychological well-being in older people with subjective memory complaints. Shellington et al [30] argue that sixty percent found the app was easy to use or similar to what they experienced with square-stepping exercise in the laboratory setting. Most said they would continue to use the HealtheBrain app and would recommend it to friends and family. Chan et al [29] stated that the results yielded evidence for more significant improvement over time in the iPad intervention compared with the control groups for processing speed and episodic memory. Thus, the program was successful at improving cognitive performances through productive engagement and provided an added benefit of technological mastery. Finally, Yasini and Marchand [28] indicate that the use of tablets and the structure of serious games in close cooperation with health professionals and elderly patients are likely to provide satisfactory results to improve health care provided for elderly patients suffering from cognitive disorders.

According to the analysis carried out after the cognitive intervention in this study, Both EG and CG obtained better results in the neuropsychological evaluation, even when the CG could not execute the exercises repetitively. Concerning the adult who obtained a low mark in the postevaluation he is suspected to have been distracted during the evaluation. As to the validation of the app, it was found that most of the participants showed a positive attitude regarding its use. This indicates that it is easy to use, accessible and that it allows cognitive stimulation to be efficient and friendly. Also, the adults indicated that the app provides an attractive interface, which improves cognitive performance and slows cognitive deterioration processes. Some apps for older adults are focused on cognitive training or cognitive assessment. Health care professionals use other apps only for interpretation and presentation of results. The app in this study combines training and presents the results for all users. Likewise, the exercises included in the app were specially designed for the elderly population and were based on standards and validated tests, such as the MMSE and the Neuropsi. It is important to highlight this point because it allowed seniors to have a better perception of instructions, images, and interaction with the app. This is unlike other apps created to suit the specific needs of only the physician. Finally, in Mexico, there is no documented evidence of a similar app for the older adult. This is the first pilot study on this topic in the country. Lastly, participants perceived this digital support as more attractive and ludic, resulting in higher motivation and emotional levels. An element that played an essential role in the participants' acceptance of the technology was the fact that the EG participated in a Digital Literacy Workshop before implementation. This might have generated greater confidence when executing exercises on the tablet.

Limitations

There are many limitations to this study. They are mainly related to the number of adults who took part in the intervention. This sample is a nonrepresentative one, and underrepresentation of the whole population could have taken place. Nevertheless, we followed the World Medical Association Declaration of Helsinki [41] on the C30 principle, and every subject had access to the diagnostic and therapeutic methods. Even though it is necessary to consider that very few interventions of this kind have been implemented and documented in Mexico, this pilot study may be used to gain funding for a larger, more thorough research project. A more systematic study and with a broader scope is required to determine if the benefits found in this pilot study could be replicated. Randomized trials in subsequent studies may prove this type of treatment efficacious.

Conclusions

This article describes a pilot study and the validation of a cognitive stimulation app for adults over 60 years of age. The technical developments considered for the design of the app emphasize the importance of adopting user-centered design methodologies, especially for the development of apps aimed at the elderly population. The results of this study highlight that both groups obtained better results in the postevaluation. The participants were able to execute the exercises repetitively, which the CG could not accomplish since they had to respond on the manual and no further attempts were provided. However, both groups increased their score in the neuropsychological evaluations. Even when the MMSE and the Neuropsi evaluate almost the same psychological functions, the Neuropsi considers 130 as its maximum score, versus the 30 items of the MMSE. Therefore, a general improvement in both groups seems to have taken place.

Another important point is that the exercises were not the same as the tests, and besides levels of difficulty were added, even

when a learning effect might have been taken place in both groups. It was possible to demonstrate that the stimulation provided by using an app is appropriate and that it allows adults to stimulate or maintain their cognitive capacity. This was reflected in better results and the preservation of cognitive capacity.

Validation of the app emphasizes the perceived benefits and the relevance of adopting ICTs by older adults, especially for their health care. In the validation analysis, all the participants were aware of the convenience of ICTs for cognitive stimulation. Since the 22 participants reported to have the intention of using technological methods to improve their cognitive skills, it is clear that there is a specific need for creating more services like this one.

Finally, it must be recognized that to carry on this study, technical and institutional requirements had to be fulfilled. Older adults must have access to this technology to gain access to mobile cognitive stimulations due to institutional agreements and permissions. The purchase of ICT devices had to be done because some older adults could not afford their cost. It has been demonstrated that interventions are capable of improving cognition, but the importance of their structure and deliverance to ensure that people become engaged must also be considered.

For future work, more exercises are being designed to be integrated into the app. These exercises seek to stimulate other cognitive areas that were not included in this study. We will continue with the commitment of digital literacy of elderly adults from the state of Hidalgo, Mexico. This will help the elderly adults to develop the necessary technical skills that allow them to use the app more efficiently. Also, the authors consider using a "waiting group" in the future to compare this functioning.

Acknowledgments

We thank the seniors for their participation in this study. Also, we thank Patricia Padilla Muñoz, the Coordinator of the IGC de Punta Azul for the facilities granted to complete this research. We thank the Instituto de Ciencias de la Salud (ICSa) for allowing access to computer rooms. Finally, we thank Reyna Lopez-Ble for the revision of the English language manuscript. RMA received a fellowship from Academia Mexicana de Ciencias (June-August 2017). The authorities of the Instituto de Ciencias de la Salud (ICSa) of the Universidad Autónoma del Estado de Hidalgo (UAEH) accepted this research. It belongs to the project titled "Design of Tests to Prediagnose and Diagnose Elderly Adults in Hidalgo at the Bio-Psycho-Social Areas" registered with the CONACyT, through its "Cátedras CONACyT" program. This publication was financed with resources from PRODEP 2018.

Authors' Contributions

CIMA, ARL, and EHA contributed the neuropsychological testing and selection of the exercises. CIMA and RMA planned and implemented the app. CIMA largely contributed to the description and validation of the app sections and helped design the tables and figures. CIMA, ARL, EERT, and BIO prepared the statistical analysis. All contributors verified the analysis and helped with the discussion of the manuscript. EHA and RMA helped with the references.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Cognitive interventions based on Information and Communication Technologies (ICT) reported by type of intervention, population, country, cognitive functions and significant findings.

[PDF File (Adobe PDF File), 27KB - resprot_v7i8e172_app1.pdf]

Multimedia Appendix 2

Informed consent.

[PDF File (Adobe PDF File), 72KB - resprot_v7i8e172_app2.pdf]

Multimedia Appendix 3

Description of the cognitive stimulation exercises included in the intervention.

[PDF File (Adobe PDF File), 9KB - resprot_v7i8e172_app3.pdf]

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Abbreviations

ADL: activities of daily living
ANOVA: analysis of variance
CG: control group
EG: experimental group
IGC: Centro Gerontológico Integral of Pachuca de Soto

ICT: Information and Communication Technologies
ICSa: Instituto de Ciencias de la Salud
MCI: mild cognitive impairment
MMSE: Mini-Mental State Examination
PHP: hypertext preprocessor
UAEH: Universidad Autónoma del Estado de Hidalgo
TAM: Technology Acceptance Model

Edited by G Eysenbach; submitted 08.12.17; peer-reviewed by S Aggarwal, A Blokland, R Matek; comments to author 28.12.17; revised version received 08.01.18; accepted 29.06.18; published 21.08.18.

Please cite as:
Martínez-Alcalá CI, Rosales-Lagarde A, Hernández-Alonso E, Melchor-Agustin R, Rodriguez-Torres EE, Itzá-Ortiz BA
A Mobile App (iBeni) With a Neuropsychological Basis for Cognitive Stimulation for Elderly Adults: Pilot and Validation Study
JMIR Res Protoc 2018;7(8):e172
URL: http://www.researchprotocols.org/2018/8/e172/
doi:10.2196/resprot.9603
PMID:30131319

Protocol

Evaluating the Diagnostic Accuracy of Reflectance Confocal Microscopy to Diagnose Skin Cancer: Protocol for a Prospective, Multicenter Study

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Abstract

Background: In the United Kingdom, 350,000 patients per year are referred to hospital clinics with suspicious moles, and approximately half undergo a biopsy to identify the 5%-10% who require further treatment. If cancer cannot be ruled out clinically and on the basis of biopsy results, the lesion is surgically removed. One type of precancerous mole, called lentigo maligna, is particularly challenging to delineate and treat. Reflectance confocal microscopy (VivaScope, Caliber Imaging & Diagnostics) is an imaging technique that can supplement dermoscopy in identifying whether a clinically suspicious mole is malignant and can better assess lentigo maligna margins for excision. It allows clinicians to visualize the skin lesion to a depth of 200 microns with subcellular resolution, described as quasi-histological, and therefore better guide more accurate diagnoses.

Objective: The aim of this paper is to describe a prospective, single blinded, multicenter study to examine patients with clinically suspicious moles or lentigo maligna to determine whether confocal microscopy can both reduce the number of unnecessary biopsies of moles and more accurately guide the surgical excision margins of lentigo maligna.

Methods: This study will prospectively recruit adults into the following two cohorts: diagnostic accuracy and margin delineation. The diagnostic accuracy cohort will assess people with clinically suspicious lesions suspected of being diagnosed with melanoma and having an equivocal finding on dermoscopy or persistent clinical suspicion despite normal dermoscopy. Diagnostic accuracy will include the sensitivity and specificity of VivaScope in comparison with the histological diagnosis as the gold standard for patients. The margin delineation cohort will assess the ability of VivaScope to accurately delineate the margins of lentigo maligna compared with that of dermoscopy alone using margins taken during Mohs micrographic surgery as the gold standard. The primary study outcomes will be the diagnostic accuracy of VivaScope for the first cohort of patients and margin agreement between VivaScope and the final pathology report for the second cohort of patients.

Results: Funding for this proposed research is being secured.

Conclusions: The outcomes of the proposed study will indicate how many biopsies of nonmelanoma lesions, which are potentially unnecessary, could be prevented. This would reduce patient anxiety and cost to the National Health Service (NHS) in the United Kingdom. Improved margin delineation of lentigo maligna could also improve the surgical clearance rates and decrease overall cost. The results would demonstrate whether the adoption of VivaScope would potentially benefit patients and the NHS.

Registered Report Identifier: RR1-10.2196/9296

(JMIR Res Protoc 2018;7(8):e170) doi:10.2196/resprot.9296

KEYWORDS

melanoma; lentigo maligna; biopsy; dermoscopy; reflectance confocal microscopy

Introduction

Background

In the United Kingdom, 350,000 patients per year are referred to hospitals with suspicious moles, and approximately half undergo a biopsy to identify the 5%-10% who require further treatment [1]. Typically, a dermatologist diagnoses skin cancer based on clinical history and examination that is aided by a dermatoscope. If cancer cannot be ruled out, the lesion is surgically removed or in some cases, it is monitored by repeated visits to the clinic. Lentigo maligna (LM), a premalignant lesion that grows slowly on sun-exposed sites and can transform into a melanoma, is particularly challenging to treat. Because it is difficult to identify the transformation of LM into a melanoma, it is usually treated when it is found, before malignant transformation. Its margins are difficult to assess in a visual examination with or without the aid of a dermatoscope. The consequence of this uncertainty is that despite surgery with a 5 mm margin around the clinical edge, the treatment has high rates of incomplete excisions and recurrence rates are high [2].

Reflectance confocal microscopy (RCM) is a noninvasive real-time imaging technique used at the bedside. The VivaScope 1500 and 3000 (Caliber Imaging & Diagnostics) use near-infrared point-laser light to image the top layers of the skin, blood vessels, and pigment with a cellular resolution [3]. The technology can help identify whether a clinically suspicious mole is histologically suspicious and needs to be removed. It can also guide visualization of the true margins of LM prior to surgical removal. In these cases (as in this study), Mohs surgery can be used, which involves examination of the entirety of the surgical margins in multiple stages to ensure that the whole tumor is removed.

In 2015, the National Institute for Health and Care Excellence (NICE) Diagnostics Assessment Programme published Diagnostics Guidance 19 (DG19) [3], which examined the use of VivaScope and its potential role in the National Health Service (NHS). DG19 stated that there was insufficient evidence to recommend the routine adoption of VivaScope in the NHS for the assessment of skin cancer. The guidance identified a number of studies that have shown that VivaScope can improve the specificity of melanoma diagnosis when used as an adjunct to dermoscopy [3].

VivaScope examination in patients with difficult-to-diagnose moles has been shown to have higher specificity than dermoscopy [4]. This can potentially reduce unnecessary biopsies by enabling a more accurate clinical diagnosis.

VivaScope can also more accurately define the edges of LM in comparison with dermoscopy [5]. This is particularly important because these lesions occur on the face in the elderly and are often large, requiring complex reconstructive surgery. A more refined definition of LM margins is expected to better guide patients' expectations of treatment, improve surgical planning and cure rates, and decrease the amount of normal tissue removed during surgery.

Although VivaScope may improve patient care and management [4-11], there is a lack of data from the United Kingdom [3]. It is felt that the applicability of the existing evidence to a UK population is unclear. Relevant differences between the United Kingdom and other countries with evidence of the impact of VivaScope are as follows: the underlying incidence of melanoma in different patient populations, the fact that most treatment in United Kingdom is performed by a public health system (NHS), there are fewer dermatologists in the United Kingdom, and most screening in the United Kingdom occurs in primary care prior to specialist referral. Therefore, the guidance recommended further research to address uncertainties in the potential benefits of using VivaScope to patients and the NHS.

The proposed diagnostic accuracy study will (1) assess the specificity, sensitivity, and positive and negative predictive value of VivaScope (following dermoscopy) to diagnose melanoma using the histological assessment of the surgically excised lesion as the gold standard and (2) assess the ability of VivaScope to accurately delineate the pathological margins of LM compared with that of dermoscopy alone using histological assessment of the lateral margins taken during Mohs micrographic surgery as the gold standard. If the outcomes of the proposed study are in favor of VivaScope, its adoption would potentially benefit patients and the NHS.

Objectives

The aim of this study is two-fold; the study aims (1) to assess the efficacy of VivaScope as an additional diagnostic tool prior to the surgical management of patients with suspected melanoma (first cohort) and (2) to define the surgical margins before the surgical management of LM (second cohort).

Methods

Type of Study

This is a prospective, experimental, multicenter study with a diagnostic accuracy cohort and a margin delineation cohort. The study design was chosen because it is pragmatic and represents the current NHS pathway for the diagnosis of melanoma.

Setting

For a UK study, patient recruitment for the diagnostic accuracy cohort should occur in skin cancer screening clinics within the NHS. Image interpretation should also be carried out at additional reporting sites. The sites can be linked to the image interpretation sites with VivaNet, a Web-based portal for image viewing and reporting provided by the manufacturer of VivaScope.

Recruitment to the margin delineation cohort must be from a Mohs center in the United Kingdom. The involvement of additional independent reporting clinicians for the margin delineation protocol is not possible because the handheld

VivaScope 3000 is used to delineate the margin using the real-time images.

Study Population

Consecutive patients will be included if they are at least 18 years of age and can give written informed consent.

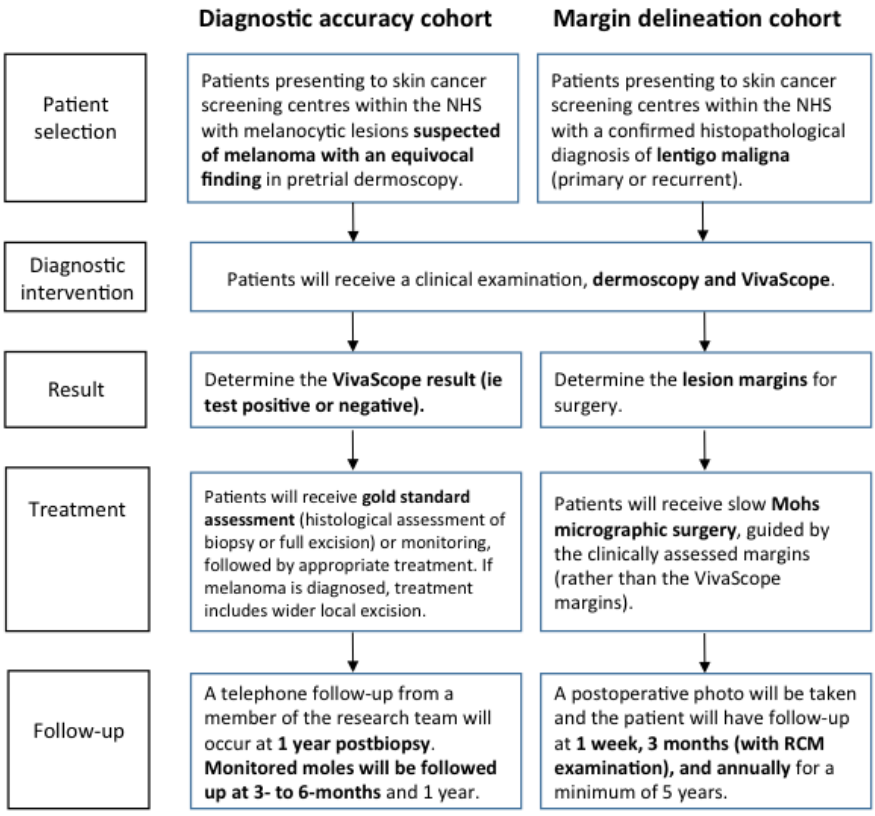
Diagnostic Accuracy

The diagnostic accuracy cohort will include patients with pigmented lesions suspected of being diagnosed with melanoma and having an equivocal finding on dermoscopy or persistent clinical suspicion (despite normal dermoscopy), who are undergoing excision or being followed up for monitoring. In addition, patients with equivocal lesions that are being monitored will also be imaged but will not have a histologically confirmed diagnosis. Such patients will be reviewed at 3 months and followed up at 1 year. If the lesion has not been removed by 1 year, this will be used as a surrogate marker for true negatives. Potentially, lesions considered equivocal on dermoscopy and initially intended for monitoring, but subsequently considered suspicious of melanoma on confocal microscopy, could be considered for excision. It will be documented if this influenced the decision to excise the lesion at this time. Where a patient has more than one eligible lesion, a maximum of one lesion per patient will be assessed. In these cases, the clinician will be instructed to include the most suspicious lesion in the study. Assessment will done by an experienced dermatologist.

Patients will be excluded from the diagnostic accuracy cohort if they have a clear positive finding (melanoma) from dermoscopy, as assessed by an experienced dermatologist or have a clear negative finding (no melanoma) from dermoscopy, as assessed by an experienced dermatologist, unless there is persistent clinical suspicion. Patients who have atypical mole syndrome or a genetic disease with high risk of melanoma (eg, xeroderma pigmentosum), hyperkeratotic lesions, and lesions within mucous membranes (eg, inside the mouth, very close to the eyes, and on the genitals), where it is not possible to perform imaging, will also be excluded.

Patients are assessed for inclusion or exclusion based on the clinical examination of the mole (usually includes a clinical history, unaided visual and dermoscopic assessment of the mole, and assessment of a patient's other moles for comparison). The assessment by the referring clinician that a mole is equivocal is made primarily on the basis of dermoscopy findings but other aspects of the assessment will also influence this. The dermoscopic assessment of the lesion being equivocal by a referring clinician will be based on a combination of algorithmic and intuitive approaches. This may result in a mole being deemed equivocal despite a normal formal dermoscopic assessment score. Because the inclusion criteria for this study are designed to reflect the clinician's suspicion and normal clinical practice, the referring clinician will not be expected to formally document a dermoscopic score, only to indicate the reason for referral (ie, monitoring or excision). On entering the study, the patient will be assessed via a second dermoscopy examination by the research team. This examination will be formally scored and the dermoscopic image photographed. The patient will remain in the study despite the outcome of the study dermoscopy for the reasons explained above.

Figure 1. Study procedure. NHS: National Health Service; RCM: reflectance confocal microscopy.



Margin Delineation

The margin delineation cohort will include patients with a confirmed histopathological diagnosis of LM (primary or recurrent) who are undergoing Mohs surgery. Patients will be excluded if LM melanoma is diagnosed during the Mohs procedure.

Study Procedure

The primary study outcomes will be the diagnostic accuracy of VivaScope for the first cohort of patients and margin agreement between VivaScope and the final pathology report for the second cohort of patients.

The study procedure is outlined in Figure 1.

Diagnostic Accuracy

In the diagnostic accuracy cohort, after the participant is enrolled and provides consent, VivaScope imaging will be used as an adjunct to clinical examination for all equivocal moles. The clinical examination will take approximately 5 minutes with the dermatoscope and approximately 15 minutes with VivaScope 1500 (fixed head). The investigating clinicians will assess the moles as safe, equivocal (either monitor or excise), or suspicious. Based on current practice, moles that are monitored are followed up at 3 months to assess changes over time. At this appointment, a decision is usually made to either excise the mole or discharge the patient. Lesions considered equivocal on dermoscopy but suspicious of melanoma on confocal microscopy may be reclassified for excision, in which case this would be documented.

A medical photograph, including dermoscopic images of the lesion, will be taken prior to surgical excision or monitoring of the lesion. To avoid potential bias, the dermoscopy score of the lesion assessed by the research team, medical photograph, type of clinical concern, clinical history, and patient risk factors for melanoma will all be assessed and documented before any histological results are available and made known to the investigator. For patients with multiple lesions, the most suspicious equivocal lesion will be imaged.

Margin Delineation

For the margin delineation cohort, once the participant is enrolled and consent is obtained, relevant clinical history and a preoperative photograph will be taken. The clinical margins of LM will be determined by clinical and dermoscopic examination, which will take approximately 15 minutes. A trained professional will also examine the lesion margins with the handheld VivaScope 3000 device, which will take approximately 45 minutes. The aim will be to delineate the tumor circumferentially, imaging radially outwards from the center in 4-8 directions. Where no features of LM are seen, a mark will be placed on the skin. A photograph of the marks will be taken with a ruler placed on the skin for scale and with this information, the preoperative size can be calculated via computer software.

Prior to surgery, the margin will be delineated clinically and then using VivaScope. These margins will both be photographed so that any differences can be calculated. Margin assessment may be performed during the surgical preassessment stage and not on the day of surgery, so as not to delay surgery on the day. For cases not delineated by both techniques on the day, the clinical margin will be redrawn and photographed again. Because LM grows slowly, we do not expect any differences in the measured clinical size of LM (between the preoperative assessment and on the day of surgery). Any differences seen will be assumed to be attributable to variation in the measuring technique, unless photography shows an unequivocal change in the size and shape of LM.

All patients going through surgery will undergo slow Mohs micrographic surgery. The margins, as assessed by visual examination (including dermoscopy), will be used to guide the first stage of surgery rather than the RCM-measured margin. The first stage of slow Mohs surgery will be performed with a 2-mm margin, in addition to the clinical margin. The excised tissue will be fixed in formalin and then sectioned and stained using hematoxylin and eosin stains the following day. All slides will be read by a Mohs surgeon and a histopathologist. During each further stage of Mohs surgery, 2 mm of tissue around the positive margin will be removed.

Once the lesion is histologically clear, the number of layers (number of small pieces of skin removed during Mohs surgery) and their locations (taken from photographs) can be used to calculate the increase in size from the clinical margin. This will be aided by the digital measurements obtained from clinical photography to determine the surgical defect size, and this method may account for skin tension (which is lost once the skin is cut and changes in size and color). Therefore, for example, if the clinical margin were correct initially, the surgical defect size would be measured to be exactly 2 mm larger in all directions. This same approach will be used to compare the clinically and confocally delineated margins. The difference between the presurgical margins previously measured using VivaScope and the calculated margins of the surgical defect will be calculated.

LM patients will have follow-up at 3 months and annually for a minimum of 5 years to monitor recurrence.

Outcome Assessment and Data Collection

Diagnostic Accuracy

Clinical assessment of the lesion and confocal imaging will be performed prior to surgical excision. It will be documented if VivaScope imaging findings are positive, negative, or the lesion could not be imaged (due to technical reasons). As noted previously, it will also be documented if the imaging resulted in an equivocal mole being reclassified as a suspicious melanoma, affecting the decision to excise the lesion. Additional remote clinicians will also perform an assessment independently. These remote assessing clinicians will have access to the relevant clinical history, dermoscopy, and clinical and confocal images. However, they will be blinded to the histological diagnosis. The clinicians will be asked to complete a Web-based evaluation form that will include a description of VivaScope imaging findings as well as a diagnostic judgment rated as positive or negative for the presence of cancer. VivaNet, a telepathology network for reviewing VivaScope imaging (not in real time), will be used to assess the images remotely.

Histopathological assessment, the reference standard for diagnostic accuracy, will be performed by a consultant dermatopathologist blinded to the result of RCM examination to eliminate review bias.

Margin Delineation

For the second cohort, the size of the margins will be recorded for VivaScope measurement as well as for slow Mohs surgery. The calculation of the surgical defect will also be recorded. The outcome measure will be the difference between the predicted margins using VivaScope and the Mohs size of the defect in the same patient. Thus, we are comparing the confocal microscope margin with the clinically predicted margin in each patient. Additional data will be collected on the time it takes to obtain test results, interobserver variability in the interpretation of VivaScope imaging, imaging failure rate, morbidity associated with biopsy or surgery, and adverse events from biopsy or surgery. The clinician administering the tests will record results on data collection forms by hand.

Sample Size

Diagnostic Accuracy

Based on a systematic review and meta-analysis, the expected VivaScope specificity compared with the gold standard of histopathology is 90% [4], but for this calculation, a conservative estimate of 80% was used. A sample of 100 (true negatives) would provide a 95% CI for this VivaScope specificity of 70.8%-87.3%. This would allow us to conclude that the true specificity is >70%.

Assuming a disease prevalence of 20% (among this patient group who are equivocal on dermoscopy), 80% of patients tested will be true negatives on biopsy or after 1 year of monitoring without excision. Therefore, to achieve 100 true negatives, 125 patients will be included in this study (ie, tested by VivaScope, dermoscopy, and biopsy or monitoring).

Margin Delineation

The actual surgical margins achieved (which will have been guided by dermoscopy) will be compared with the hypothetical margins indicated by VivaScope for each patient. The paired mean difference in margins between surgery and VivaScope will be compared using the paired *t* test. Assuming a moderate standardized effect size of 0.4 and 90% power, a sample of 68 patients is required (PASS v15.0 software; NCSS, Utah, USA). A standardized effect size has been used owing to the absence of any known SD for paired differences in margins between these two approaches.

Statistical Analyses

Diagnostic Accuracy

We will calculate the specificity of VivaScope (95% CI) in predicting true negatives, as defined by histopathology or 1 year of monitoring without excision of the lesion. Specificity is calculated as negative VivaScope results divided by true negatives. The sensitivity of VivaScope will also be calculated, as positive VivaScope results in the numerator divided by true positives in the denominator, to check that the expected gain in specificity is not at the cost of sensitivity. True positives will be defined by the histopathology of excised lesions, including those excised during the 1-year monitoring period. Positive and negative predictive values will also be calculated.

We will compute kappa statistics to calculate the interobserver agreement. The conventional classification on the basis of kappa statistics from almost perfect agreement (>.81), moderate agreement (.41-.60), and slight to poor agreement (<.20) will be used [12].

Margin Delineation

McNemar's test will be used to compare the frequency of surgery documenting clear margins for VivaScope compared with clinical examination with dermoscopy, and the paired *t* test will be used to compare the mean margins.

Ethics and Governance

Prior to initiating this study, the protocol would need Health Research Authority (HRA) approval, wherein HRA staff and an independent Research Ethics Committee will assess governance and ethical compliance for projects led from the NHS in the United Kingdom. Patients in the diagnostic accuracy cohort will be approached after their initial appointment if they are eligible to participate, and LM patients will be approached during their first consultation. Patients will be given information about the study and asked whether they would like to participate. If the patient is interested, the clinician will explain the aims, methods, and anticipated benefits of the study. The patient will be able to ask any questions or voice any concerns about the study prior to giving written consent. The patient will be able to withdraw from the study at any time.

The investigator has a responsibility to ensure that patient anonymity is protected and maintained. The investigator will ensure that identities are protected from any unauthorized parties. Information regarding study patients will be kept confidential and managed in accordance with the General Data Protection Regulation, NHS Caldicott Guardian requirements, The Research Governance Framework for Health and Social Care, and Research Ethics Committee approval. A pseudoanonymized identifier will be necessary for the margin delineation cohort.

Data will stay in the NHS and within the University sponsor's computer system under normal arrangements for patient confidentiality and will include encryption and locked storage of all patient data. The chief investigator, principal investigator, and authorized researchers on the study team will have access to the information for purposes of data monitoring, validation, and analyses.

Results

Funding for this proposed research is being secured.

Discussion

Strengths

This study aims to address the uncertainties identified in NICE DG19 by carrying out a prospective diagnostic accuracy study in the United Kingdom. NICE DG19 states that additional

evidence should be collected relating to the use of VivaScope to inform decisions as to whether to biopsy and excise suspicious skin lesions as well as to define margins in LM patients.

The implementation of VivaScope in clinical practice has the potential to improve the accuracy of the diagnostic process. VivaScope is noninvasive and would reduce the number of surgical interventions. It would also lead to a better patient experience, particularly lessening patient anxiety due to uncertainty while waiting for a diagnosis. In the margin delineation cohort, VivaScope could minimize the amount of normal tissue excised unnecessarily and reduce the duration and number of stages of the Mohs surgery.

The outcomes captured in the study aim to address the recommendations from NICE DG19, which prompted the development of this protocol. NICE will update its guidance for clinical use if substantive evidence is generated as part of this study on VivaScope. NICE guidance would give a strong steer to the national and international adoption of VivaScope. Thus, this study would have a high impact.

Challenges

Extending the study to multiple sites may be a better demonstration of applicability to the NHS. A major current drawback to this is the lack of suitable clinical centers in the United Kingdom that currently have the expertise in using VivaScope. In practice, the variable levels of expertise and cost of training could be a barrier for the adoption of the device. There is potential to find greater benefit in clinics with a large cohort of patients being monitored for high-risk moles but this would apply to only a limited number of services in the United Kingdom, as opposed to every hospital that has referrals for skin cancer.

Future Directions

This study should influence a wider uptake of VivaScope for the diagnosis of pigmented lesions at the bedside, reducing unnecessary excisions. The results from this study should also increase the use of VivaScope for margin delineation in LM patients in the United Kingdom. As the technique becomes more established, it will be useful to conduct further research on the use of VivaScope to replace confirmatory biopsies for basal cell carcinomas prior to definitive treatment.

Acknowledgments

King’s Technology Evaluation Centre is commissioned by the NICE Medical Technologies Evaluation Programme to deliver evidence preparation and assessment services. The views expressed are those of the authors and not necessarily those of NICE or the NHS. This work was supported by the Wellcome Engineering and Physical Sciences Research Council (EPSRC) Centre for Medical Engineering (WT 203148/Z/16/Z).

Authors' Contributions

AC and NDH led the development of the design of the study protocol. NDH led on drafting the manuscript. All authors participated in critical review of the methods and read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DG19: Diagnostics Guidance 19
LM: lentigo maligna
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
RCM: reflectance confocal microscopy

Edited by G Eysenbach; submitted 30.10.17; peer-reviewed by C Eldredge, B Ansa; comments to author 15.03.18; revised version received 07.05.18; accepted 11.05.18; published 09.08.18.

Please cite as:
Herz ND, Chalkidou A, Reid F, Keevil SF, Coleman A, Craythorne E, Patalay R
Evaluating the Diagnostic Accuracy of Reflectance Confocal Microscopy to Diagnose Skin Cancer: Protocol for a Prospective, Multicenter Study
JMIR Res Protoc 2018;7(8):e170
URL: http://www.researchprotocols.org/2018/8/e170/
doi:10.2196/resprot.9296
PMID:30093369

Protocol

A Multicenter Before-After Study on Reducing Unnecessary Diagnostics by Changing the Attitude of Caregivers: Protocol for the RODEO Project

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Abstract

Background: Appropriate use of diagnostic laboratory tests is challenging, and estimates of 20% for overutilization and 45% for underutilization have been reported. Introducing effective and sustainable solutions to stimulate optimal use of laboratory testing in clinical practice is a challenge. A recent pilot study from our group, focusing on increasing the awareness about appropriate laboratory testing with the aim of changing the mindset of health care workers, has shown promising results. In this project, we aim to extend this multistep intervention to the internal medicine departments of 4 large Dutch hospitals. We aim to reduce unnecessary laboratory testing by 5%.

Objective: Our primary objective is to determine the effect of our intervention on diagnostic laboratory test order volume. Our secondary objectives are to determine the effect of our intervention on laboratory expenditure and order volumes, expenditures for other diagnostic modalities, and clinical patient outcomes. We will also analyze the barriers and facilitators for deimplementation of unnecessary laboratory testing.

Methods: The main interventions of this before-after study will be an intensified supervision of residents by experienced physicians regarding test ordering, creating awareness through education and monthly feedback on ordering patterns, and changes in (computerized) order entry systems.

Results: At the time of publication of this protocol, the project is in the phase of data collection. We expect to present data on reduction early in the fourth quarter of 2018.

Conclusions: In this project, we aim to reduce the unnecessary diagnostic testing in the internal medicine departments of 4 teaching hospitals. Although the main interventions will be similar, each clinic is given the opportunity to focus on the specific facets of the interventions as deemed useful according to the local situation. If effective, the study provides a framework for a nationwide initiative for reducing inappropriate laboratory testing.

Registered Report Identifier: RR1-10.2106/10473

(JMIR Res Protoc 2018;7(8):e10473) doi:10.2196/10473

KEYWORDS

diagnostic laboratory test; diagnostic testing; protocol; implementation

Introduction

Over the past decades, a marked rise in health care expenses has been observed in Western countries. In the Netherlands, the burden of health care on the gross domestic product has increased from 7.9% in 1998 to 10.5% in 2016, corresponding to an increase from approximately 30.9 to 73.7 billion euros. A large part of the total health care expenditure consists of hospital care, including diagnostic testing [1,2]. The volume, and consequently the costs, of performing diagnostic tests is increasing, with earlier studies reporting a doubling of the rate every 5-10 years over the past decades [3].

In 2015, Kobewka et al [4] reviewed numerous international studies and concluded that a considerable proportion of performed (laboratory) tests were unnecessary, that is, they did not contribute to patient care. A review addressing the appropriateness of diagnostic laboratory testing, as judged by the presence of multiple appropriateness criteria (eg, criteria based on testing frequency, choice of test compared with possible alternatives, and probability of abnormal test results), has reported a mean rate of overutilization of approximately one-fifth from 1997 to 2012 [5]. Consequently, laboratory testing is often targeted in efforts to reduce health care expenditure. Besides the financial impact, overutilization increases the number of false-positive results, which leads to more, sometimes invasive and potentially harmful, tests [6]. Also, excessive blood draw can result in iatrogenic anemia and can lead to less patient-friendly practice, for example, through painful punctures and unnecessary trips to the hospital [7].

In 2009, a multifaceted intervention focusing mainly on laboratory test reduction was implemented at the internal medicine department of the VU University Medical Center (VUmc). Utilization of other diagnostics, such as radiology, declined too. Our efforts resulted in a 13% gross reduction in diagnostic expenditure compared with that in the previous year. When extrapolating these results, nationwide implementation of these interventions could result in a potential saving of millions of euros.

In the "Reduction of unnecessary diagnostics through attitude change of the caregivers" (RODEO) project, we will assess the effects of a multifaceted intervention aimed at improving awareness about (in)appropriate laboratory testing on the volume and costs of diagnostic testing and clinical outcomes of patients in the internal medicine departments of multiple peripheral teaching hospitals over 6 months. We aim to reduce (unnecessary) diagnostic testing by 5%. Our primary focus will be on laboratory testing, although we will also assess the effects of our intervention on the volume and costs of other diagnostics modalities. In addition, we will assess the sustainability of the interventions during an additional 8-month period. We will also analyze the process of deimplementation of unnecessary laboratory testing in the participating hospitals, aiming to identify barriers and facilitators.

This project is a part of the "To do or not to do? Reducing low-value care" program aimed at reducing low-value care [8]. The program was initiated by the Dutch Federation of University Medical Centers.

Methods

Study Design and Setting

This multicenter before-after study was conducted at the internal medicine departments (inpatient, outpatient, and emergency departments) of the Zaans Medical Center (Zaandam), Meander Medical Center (Amersfoort), North-West Hospital group (location Alkmaar), and Spaarne Gasthuis (locations Haarlem and Hoofddorp), which are all teaching hospitals in the Netherlands; in the rest of the document, we have referred to these participating hospitals anonymously as hospital 1-4.

Access to timely data on volume and costs of different diagnostic modalities (laboratory, radiology, microbiology, pathology, and nuclear medicine) for the duration of the project and for the 3 preceding years was a criterion for inclusion. Another criterion for inclusion was consent of the participating hospital's Board of Directors. The project protocol was assessed by the Medical Ethics Review Committee of VUmc. They determined that the Medical Research Involving Human Subjects Act does not apply to this project and that official approval by the Medical Ethics Review Committee is not required. Local feasibility was approved by the local ethics committees and Board of Directors of all participating hospitals. Data were collected anonymously.

Deimplementation Strategy

The study consists of 3 time periods: 3-4 months of preintervention, 6 months of intervention, and 8 months of postintervention. The study was started in August 2016; after the study period ends, we plan to continue monitoring these interventions to assess sustainability.

Before the start of the preintervention period, the internal medicine departments of the participating hospitals were contacted and informed about the project. Upon inclusion of a department, cooperation agreements were signed by the principle investigator of the hospital, and thereafter, a project team consisting of a senior internist (ambassador), internal medicine resident, a business intelligence collaborator, and a clinical chemist were formed.

Preintervention Period (3-4 Months)

During the preintervention period, data on volume and costs of diagnostics as well as on patient outcomes from the previous 3 years were collected. Also, data on the characteristics of the participating departments such as the number and years of experience of residents and supervising physicians, methods

and frequency of supervision of residents, and characteristics of ordering systems were collected. The preintervention period started in August 2016 at hospitals 1 and 2, in September 2016 at hospital 3, and in November 2016 at hospital 4.

Intervention Period (6 Months)

At the start of the intervention period, a launching conference took place with the members of all the participating project teams. Each project team was requested to give a presentation on the characteristics of their department, data on their ordering patterns over the previous years, and previous projects related to this topic. In addition, each project team was requested to present interventions tailor-made for their department structure.

We also assessed foreseen barriers and facilitators for deimplementation and discussed how to tackle them, if necessary. The program of this launching conference can be found in Multimedia Appendix 1.

Upon starting the intervention period, data collected in the preintervention period and planned interventions were presented by the local project teams to the caregivers working in their departments. During the intervention period, the local project teams performed the interventions and had frequent periodic progress meetings with the coordinating project team. The interventions performed and how they were developed have been described in more detail in the subsection "Description of interventions."

A second conference was organized in which the project teams presented their results from the initial months, exchanged experiences and ideas on how to proceed in the remaining months of the project, and discussed how to sustain the effects after the termination of the active intervention period. The program of this conference can be found in Multimedia Appendix 1.

The intervention period started in November 2016 at hospitals 1 and 2, in January 2017 at hospital 3, and in March 2017 at hospital 4.

Postintervention Period (8 Months)

In the postintervention period, the sustainability of the intervention was analyzed. During this period, a third joint conference was organized with all the participating project teams in which the project teams were requested to present their results and exchange experiences and ideas on how to further sustain the achieved effects. The program of this conference can be found in Multimedia Appendix 1. Data on diagnostic volume and costs and patient outcomes were reanalyzed.

The postintervention period started in May 2017 at hospitals 1 and 2, in July 2017 at hospital 3, and in September 2017 at hospital 4. The postintervention period ended in December 2017 at hospitals 1 and 2, in February 2018 at hospital 3, and in April 2018 at hospital 4. We will continue to monitor the progress and results for 12 months.

At the time of publication of this protocol, the project is in the data collection phase.

Description of Interventions

Target items for interventions were determined by the project team from different angles: tests that are known to be frequently overused, tests ordered in high frequency or generating high costs to the department, and diagnosis-related groups occurring in high frequency or generating high costs (compared with the benchmark, when available). All participating hospitals were given the opportunity to focus on the specific facets of the intervention as deemed useful in the local situation, thus, "tailoring" their interventions.

The interventions performed in this project were partly derived from previous literature [4,9], in which the interventions were divided into the following categories: education, audit and feedback methods, (computerized) provider order entry system changes, and others. To develop and classify the interventions in the RODEO project, we used slightly different categories.

The main interventions were intensified supervision, creating awareness, and modifications in (computerized) order entry systems. Intensified supervision of residents by senior physicians refers to explicitly focusing on indications for ordering laboratory tests and asking critical questions ("Does the result of this test add value for diagnostics, treatment, or prognosis?" "Is repetition of this test necessary at this moment?" "Is it necessary to order these tests combined?") during morning reports, daily supervision meetings, grand rounds, and other clinical meetings.

In addition to paying more attention to laboratory ordering, awareness was also created through educational sessions or emails, posters displaying recommendations and general agreements on ordering of (specific) tests, and distribution of pocket-cards containing charges for frequently ordered tests. Awareness was also created by providing feedback on (changes in) ordering patterns to the physicians working in the department.

Modifications in (computerized) order entry systems included instating time limits on ordering tests for which a repeat test is not necessary within a certain time interval and modification of existing order panels.

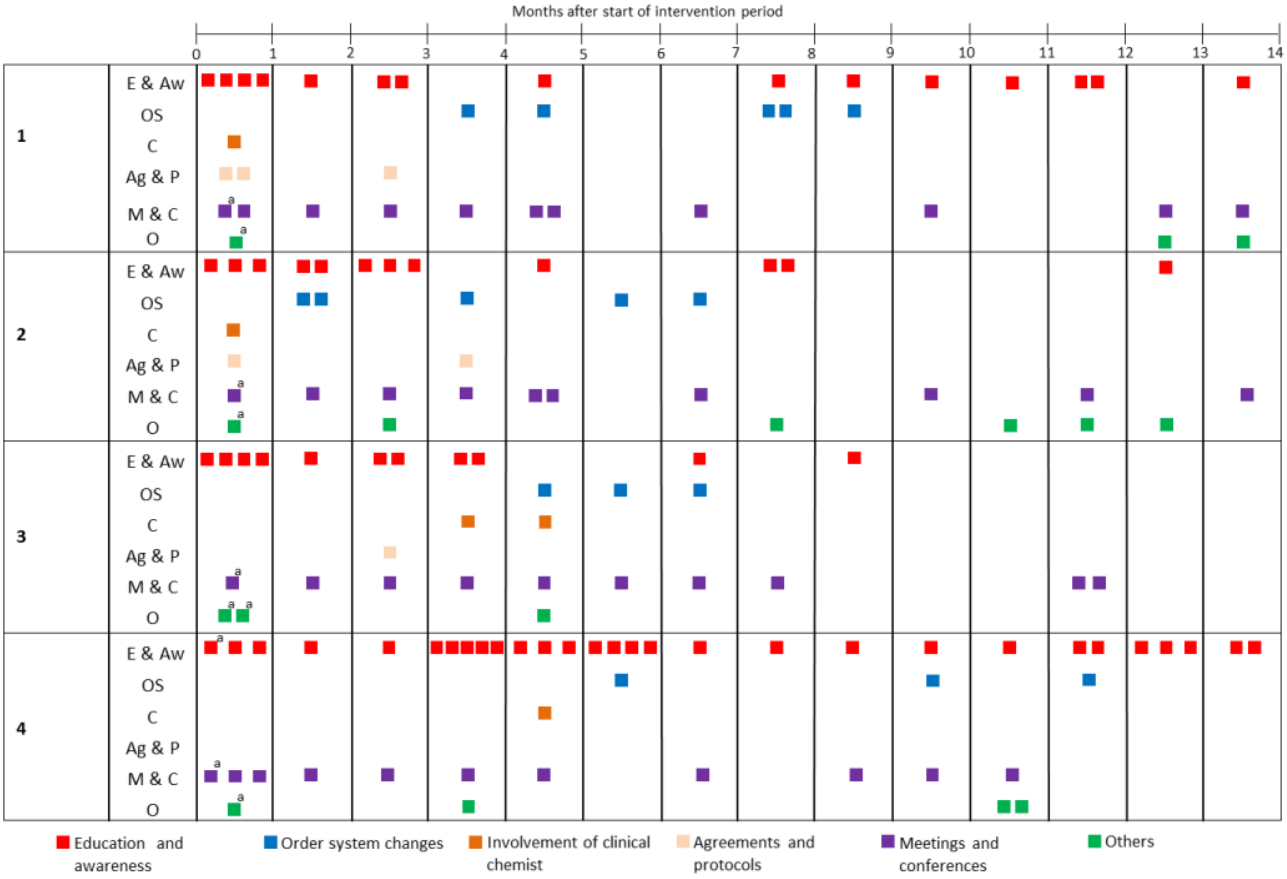
The coordinating project team and the local project teams held monthly meetings during the intervention period and bi- or tri-monthly meetings during the postintervention period. In these meetings, the progress of (development of) each intervention was discussed. Also, changes in total order volume and costs were discussed using data acquired from Business Intelligence or Business Control collaborator. If explicit focus was placed on specific tests, changes in the order volume of these tests were discussed separately.

The interventions performed in each clinic, classified by category, are displayed in Figure 1. Details on each intervention can be found in Multimedia Appendix 2.

Endpoints and Data Collection

In the RODEO project, we aim to reduce the amount of (unnecessary) diagnostic laboratory testing. Based on previous experience from our pilot study, we decided to aim for a conservative estimate of 5% reduction in total test volume.

Figure 1. Timeline of interventions. a: action took place before the intervention period. E & Aw: education and awareness; OS: order system changes; C: involvement of clinical chemist; Ag & P: agreements and protocols; M & C: meetings and conferences; and O: others.



Primary Endpoint

The primary endpoint is diagnostic laboratory test order volume in the internal medicine department (inpatient, outpatient, and emergency).

Laboratory test order volume will be assessed as the total number of orders for laboratory tests and will be corrected for patient census using "standardized patient units," a measure that will be calculated using the numbers of admissions, in-hospital admission days, day care admissions, and number of first outpatient consultations [10]. Order volume and data required for calculation of the number of standardized patient units will be acquired through the Department of Business Intelligence or Business Control and the Department of Clinical Chemistry.

Secondary Endpoints

Secondary endpoints are laboratory expenditure, order volumes and expenditure for other diagnostic modalities, and clinical patient outcomes.

Laboratory expenditure will be assessed as total expenditure and corrected for patient census. Order volumes and expenditure (if possible) for other diagnostic modalities (radiology, microbiology, pathology, and nuclear medicine considered separately) will be assessed as the total number or costs of orders and will also be corrected for patient census.

To ensure that a reduction in diagnostic testing does not affect patient outcomes, we will take into account clinical patient outcomes before and after the intervention based on duration of hospital stay, 30-day readmission rate, rate of repeated outpatient visits relative to first outpatient visits, and glycated hemoglobin.

Expenditure, order volumes, data required for calculation of the number of standardized patient units, and data on clinical outcomes will be acquired through the Department of Business Intelligence or Business Control and the Department of Clinical Chemistry.

Evaluation of Barriers and Facilitators

An important part of the RODEO project is evaluating the barriers and facilitators of deimplementation of unnecessary laboratory testing. To identify these factors, questionnaires (Multimedia Appendix 3) on these topics were administered to each project team during the (pre)intervention period. During the remainder of the project, these factors were discussed during multiple conferences.

Statistical Analysis

All statistical analyses will be performed using R version 3.4.2. We will assess the volume of diagnostic tests ordered (total volume and volume of laboratory, radiology, microbiology, pathology, and nuclear medicine tests separately) during the year after the start of the intervention (ie, intervention period and postintervention period) and the preceding years.

We will adjust for patient census using "standardized patient units," a concept previously used by Dutch insurance companies

for reimbursement purposes. The number of standardized patient units will be calculated using the following formula:

(10 × number of admissions) + (0.5 × number of patient days) + (3.5 × number of day admissions) + (1.2 × number of first outpatient consultations)

An interrupted time series analysis will be performed to assess the effects of the intervention on test volume. We will use an autoregressive integrated moving average model to analyze whether the intervention led to a (more profound) change in the number of tests per standardized patient unit after the intervention. We will adjust for seasonal variation.

Results

We expected the study period to end in April 2018. Furthermore, we expect to be able to present data on reduction early in the fourth quarter of 2018.

Discussion

In this protocol, we have described the objective, design, deimplementation strategy, and endpoints of the RODEO project, aiming to reduce unnecessary diagnostic testing in the internal medicine departments of 4 large teaching hospitals in the Netherlands.

The approach used in this project was derived from an approach previously used in a pilot project within different departments of VUmc [1]. In this project, a senior physician was designated as “ambassador” or “local champion” who was responsible for coordinating and performing the interventions in the participating departments, which consisted mainly of intensified supervision, education, and feedback. During this pilot project, no modifications were made in the (computerized) order entry system. Although commitment of a supervisor has been shown to play a crucial role in the success of a project, the VUmc project identified a prominent role for residents as one of the key success factors. Furthermore, the VUmc study team found that the Clinical Chemistry department played an important role in the pilot project. Therefore, we appointed a central project team at each participating department consisting of an internal medicine supervisor and a resident, a clinical chemist, and a collaborator from the Department of Business Intelligence or Business Control.

Although the main interventions were intensified supervision, creating awareness through education and feedback, and changes in (computerized) order entry systems, each hospital was given the opportunity to focus on the specific facets of the interventions as deemed useful in the local situation. Each clinic, thus, had the opportunity to “tailor” its interventions as deemed fit, which can be considered as a strength of our approach. Another strength of our project is the inclusion of 4 relatively large teaching hospitals. A potential limitation of our approach is the nonexistence of a control group. Also, it was not possible to determine the effect of individual aspects of this multistep intervention due to the limited time available for this project. Furthermore, we did not include patients in our efforts to reduce laboratory testing. We expect the study period to end in April 2018. If effective, this study will provide a framework for a nationwide initiative for reducing inappropriate laboratory testing.

Acknowledgments

This work was supported by the Netherlands Organization for Health Research and Development (ZonMW), grant number 80-83920-98-400. This body has no role in the design of the study and collection, analysis, and interpretation of data.

Authors' Contributions

RSB, MVB, PWBN, and MTB designed the project and drafted the protocol. Funding application was arranged by RSB, MVB, PWBN, MTB, WvS, and MK. We would also like to acknowledge the contribution of “RODEO consortium” (collaborators): F Stam, Department of Internal Medicine, North-West Hospital Group Alkmaar, Alkmaar, The Netherlands; E ten Boekel, Department of Clinical Chemistry, Hematology and Immunology, North-West Hospital Group Alkmaar, Alkmaar, The Netherlands; D ten Oever, Department of Internal Medicine, North-West Hospital Group Alkmaar; J de Gans-de Wit, North-West Hospital Group Alkmaar; B ten Dam, Department of Internal Medicine, North-West Hospital Group Alkmaar; R Fijnheer, Department of Internal Medicine, Meander Medical Center, Amersfoort, The Netherlands; AW Boerman, Department of Internal Medicine, Meander Medical Center, Amersfoort, The Netherlands; JAJ Traa, Business Intelligence, Meander Medical Center; R Soetekouw, Department of Internal Medicine, Spaarne Gasthuis, Hoofddorp and Haarlem, The Netherlands; NN Radhakishun, Department of Internal Medicine, Spaarne Gasthuis, Hoofddorp and Haarlem, The Netherlands; D Castelijn, Department of Internal Medicine, Spaarne Gasthuis, Hoofddorp and Haarlem, The Netherlands; JS ten Kulve, Department of Internal Medicine, Spaarne Gasthuis; MM Buijs, Atalmedial Diagnostics Centers, Hoofddorp, the Netherlands; BA Wevers, Atalmedial Diagnostics Centers, Hoofddorp, the Netherlands; N Slager, Department of Business Intelligence, Spaarne Gasthuis; M Pels, Department of Business Intelligence, Spaarne Gasthuis; Y Bandt, Department of Clinical Pharmacy, Zaans Medical Center, Zaandam; N Osmanovic, clinical chemist, Zaans Medical Center, Zaandam; W van der Wekken, Department of Internal Medicine, Zaans Medical Center, Zaandam, The Netherlands; J Plaisier, Department of Internal Medicine, Zaans Medical Center; H Schotman, Department of Clinical Chemistry, VU Medical Center, Amsterdam, The Netherlands; J de Groot, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands, Department of Clinical Chemistry and Hematology, University Medical Center Utrecht, Utrecht, the Netherlands.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Program conferences.

[PDF File (Adobe PDF File), 40KB - resprot_v7i8e10473_app1.pdf]

Multimedia Appendix 2

Interventions by hospital.

[PDF File (Adobe PDF File), 38KB - resprot_v7i8e10473_app2.pdf]

Multimedia Appendix 3

Questionnaire "Willingness to Change".

[PDF File (Adobe PDF File), 37KB - resprot_v7i8e10473_app3.pdf]

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Abbreviations

RODEO: Reduction of unnecessary diagnostics through attitude change of the caregivers

Edited by G Eysenbach; submitted 26.03.18; peer-reviewed by N Delvaux, R Buie; comments to author 26.04.18; revised version received 14.05.18; accepted 28.05.18; published 21.08.18.

Please cite as:
Bindraban RS, van Beneden MLH, Kramer MHH, van Solinge WW, Neppelenbroek SIM, van Wijnen M, Griffioen-Keijzer A, Al-Dulaimy M, ten Berg MJ, Nanayakkara PWB
A Multicenter Before-After Study on Reducing Unnecessary Diagnostics by Changing the Attitude of Caregivers: Protocol for the RODEO Project
JMIR Res Protoc 2018;7(8):e10473
URL: http://www.researchprotocols.org/2018/8/e10473/
doi:10.2196/10473
PMID:30131316

Protocol

Postoperative Bio-Chemoradiotherapy Using Cetuximab and Docetaxel in Patients With Cis-Platinum–Intolerant Core High-Risk Head and Neck Cancer: Protocol of a Phase 2 Nonrandomized Clinical Trial

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Abstract

Background: We confirmed the safety of postoperative bio-chemoradiotherapy using cetuximab and docetaxel in a small number of patients with cis-platinum–intolerant core high-risk head and neck cancer.

Objective: To assess treatment efficacy, we planned a phase 2 study of postoperative bio-chemoradiotherapy for patients with cis-platinum–intolerant core high-risk head and neck cancer and will compare the results to those of previously collected radiotherapy data.

Methods: Patients who underwent definitive surgery for oral cavity, laryngeal, oropharyngeal, or hypopharyngeal advanced cancer, whose postoperative pathological results indicated core high risk for recurrence (eg, positive margin in the primary site or extranodal extension) and who were cis-platinum–intolerant, will undergo postoperative bio-chemoradiotherapy. The primary end point is 2-year disease-free survival.

Results: The expected 2-year disease-free survival is set at 55%, and the calculated sample size is 35 patients, according to a statistical analysis based on previous reports.

Conclusions: This treatment method is expected to improve the survival rate of patients with severe head and neck cancer.

Trial Registration: UMIN Clinical Trials Registry UMIN000031835; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000036355 (Archived by WebCite at http://www.webcitation.org/71fejVjMr)

(JMIR Res Protoc 2018;7(8):e11003) doi:10.2196/11003

KEYWORDS

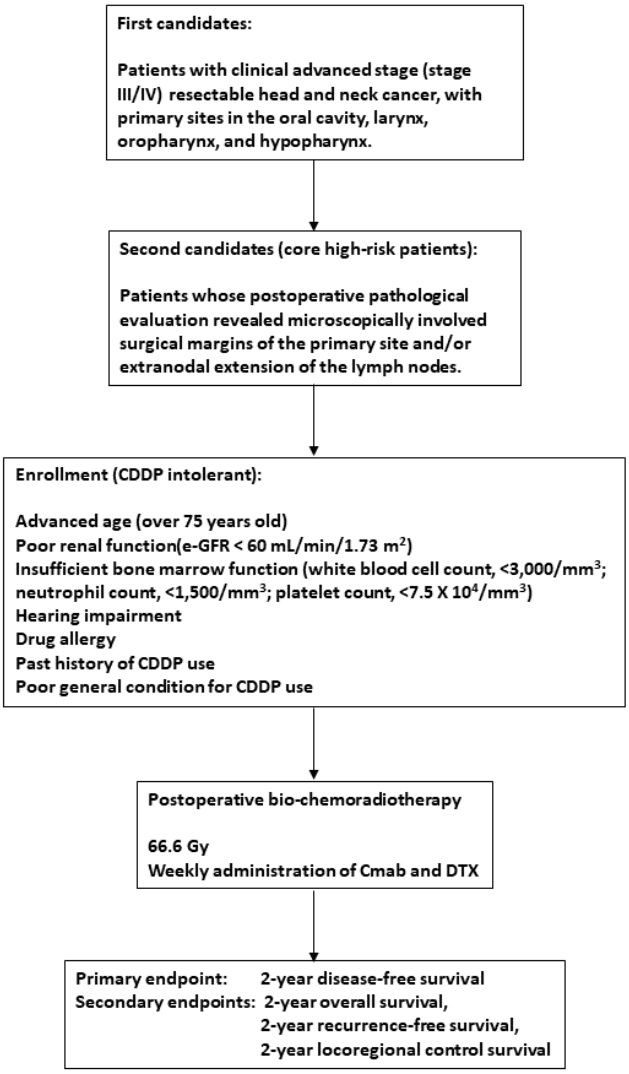
core high-risk head and neck cancer; postoperative bio-chemoradiotherapy; cetuximab; docetaxel; cis-platinum intolerant

Introduction

Most patients with head and neck cancers present with advanced disease stages during their first hospital visit. For patients with advanced head and neck cancers, surgery is a common definitive therapy. After surgery, a pathological evaluation is necessary to decide upon additional therapy. The pathological risk factors for recurrence and/or distant metastases after surgery are as follows: positive surgical margins, T3 and T4 pathologies, positive perineural invasions and/or vascular tumor embolism of the primary site, and extranodal extension (ENE) and/or multiple positive metastasis to lymph nodes. Patients with these results are recommended to undergo postoperative radiotherapy [1,2]. Among these risk factors, microscopically involved surgical margins of the primary site and ENE are considered to be core high-risk factors that indicate a poor prognosis. The outcome for patients with these core high-risk factors could be improved by concurrent chemotherapy during postoperative radiotherapy [3].

The standard protocol for postoperative chemoradiotherapy is the concurrent use of cis-platinum (CDDP; 100 mg/m^2 once every 3 weeks) during radiotherapy (total dose of 66 Gy) for patients with core high-risk factors [1-3]. However, many of these patients are intolerant to CDDP due to advanced age, poor renal function, hearing impairment, and/or poor general condition. One option to overcome these problems is the combined administration of cetuximab (Cmab) and docetaxel (DTX) during postoperative radiotherapy. This regimen has been shown to afford favorable outcomes with improved disease-free survival (DFS) and overall survival (OS) and less toxicity compared to high-dose CDDP administration [4]. A phase 2/3 trial (RTOG 1216) of this regimen is ongoing. Focusing on the reduced toxicity of this regimen, we administered the combination of Cmab and DTX during postoperative radiotherapy for a limited number of patients with CDDP-intolerant core high-risk head and neck cancer, and established the safety of this procedure [5]. Here, we propose a multicenter, single-arm phase 2 trial to confirm the efficacy of postoperative bio-chemoradiotherapy (B-CRT) using Cmab and DTX for patients with CDDP-intolerant core high-risk head and neck cancer (Figure 1).

Figure 1. Patient enrollment, treatment, and analysis. CDDP: cis-platinum; Cmab: cetuximab; DTX: docetaxel; e-GFR: estimated glomerular filtration rate.



Methods

Study Setting

This will be a multicenter single-arm open-label nonrandomized trial. The central hospital is Yokohama City University Hospital, and the corporate hospitals are Yokohama City University Center Hospital and Yokohama Rosai Hospital.

End Points

The primary end point is 2-year DFS, and the events are uncontrollability of existing cancer (locoregional remnant, locoregional recurrence, and/or distant metastasis), appearance of new primary cancer, and death. The secondary end points are 2-year OS, 2-year recurrence-free survival (RFS), and 2-year locoregional control survival (LCS). The event of OS is death, events of RFS are locoregional recurrence and distant metastasis of existing cancer and death, and events of LCS are locoregional recurrence and death. In patients with locoregional recurrences of advanced head and neck cancer, 60% to 70% of these recurrences become apparent within 1 year after the initial treatment and 90% to 100% become apparent within 2 years [6,7]. Accordingly, the end point is set at 2 years.

Ethics Approval

Ethics approval for this study was obtained from the Yokohama City University Institutional Review Board (#B180301010). Written informed consent was obtained from the participants in this study.

Eligibility Criteria

Candidates

Head and neck cancer is classified according to the 8th edition of the TNM Staging System [8]. Patients with clinical advanced stage (stage III/IV) oral cavity, laryngeal, oropharyngeal, and hypopharyngeal carcinomas, which are considered resectable by definitive surgery, are the first candidates. Among the first candidates, patients with a postoperative pathological evaluation that reveals a microscopically involved surgical margin of the primary site or ENE are the second candidates. Among the second candidates, patients defined as CDDP-intolerant are enrolled.

Inclusion Criteria

Prior to enrollment in this trial, the patients must meet all of the following criteria: pathologically proven carcinoma; primary tumor located in the oral cavity, larynx, oropharynx, or hypopharynx; clinically advanced stage (stage III or IV) on visual, endoscopic examinations, imaging examinations (eg, computed tomography [CT], magnetic resonance imaging [MRI], ultrasonic echo [US], and positron-emission tomography [PET]-CT); primary site assessed as resectable by definitive surgery and regional lymph node assessment by neck dissection on CT, MRI, or US; no distant metastasis on PET-CT (cM0); age over 20 years (regarded as a legal adult in Japan); performance score (PS) 0 to 2 on Eastern Cooperative Oncology Group (ECOG) criteria; sufficient general condition for operation under general anesthesia; CDDP-intolerant (eg, advanced age [over 75 years], poor renal function [estimated glomerular filtration rate <60 mL/min/1.73 m^2], insufficient bone marrow function [white blood cell count <3000/mm^3, neutrophil count <1500/mm^3, platelet count <7.5×104/mm^3], hearing impairment, drug allergy, past history of CDDP use, or poor general condition); and provision of written informed consent.

Exclusion Criteria

Prior to enrollment in this trial, the patients must not meet any of the following criteria: incurable synchronous malignancies, priority systemic diseases, or refusal to undergo definitive surgery and/or postoperative radiotherapy.

Treatment Methods

Surgery

Definitive primary resection is performed for the primary site with simultaneous neck dissection for node-positive cases.

Bio-Chemoradiotherapy

Radiotherapy is administered in conventional fractions of 1.8 Gy for a total dose of 66.6 Gy, 5 days per week, using 4 to 6 megavolt x-rays. The reason for 1.8 Gy dose fraction, not 2.0 Gy, is to reduce radiation-associated adverse events (eg, mucositis and dermatitis), with concurrent use of chemotherapy in the whole-neck field with advanced stage patients. The radiation fields are set up for the primary tumor and prophylactically, the bilateral cervical lymph node area (levels I-V and the retropharyngeal lymph node area). The cervical lymph node area is administered prophylactic doses of 45 Gy, with lateral opposed fields to the upper and anterior lower neck. The B-CRT regimen consists of weekly Cmab (week 1: 400 mg/m^2; subsequent weeks: 250 mg/m^2) and weekly DTX (15 mg/m^2). Cmab is discontinued for grade 3-4 hypersensitivity, and DTX is discontinued for grade 4 hyperinsensitivity. Termination or suspension of Cmab administration, DTX administration, or radiotherapy is considered based on grade 3-4 adverse events or patient status.

Adverse Event Evaluation

Adverse events are scored according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. Patients are assessed once or twice per week during radiotherapy for general status, weight, blood counts, serum levels, and adverse events.

Scheduled Analysis

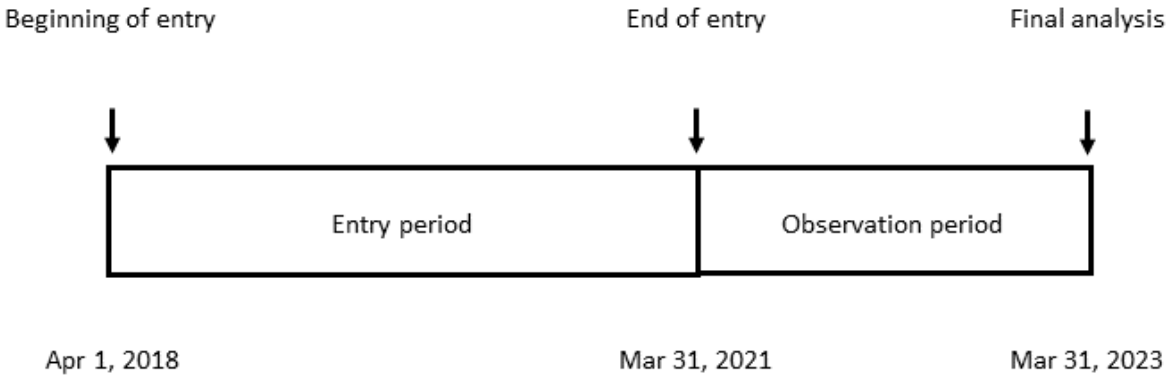
The final analysis is scheduled at the end of the observation period. The primary end point is 2-year DFS, and the secondary end points are 2-year OS, 2-year RFS, and 2-year LCS.

Statistical Analysis

The DSF of patients with postoperative advanced stage (stage III/IV) head and neck cancer who were treated with radiotherapy alone after definitive surgery was 36% at both 3 years and 5 years [1-3]. Postoperative chemoradiotherapy with high-dose CDDP for patients with advanced stage cancer revealed a 23% reduction in treatment failure risks associated with DFS compared with radiotherapy alone. The OS of patients with core

high-risk factors (eg, microscopically involved surgical margin of the primary site or ENE) significantly improved through the concurrent use of high-dose CDDP during postoperative radiotherapy [1-3]. The combined use of Cmab and DTX for patients with core high-risk factors during postoperative radiotherapy increased the 2-year DFS by 11% compared with patients who received high-dose CDDP [4]. In this study, considering that CDDP intolerance refers to the poor condition of patients with core high-risk factors, the expected 2-year DFS is set at 35% for patients treated with postoperative radiotherapy alone; Cmab and DTX could increase the survival rate by 20%. Thus, we set the expected 2-year DFS as 55%. Under the 2-tailed significance level of .05 and power of 80%, the required sample size was calculated as 35 for this analysis.

Figure 2. Expected trial schedule.



Results

The University Hospital Medical Information Network Clinical Trials Registry (UMIN000031835) was completed on March 22, 2018. Patient enrollment started on April 1, 2018, and enrollment will close on March 31, 2021. The observation period will end on March 31, 2023. The expected schedule is shown in Figure 2.

Discussion

Head and neck cancers account for approximately 5% of all malignancies in Japan, and both the incidences and mortality rates are increasing, especially in patients aged over 50 years [9,10]. The risk factors of head and neck cancer are smoking and alcohol consumption, and older patients have a longer history of these habits. Aging and a long history of smoking or alcohol consumption can induce cardiovascular disorders, pulmonary diseases, hepatic disorders, synchronous malignancies, and poor general condition. Additionally, Japanese patients with head and neck cancer show poorer renal functions with age [11], which limits the use of platinum-based drugs, especially CDDP. Such disadvantages restrict ideal treatment and are risk factors for complications during treatment.

Approximately 60% of patients with head and neck cancer present with advanced stage disease at their first visit, and surgery has been the definitive therapy for patients with advanced stage head and neck cancer despite recent improvements in treatment and diagnostic instruments. Although surgery is a fundamental treatment for locoregional control, multidisciplinary approaches, including radiotherapy and chemotherapy, are improving prognoses. Postoperative radiotherapy has been the standard adjuvant therapy for patients with high risks of locoregional recurrences or distant metastases [12,13], but radiotherapy does not show dramatic prognostic improvements. After the report of Bernier et al [3], the concurrent use of high-dose CDDP with postoperative radiotherapy has become the standard therapy for patients with core high-risk factors (eg, microscopically involved surgical margins of the primary site and ENE). Although the accepted standard regimen is CDDP administration at the dose of 100 mg/m^2 once every 3 weeks during radiotherapy, many patients with core high-risk head and neck cancer are not suited to receive this regimen due to advanced age, poor renal function, hearing impairment, or poor general status.

Cmab is an immunoglobulin G subclass 1 monoclonal antibody that inhibits ligand binding to the epidermal growth factor receptor (EGFR) and stimulates antibody-dependent cell-mediated cytotoxicity. One of the mechanisms of Cmab is that EGFR inhibition will result in decreased proliferation via mitogen-activated protein kinase and phosphatidylinositol-3-kinase pathways [14]. It has been shown that Cmab has synergistic effects with radiotherapy by modification of the radiation response through EGFR and its signal transduction pathways [15-17]. DTX is a taxane drug with a cytotoxic effect that is attributed to the inhibition of microtubule stabilization during cell divisions [18]. DTX has radiosensitizing effects by increasing G2/M phase cell fraction, reoxygenation of radioresistant hypoxic cells, radiation-induced apoptosis, and other synergistic antiangiogenetic effects [19-21]. Cmab and DTX have synergistic chemotherapeutic and radiosensitizing effects both in vivo and in vitro [22].

In a randomized phase 2 trial, Harari et al [4] reported superior 2-year OS and DFS with less toxicity in patients with core high-risk factors who received postoperative radiotherapy with Cmab and DTX compared with those who received high-dose CDDP. The 2-year OS was 79% for the Cmab plus DTX arm and 69% for the CDDP arm, and the 2-year DFS was 66% and 57%, respectively. Grade 3/4 myelosuppression was observed in 14% of patients in the Cmab plus DTX arm and 28% of patients in the CDDP arm. Regarding hematological adverse

events, a small number of grade 3/4 events (3% of lymphopenia and 0.5% of anemia [23,24]) were reported with radiotherapy with Cmab alone, and an 8% rate of leukopenia, 4% to 4.8% rate of neutropenia, 56% rate of lymphopenia, and 4.8% rate of thrombocytopenia [25,26] were reported with radiotherapy with DTX alone in patients with advanced head and neck cancer. Although the combined use of Cmab and DTX with radiotherapy tends to result in a high incidence of severe myelosuppression, in our experience it was a low percentage and was controllable compared to the myelosuppression events in patients who were administered CDDP. Following this report, we applied this regimen as postoperative B-CRT in a small number of patients (11) with CDDP-intolerant core high-risk head and neck cancer and confirmed the efficacy and safety [5]. The 2-year DFS was 55%, which was the same as the expected 2-year DFS that was calculated from previous reports in this trial. No grade 4 adverse events were observed, and the grade 3 adverse events included oral mucositis (45%), aspiration (27%), radiation dermatitis (18%), leucopenia (9%), neutropenia (9%), lung infection (9%), and hyponatremia (9%). These adverse events were controllable and tolerable. Both Cmab and DTX are considered to have less usage restrictions compared with CDDP. We consider that these merits make the combined use of Cmab and DTX as postoperative B-CRT suitable for patients with CDDP-intolerant core high-risk head and neck cancer. We will clarify the efficacy of this regimen in this phase 2 trial. A limitation to this study is that it has a single arm with a limited number of patients.

Authors' Contributions

GN and NO collectively drafted the study protocol and ethical approval. GN participated in the central monitoring of data collection, trial management, and data analysis. HH, OS, MK, DS, KY, YA, KS, YC, and TT participated in patient diagnosis, treatment, and follow-up. NO, who is the principal investigator of this study, had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. MT is the statistician of this trial. All authors read the manuscript critically, made contributions, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

B-CRT: bio-chemoradiotherapy
CDDP: cis-platinum
Cmab: cetuximab
CT: computed tomography
DFS: disease-free survival
DTX: docetaxel
ECOG: Eastern Cooperative Oncology Group
EGFR: epidermal growth factor receptor
ENE: extranodal extension
LCS: locoregional control survival
MRI: magnetic resonance imaging
OS: overall survival
PET: positron-emission tomography
RFS: recurrence-free survival

US: ultrasonic echo

Edited by G Eysenbach; submitted 09.05.18; peer-reviewed by A Homma, K Okami; comments to author 31.05.18; revised version received 18.06.18; accepted 19.06.18; published 23.08.18.

Please cite as:
Nishimura G, Hatakeyama H, Shiono O, Taguri M, Komatsu M, Sano D, Sakuma N, Yabuki K, Arai Y, Shibata K, Chiba Y, Tanabe T, Oridate N
Postoperative Bio-Chemoradiotherapy Using Cetuximab and Docetaxel in Patients With Cis-Platinum–Intolerant Core High-Risk Head and Neck Cancer: Protocol of a Phase 2 Nonrandomized Clinical Trial
JMIR Res Protoc 2018;7(8):e11003
URL: http://www.researchprotocols.org/2018/8/e11003/
doi:10.2196/11003
PMID:30139721

Protocol

A Multilevel Tailored Web App–Based Intervention for Linking Young Men Who Have Sex With Men to Quality Care (Get Connected): Protocol for a Randomized Controlled Trial

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Abstract

Background: HIV epidemic among young men who have sex with men (YMSM) is characterized by strong racial disparities and concerns about the availability and access to culturally appropriate HIV prevention and care service delivery. Get Connected, a Web-based intervention that employs individual- and system-level tailoring technology to reduce barriers to HIV prevention care (eg, HIV or sexually transmitted infection [STI] testing, pre-exposure prophylaxis [PrEP]), was developed for YMSM (age 15-24 years). This protocol details the design and procedures of a 2-phase project that includes mystery shopping and a randomized controlled trial (RCT) to test the efficacy of Get Connected among YMSM in Philadelphia, Atlanta, and Houston.

Objective: The objective of mystery shopping is to examine the quality of HIV test counseling and PrEP-related referrals for YMSM within local HIV or STI testing sites. The objective of the RCT is to test the efficacy of Get Connected for increasing HIV-negative or HIV-unknown YMSM's successful uptake of HIV prevention services (eg, routine HIV or STI testing), PrEP awareness, and likelihood to start PrEP (PrEP willingness), compared with those in the control condition, over a 12-month period.

Methods: For Phase 1, we will create a master list of HIV and STI testing sites in each city. We will enroll and train 10-15 mystery shoppers per city; each testing site will be separately visited and assessed by 2 mystery shoppers. After each site visit, the mystery shoppers will complete a site evaluation to record their perceptions of various measures including lesbian, gay, bisexual, transgender, queer visibility and inclusivity, privacy and confidentiality, provider-patient interactions, and clinic environment. For Phase 2, we will enroll 480 YMSM for 12 months across the 3 iTech cities into a 2-arm prospective RCT. Participants randomized to the control condition are directed to the AIDSVu.org testing site locator. Participants randomized to the intervention condition will be granted access to a Web app with content tailored to their specific demographic characteristics (eg, age, race or ethnicity, location, and relationship status), HIV and STI risk behaviors (eg, HIV and STI testing history, substance use, communication with partners regarding status) and sociocultural context (eg, homelessness, incarceration). Study assessments will occur at enrollment and at 1, 3, 6, 9, and 12 months postenrollment.

Results: Get Connected research activities began in September 2016 and are ongoing. To date, institutional review board (IRB) submission is complete and IRB authorization agreements are pending at several other universities.

Conclusions: The deployment of Get Connected through a mobile-optimized Web app seeks to optimize the intervention's acceptability, accessibility, availability, and long-term affordability among YMSM.

Trial Registration: ClinicalTrials.gov (NCT03132415); https://clinicaltrials.gov/ct2/show/NCT03132415 (Archived by WebCite at http://www.webcitation.org/70j4gSFbZ)

Registered Report Identifier: RR1-10.2196/10444

(JMIR Res Protoc 2018;7(8):e10444) doi:10.2196/10444

KEYWORDS

HIV infections; AIDS; adolescent; internet; men who have sex with men; prevention; pre-exposure prophylaxis; awareness

Introduction

Background

Young men who have sex with men (YMSM) now account for 72% of new HIV infections among people aged 13-24 years and 30% of all new infections among men who have sex with men (MSM) [1]. From 2008 to 2011, YMSM aged 13-24 years had the greatest percentage increase (26%) in diagnosed HIV infections [2], with approximately 93% of all diagnosed HIV infections from male-to-male sexual contact [2]. Among the drivers of the HIV epidemic among YMSM are large numbers of HIV-positive youth who are not virally suppressed or are not aware of their serostatus [3]. Increasing HIV testing among YMSM is thus a public health priority [4]. The success of the National HIV/AIDS Strategy's test and treat approach rests on the ability to increase the number of YMSM receiving routine testing [5]. Getting tested is the cornerstone of almost all prevention approaches and the gateway to both biomedical prevention tools (eg, pre-exposure prophylaxis [PrEP]) and to HIV care for those who test positive.

Successful engagement in HIV prevention for HIV-negative youth (routine HIV testing, consistent condom use, PrEP adoption) requires that YMSM overcome a series of multilevel barriers at the individual (eg, risk awareness, self-efficacy to get tested), system (eg, costs, medical mistrust, lack of culturally competent care), and structural (eg, homelessness, stigma) levels [6-12]. Strategies to promote HIV or sexually transmitted infection (STI) status awareness among YMSM requires the creation of interventions that are culturally sensitive to the psychosocial needs of YMSM [13] and facilitate access to comprehensive sexual health services [14].

HIV prevention tools that are culturally and developmentally appropriate for YMSM are needed [1,7,15,16]. Web-based interventions are a promising mode of HIV or STI prevention given their ability to deliver responsive and interactive content specific to each user's characteristics (ie, tailored content), with extended reach across geographic regions and increased convenience to access content at any time through tablets, laptops, and mobile phones. Furthermore, Web-based content can be updated to be contextually responsive over time, particularly as YMSM become sexually active, meet new partners, and engage in different risk behaviors. Collocating Web-based interventions is also important as YMSM often rank the Web as their top resource to access comprehensive sexual education, learn about their sexuality and sexual behavior, and meet partners [17].

Researchers and practitioners have sought to encourage routine HIV or STI testing by creating Web-based tools that provide the physical location of testing centers in a given geographic area (ie, testing locators). These testing locator interventions have demonstrated a wide reach when evaluated (eg, AIDS.gov test locator had over 16,000 searches and was adopted by over 100 websites in its first year [18]); however, there are limited data examining the quality and adequacy of these listed sites for YMSM. This is concerning for several reasons, as it is expected that testing agencies are youth and lesbian, gay, bisexual, transgender, questioning or queer (LGBTQ) friendly; however, there is little empirical evidence to support this assumption, and in fact evidence to support the contrary [19-23]. Using a mystery shopper methodology to evaluate the LGBTQ cultural competency and the quality of services offered in HIV and STI testing sites in Southeast Michigan (n=47 testing sites), we assessed the sites across 13 domains, including the clinic's structural characteristics, and the test counselors' compliance with the Centers for Disease Control and Prevention (CDC) HIV testing and counseling protocols [6]. After the mystery shopping assessment, we sent each site a letter describing our process and encouraged them to schedule a meeting with us to discuss the shoppers' experiences at their agency. The agency staff was eager for the feedback and technical assistance, and 66% (31/47) of the sites requested to meet. In these meetings, we offered a packet of personalized results, summarizing how they compared on various quantitative indicators to other sites, and provided feedback from the open-ended portion of the evaluation. Several agencies noted that the report from the site evaluation would help focus their efforts and address identified areas for improvement.

Theoretical Framework for Intervention

Building on the efficacy of the CDC's project Connect Health Systems Intervention to link heterosexual adolescents to competent comprehensive sexual health care services [24], we developed Get Connected (GC), a Web-based brief intervention that employs individual- and system-level tailoring technology to reduce barriers to HIV prevention care (eg, HIV or STI testing, PrEP) for YMSM. The deployment of GC through a mobile-friendly Web app seeks to optimize the Web-based intervention's acceptability, accessibility, availability, and long-term affordability among youth [4,7,25]. Using a consensus approach [26] to conceptualize health behavior change, the model guiding GC synthesizes the Integrated Behavioral Model [27] and Self-Determination Theory [28,29] as the theoretical underpinnings of our intervention. Consistent with these theories [30,31], GC content follows motivational interviewing principles

[31-33] by focusing on resolving ambivalence about HIV prevention behaviors, increasing self-efficacy for change, and enhancing motivation moving toward action. GC participants are then recommended high-performing sites based on mystery shopper scores.

Participants in the pilot trial were randomized to receive a full GC intervention or an attention-control condition. Data [34] from this pilot randomized controlled trial (RCT; n=130 YMSM; age 15-24 years) indicated high acceptability and feasibility (80% retention, 104/130) for GC, and clinically meaningful effect sizes (ES) in self-efficacy to discuss HIV testing with partners (ES=0.50-0.64), trust in their providers (ES=0.33-0.35), reductions in number of sexual partners (ES=0.21), and HIV or STI testing behavior (ES=0.34; 30 participants tested for HIV or STIs) at the 30-day postintervention follow-up. Participants who received the GC intervention reported that the testing site information was more accurate than those in control condition. For all other acceptability items, the GC intervention was equally or slightly better received than the control condition. More than 90% (102/104, 92.3%) of participants reported that the GC intervention had been useful to identify a HIV or STI clinic that met their needs. We identified 1 incident HIV-positive case and 2 STI (herpes and chlamydia) cases over the 30-day study period.

As a step toward filling the current gap in efficacious Web-based interventions for HIV prevention and care among YMSM, we propose to implement and test the efficacy of GC 2.0 across 3 iTech cities heavily impacted by HIV: Philadelphia, Atlanta, and Houston. This protocol describes the methods for the testing of the intervention.

Methods

Trial Registration, Ethics, Consent, and Institutional Review Board Approval

The research and ethics presented in this study were approved by the IRB of the University of North Carolina at Chapel Hill (16-3183). A Certificate of Confidentiality has been obtained from the National Institute of Child Health and Human Development, and a waiver of parental consent or assent has been obtained for participants who are 15-17 years old. This study is also registered on ClinicalTrials.gov (NCT03132415).

Phase 1: Mystery Shopping

Design

We will enroll mystery shopping participants (10-15 mystery shoppers per city) to conduct the mystery shopper assessment in 3 iTech cities: Philadelphia, Atlanta, and Houston. This approach follows best practices suggesting that youth involvement is vital when designing relevant and appropriate HIV interventions for the target population. We will work with iTech subject recruitment venues (SRV) in each city to recruit and enroll HIV-negative YMSM (age 18-24 years) who are interested in serving as mystery shoppers. We will apply a multimodal recruitment strategy, including ads in Web-based LGBTQ listservs, flyers in HIV or AIDS community-based organizations, local coffee shops and bars, college listservs, and Web-based advertisements on social media sites such as Facebook.

Mystery Shopper Participants

Eligible mystery shoppers are participants assigned male sex at birth and who currently identify as male; must be 18-24 years old (inclusive) at the time of screening; self-report as HIV-negative, speak and read English, live in Philadelphia, Atlanta, or Houston; must be able to travel to and from HIV or STI testing sites; report same-sex attraction; and have access to the internet via a computer or mobile phone.

Sample Size

We will recruit and enroll 10-15 mystery shoppers per city. Each participant can visit up to 10 unique testing sites in their city, with 2 mystery shoppers visiting each testing site, separately. Testing sites will be identified in collaboration with each city's health department and by crosschecking sites with AIDSVu.org. We will employ a stratified purposive sampling strategy to ensure age and racial or ethnic diversity across mystery shoppers. Of the 10-15 mystery shoppers per city, 5-8 will be aged 18-20 years (2-3 Black or African American, 2-3 White, and 1-2 Hispanic or Latino) and 5-8 will be aged 21-24 years (2-3 Black or African American, 2-3 White, and 1-2 Hispanic or Latino).

Incentives

The mystery shoppers will receive a maximum of US $600: US $100 for attending the 1-day training session and US $50 for each testing site visit (10 maximum site visits).

Procedures

Once the mystery shoppers are consented and enrolled, they will attend a 1-day training at the iTech SRV where they will learn about the fundamentals of HIV or STI transmission, the guidelines and protocols surrounding HIV or STI testing and PrEP eligibility, and how to use the Web-based site assessment survey to evaluate their site visits. State-specific guidelines and policies will also be discussed in each city. Additionally, they will receive training to strengthen their self-efficacy to feel empowered as clients. Specifically, we will conduct role-plays with scenarios and interactions that might occur during a visit. We will underscore the importance of being well-versed in their rights and procedures and provide skills on how to respond to worst-case scenarios (eg, how to turn down any unwanted procedures), were they ever to occur. The mystery shoppers will be instructed to be honest about their sexual behaviors during their visits. By avoiding creating "personas" or "scripts," shoppers will increase the social validity of the assessment and avoid arousing suspicion due to exaggerated or unrealistic scenarios.

The study staff will create and use a secure database to manage the mystery shoppers, site assignments, and testing schedules. Upon completion of the 1-day training, study staff will assign the mystery shoppers a specific day and time for their initial testing site visit. The mystery shoppers will report to the iTech SRV before each scheduled site visit to check in with a staff member and receive their site assignment. They will be loaned a mobile phone equipped with a car share app to use for travel

to and from testing sites. All car share trips will be tracked and paid for by the study, so no transportation costs will be incurred by the mystery shoppers.

Once at the testing site, the mystery shoppers will state that they have no income, health insurance, or any proof of identification. In doing so, we will be able to ascertain whether these would be potential barriers to testing at a given location and ascertain the lowest possible fees that would be charged to YMSM. As in the original study [34], we will reimburse the mystery shoppers for any charges linked to their testing experiences. Upon completion of a testing visit, the mystery shoppers will use the mobile phone's car share app to travel back to the iTech SRV. They will complete the site assessment survey on the mobile phone or on a computer at the iTech SRV. Mobile phones will be returned to the study staff upon return to the SRV.

The site assessment survey will record shoppers' perceptions of their testing experience, specifically LGBTQ visibility, medical form inclusivity, clinic environment, privacy and confidentiality, PrEP information and dialogue, patient-provider relationship context, patient-provider counseling, safer sex education, perceived provider competency, and participant-provider interactions (Textbox 1). The mystery shoppers will also have the opportunity to leave qualitative feedback in an open text field if they wish to explain any of their responses or record any other information pertinent to their experience that the quantitative assessment did not already capture.

In addition to the site assessment survey, the mystery shoppers will complete a secure video chat session with study staff to discuss their testing experience and have the opportunity to share any adverse interactions. These video chat sessions will not be recorded; their purpose will be to ensure mystery shoppers' safety and prevent subsequent mystery shoppers from being exposed to a site reported to be risky or unsafe (physically or emotionally). Following the video chat session, the mystery shoppers will be given their incentive for the visit and their next visit with study staff will be scheduled before leaving the iTech SRV.

Outcomes

The mystery shoppers' site assessment scores will be aggregated for use in Phase 2 of the research activities: RCT to test the efficacy of GC. Specifically, the scores for each site will be averaged and embedded in the intervention condition of the GC Web app: when participants search for testing sites they will only see sites that rank in the top 50% for that city, sorted from highest to lowest ranking.

Phase 2: Randomized Controlled Trial

Design

The research activities involve a 2-arm 12-month prospective RCT enrolling 480 HIV-negative or status-unaware YMSM (age 15-24 years). After assent or consent and completion of a baseline survey, YMSM will be randomized on a 1:1 basis to either the control or intervention condition (intervention, n=240; control, n=240). Participants randomized to the control condition will be directed to the AIDSVU.org testing site locator. While the provision of a test locator is a low intensity intervention, we felt that withholding referrals to testing and care services would be unethical given YMSM's vulnerability to HIV and STIs. Furthermore, given the availability of search engines to locate HIV or STI testing sites, the test locator condition may be considered usual care. Nevertheless, by providing the existing testing site locator only, we will still be able to test the effect of GC (ie, user-tailored content focused on HIV or STI testing and PrEP referral and the linkage to high-quality agencies). Web-based study assessments are conducted every 3 months across the intervention and control conditions, with a total follow-up period of 12 months. At the end of RCT, we will make the intervention accessible to YMSM in the control condition.

Intervention

The GC intervention was developed by customizing content based on YMSM's psychosocial and sexual profiles (eg, sociodemographics, HIV and STI testing history and testing motivations, recent sexual behavior, sources of support, self-reported values), as reported by participants' answers to their baseline assessment. At the individual level, GC delivers tailored Web-based content specific to each user's demographic characteristics (eg, age, race or ethnicity, location, relationship status), HIV and STI risk behaviors (eg, HIV and STI testing history, substance use, communication with partners regarding status), and sociocultural context (eg, homelessness, incarceration). GC also employs tailoring at the system level using mystery shopper scores. Participants across both conditions who have been tested will be asked to rate their visit at their quarterly follow-up assessment using the same mystery shopper criteria. Sites will receive biannual summaries, including the aggregated user reviews and brief technical assistance reports, to help sites understand their performance based on quality assurance evaluations from YMSM clients and to optimize service delivery, if needed.

For the participants in the intervention condition, the tailored Web app has 4 sections of content: "What," "Why," "How," and "Where." The "What" section is split into 3 pages: "Facts," "STIs," and "Tests." On each of those pages, topics are displayed in boxes that are randomly organized and open to display additional information if the user clicks or presses. The Facts page (Figure 1) displays boxes that contain general prevention facts (eg, "You won't always know if someone has an STI.") relevant to this population. On the STIs page, if a participant clicks "chlamydia," they receive additional information about how it can be contracted, possible symptoms, testing options, and treatment options (if applicable). The Tests page displays boxes with each HIV or STI testing method (eg, blood test, swab test, urine test), and each box contains more specific information (eg, what STIs it tests for, steps for the test) upon click or press.

Textbox 1. Clinic and provider interaction visits to be recorded by the mystery shoppers.

Clinic characteristics

Session speed (min)

LGBT visibility (Cronbach alpha=0.84)

- The clinic has symbols aimed at lesbian, gay, bisexual, transgender (LGBT) people (eg, equal sign, rainbow flag)
- The clinic has printed materials (eg, brochures) aimed at LGBT people
- The clinic has LGBT welcoming symbols

Medical forms (Cronbach alpha=0.59)

- The clinic uses LGBT-inclusive language on medical forms
- The clinic uses transgender-inclusive language on medical forms

Clinic environment (Cronbach alpha=0.76)

- The office staff were generally friendly
- The office staff were judgmental (Reverse coded)
- The office staff were not lesbian, gay, bisexual, transgender, questioning or queer (LGBTQ)–sensitive (Reverse coded)
- I felt uncomfortable in the waiting room (Reverse coded)
- The clinic used LGBT-affirming language when speaking to me

Privacy and confidentiality

- The clinic staff kept patient information confidential
- Interactions between clients and staff were kept private
- The provider explained confidentiality (either verbally or via a document)

Pre-exposure prophylaxis (PrEP)–specific indicators

- The clinic had information about PrEP
- The clinic offers PrEP or PrEP referrals

Provider exchanges

Relationship context (Cronbach alpha=0.89)

- The provider asked me about my sexual orientation
- The provider asked me about my relationship status
- The provider asked if I had experienced intimate partner violence

Counselling session (Cronbach alpha=0.76)

- The provider explored my motivation for testing
- The provider offered to help me set goals
- The provider offered to help me set action steps to meet safer sex goals
- The provider offered me risk reduction options
- The provider’s recommendations were valuable

Safer sex education (Cronbach alpha=0.88)

- The provider made sure I knew how to use a condom
- The provider helped me identify a condom that works for me
- The provider helped me identify a lube that works for me
- The provider discussed PrEP as a prevention strategy with me

Perceived provider competency (Cronbach alpha=0.65)

- The provider or test counsellor appeared knowledgeable about HIV and STIs

- The provider appeared knowledgeable about LGBTQ health issues

Negative provider interactions (Cronbach alpha=0.89)

- The provider made me feel comfortable (Reverse coded)
- I felt pressured by the provider to adopt specific risk reduction options
- The provider was judgmental about the kind of sex I have (eg, anal, receptive, or penetrative, etc)
- The provider was judgmental about how many partners I have had
- The provider was judgmental about how I met my partners

Figure 1. HIV and STIs (sexually transmitted infections) facts.

The second section focuses on the "Why" on 2 pages: "Values" and "Pros and Cons." The basic design and functionality is the same as described above in the "What" section. The Values page (Figure 2) encourages participants to assess their motivations, values, and strengths regarding HIV or STI testing. Reasons for getting tested are tailored to participants' testing history (eg, "Never tested" versus "Tested for HIV, but not STIs") in order to acknowledge their prior behaviors. Building on best practices, persuasive messages regarding the importance of linking to prevention services are then presented by linking participants' values from the baseline survey (eg, being attractive, being religious, being sexy, being loved, being athletic, etc) to the desired outcomes. For example, a participant who indicated he valued being religious may see a message that says, "Finding strength in your faith. Your religious beliefs are important to you. Getting tested is one way to take care of, and honor, the body that you've been given. How might you draw on your faith to find strength to get tested?" The Pros and Cons page presents information on the perceived benefits and barriers of getting tested and of not getting tested.

The third section is about the "How" of testing and includes pages on potential "Barriers" to getting tested and "Supports" that may help a participant decide to get tested. Barriers (Figure 3) include issues like financial costs, social norms, and prioritization, which may affect participants' desire to get tested for HIV or STIs. "Supports" has information on how their strengths and social support systems can help them make a choice about testing. Recognizing that barriers and supports may shift over time, content on these pages is tailored to identify the most recent barriers and supports as indicated by YMSM in their most recent survey.

The final section is the "Where" of testing and includes a page where a user can "Customize" their search for nearby testing sites (Figure 4) and a "Your Sites" page that displays testing sites based on that customization. Participants can customize their search based on many clinic characteristics, including

whether walk-in appointments are available, if they have weekend hours, and if they accept insurance. The "Your Sites" page is a listing of providers (including contact and location information) based on the participant's customization selections. Testing sites are initially ranked using an algorithm that accounts for each site's average mystery shopping scores. These scores are updated as participants get tested and rate sites over the 12-month study period. Participants can choose sites they may want to visit and then have the site information emailed or texted to them. Along with any site a participant emails or texts to themselves, they will be provided with 7 questions they can ask a provider during a testing visit. These questions were developed by the GC youth and community advisory boards and were found to be helpful to pilot trial participants when they encountered test counselors who were not perceived to be effective.

Participants

Eligible participants will be those assigned male sex at birth who currently identify as male, aged 15-24 years (inclusive) at the time of screening, have had consensual anal sex with another man in the past 6 months, self-report as HIV-negative or unsure of their HIV status, have access to a computer or mobile phone, can read and speak English, and live within the city limits of Philadelphia, Atlanta, or Houston.

Sample Size

Our target enrollment across both conditions is 480 participants (intervention, n=240; control, n=240). This number allows for 20% loss to follow-up rate and a final analytic sample of 400 YMSM across the 3 cities. Participants may continue the study even if they miss assessments intermittently over the data collection period. We will compare those who completed different follow-up assessments with those who did not based on key predictors from the baseline assessment to check for possible bias due to missing data and informative censoring. When appropriate, we will use expectation-maximization algorithm-based imputation methods in our analyses [35,36]. The primary outcomes for the proposed trial are successful uptake of HIV prevention services (eg, HIV or STI testing) and PrEP awareness and willingness. For HIV testing, we define power as correctly identifying the difference in the proportion of YMSM who engage in HIV testing 2 or more times at least 3 months apart during the 12-month follow-up period ("frequent tester") in our treatment arm (GC) versus our control arm. For STI testing, we define it as receiving at least 1 STI test. For proportions (eg, HIV testing, PrEP awareness), our sample size calculations are based on a 2-sample test of proportions using a 2-sided significance level of 0.05.

Figure 2. Values page.

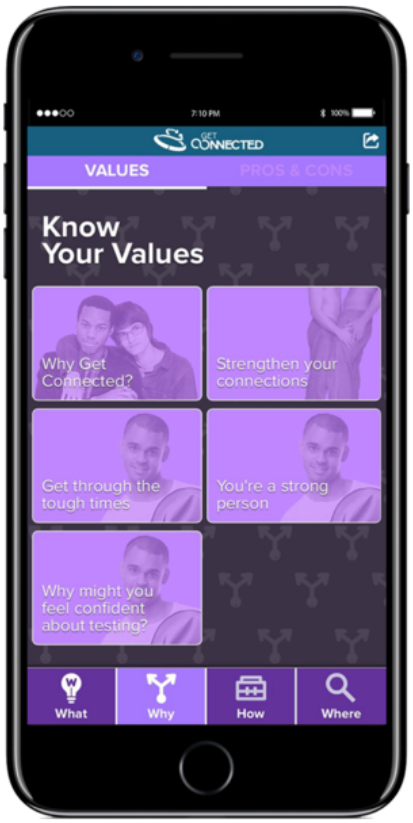
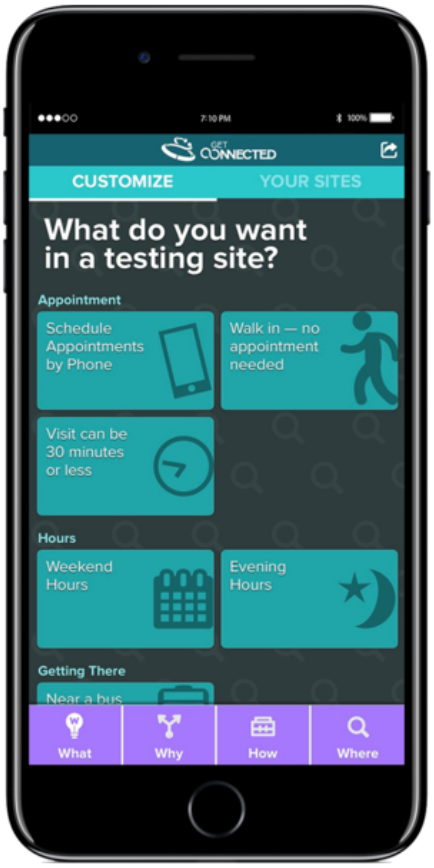


Figure 3. Barriers page.

Figure 4. Customization page.



In order to have 80% power to the intervention and control groups, we require at least 400 participants to find an absolute difference of 13% in cross-sectional analyses. Assuming a within-person correlation of 0.25, we can detect an 8.8% difference, indicating we have power to detect the smallest possible difference between arms. A less favorable within-person correlation of 0.75 allows us to detect an 11.3% difference. For mean differences across continuous outcomes (eg, PrEP willingness), our sample size calculations are based on a 2-sample *t* test, assuming equal variance using a 2-sided significance level of 0.05. We are able to detect a between-arm effect size difference of Cohen *d*=0.25 at the final follow-up time point at 80% power. For repeated measures analyses, assuming a within-person correlation of 0.25, we would be able to detect an effect size of 0.08. A less favorable within-person correlation of 0.75 allows us to detect an effect size of 0.11.

Incentives

Participants can earn up to US $155 total: Baseline survey=US $20, month 1 survey=US $20, month 3 survey=US $25, month 6 survey=US $30, month 9 survey=US $30, and month 12 survey=US $30.

Randomization

After assent or consent and completion of the baseline survey, YMSM will be randomized by city 1:1 to either the control or intervention condition (intervention, n=240; control, n=240) [37]. The stratified randomization process occurs upon completion of the baseline survey.

Outcomes

Primary Outcomes

The primary outcomes relate to the successful uptake of HIV prevention services among our sample of self-reported HIV-negative or serostatus-unaware YMSM. We have considered 3 prevention outcomes: HIV testing, STI testing, and PrEP awareness and willingness.

HIV Testing

The baseline survey will include questions on lifetime HIV testing history. Follow-up surveys will repeat the questions from the baseline and will also include questions on HIV testing in the prior 3-month period, including test results. The HIV testing outcome will be the proportion of YMSM tested for HIV 2 or more times at least 3 months apart in the 12-month follow-up period (“frequent tester”). As an additional analysis, we will also examine the proportions of participants who receive 1 HIV test.

Sexually Transmitted Infection Testing

The baseline survey will include separate questions on lifetime testing history of gonorrhea, chlamydia, and syphilis, respectively, as well as questions about ever having a genital exam, an anal pap smear, or a vaccination for Hepatitis A and B, human papilloma virus, and meningitis. Follow-up surveys will repeat the questions from the baseline but will ask about STI testing behavior in the prior 3-month period, including test results if a participant indicates they received a test. The STI testing outcome will be the proportion of YMSM tested for any STI 2 or more times, at least 3 months apart, in the 12-month follow-up period (“frequent tester”). As an additional analysis, we will also examine the proportions of participants who receive 1 STI test.

Pre-Exposure Prophylaxis Awareness and Willingness

The survey will contain a brief description of PrEP to orient the participant. Most questions were adapted from recent studies of PrEP attitudes with YMSM [38-41]. PrEP awareness will be a single-item measure of whether the participant has heard of PrEP [39]. For participants who do not report current PrEP use, PrEP willingness will be assessed by asking how likely the participant would be to start PrEP in the next 3 months and the reason(s) why the participant is not currently taking PrEP (eg, never heard of PrEP, worried about side effects, lack of support from friends or family).

Secondary Outcomes

As secondary outcomes, we will examine the uptake of PrEP, changes in sexual risk behavior, and the linkage and retention in care among newly diagnosed HIV-positive cases. While we expect a small number of newly diagnosed HIV infections, we will measure initiation of antiretroviral therapy and self-reported adherence as a secondary outcome. We are not powered to measure differences in engagement in HIV care across trial arms, so we include this as an exploratory analysis.

Mechanisms of Change

Consistent with our theoretical framework, we will assess YMSM’s psychosocial correlates predicting adoption of HIV services (ie, attitudes, norms, self-efficacy, and behavioral intentions to get HIV tested). Integrated Behavioral Model constructs will be assessed with subscales assessing YMSM’s attitudes, social norms, and behavioral intentions [42] that we have used in the past with this population [43]. Social norms assess the extent to which participants feel that friends and family believed the participants should test for HIV. Behavioral intention items assess participants’ intention to adopt HIV testing. Self-efficacy to access HIV or STI services and to discuss sexuality-related issues with partners and provider will be ascertained.

Uptake of Pre-Exposure Prophylaxis

At each follow-up assessment, PrEP-eligible (per CDC guidelines), HIV-negative YMSM will be asked whether they have begun using PrEP [39]. YMSM who report using PrEP will be asked to report their adherence to PrEP.

Sexual Risk Behavior

Sexual risk behavior will be assessed using the Sexual Practices Assessment Schedule used in previous Web-based studies with YMSM [44,45]. This assessment will explore the number of occasions of different sexual acts (oral, anal; receptive, insertive) with 3 different types of partners (romantic interest, casual partner “hookup,” or friend with benefits), use of condoms during the past 3 months, and knowledge about partners’ HIV status and PrEP use. Assessments ascertain sexual behaviors with male partners and will be conducted at baseline and each follow-up. At-risk sex will be defined as any anal intercourse without condoms or PrEP with a person of known positive and

detectable viral load or a person of unknown serostatus during the follow-up period. We will assess the number of partners with whom participants had "at-risk sex," as well as estimate the incidence of at-risk sex acts (ie, incidence density: the numerator being number of at-risk sex acts and the denominator being person-years of follow time).

Linkage and Retention in Care Among Newly Diagnosed HIV-Positive Cases

Among newly diagnosed HIV-positive cases, we will measure participants' linkage and engagement with appropriate medical care after initial diagnosis, using criteria employed in prior ATN protocols with youth [46-49]. We will define linkage as an HIV-related medical visit within 45 days of referral and engagement as a second HIV-related medical visit within 16 weeks of initial visit [48]. Onset of antiretroviral therapy initiation, self-reported adherence to ART, and viral suppression are exploratory indicators [47], as we recognize that our follow-up period may not be a sufficient amount of time to see these changes.

Covariates

We will also measure the following constructs as potential predictors or moderators in our analyses.

Sociodemographic Information

We will include questions on participants' race or ethnicity, educational attainment, employment status, place of birth, housing status, and history of incarceration, sexual identity, and "outness" to their social network.

Site Evaluations

Across both trial arms, YMSM who report testing in the prior 3 months will complete site assessments of their testing experiences to measure comfort, quality, and concerns after visiting a site for HIV or STI testing. The site assessment form is the same form used by the mystery shoppers. We will use these assessments to send aggregate data of YMSM's satisfaction with services to agencies biannually.

Substance Use and Psychological Distress

Previous studies have demonstrated higher vulnerability to HIV risk behaviors and engagement in prevention and care among YMSM who report alcohol, tobacco, and other drug (ATOD) use and psychological distress; therefore, we will measure both ATOD and psychological distress as potential effect moderators.

We will assess the frequency of ATOD use (as measured in the National Survey on Drug Use and Health) over the past 3 months in the baseline survey and follow-up surveys for alcohol, tobacco products, marijuana, nonprescription drugs, cocaine, amphetamines, inhalants, opioids (including heroin), hallucinogens, and depressants [50]. If respondents indicate any ATOD use within the past 3 months, we will ask, for each substance, how often the substance was used and if it was used immediately before or during sex.

We will measure psychological distress using existing, well-validated scales: the Patient Health Questionnaire-8 (PHQ-8) [51] and the 7-item Generalized Anxiety Disorder (GAD-7) [52] scale. We will use the first 2 items from each scale to screen participants for symptoms of depression and anxiety (PHQ-2 [53] and GAD-2 [54]). Participants who report depressive symptoms (score of 3 or more on PHQ-2) will be asked the last 6 items from PHQ-8. Participants who report symptoms of anxiety (score of 3 or more on GAD-2) will be asked the last 5 items from GAD-7.

Intervention Acceptability

At each follow-up, participants will report on the acceptability of their assigned study arm. We will use the Systems Usability Scale [55] to ascertain participants' overall satisfaction with the intervention, perception of the information quality, and perceived usefulness of their intervention to improve their health.

Use of Intervention Over Time

We will measure intervention exposure using paradata from the intervention, including counts of user sessions, length of sessions, pages visited, and functions utilized. This information will assist in examining whether intervention dosage influences the overall efficacy of the intervention and in informing the cost analysis and wider implementation and scalability [56].

Technology and Social Media

We will include Pew Internet survey questions [57] regarding the use of different devices, the number of hours spent online through each device, reasons for social media use, sites commonly frequented, and extent to which the internet supplements face-to-face interactions. We will also measure participants' frequency of social media use to look for HIV or sexual health-related information [43,58] and their online partner-seeking behaviors [59,60]. We will ask these questions at each follow-up, except for the 1-month follow-up. We will also use the eHealth Literacy Scale [61] to assess participants' perceived ability to use the internet to find health resources.

Statistical Analysis

Descriptive statistics of the psychosocial and demographic characteristics of the participants will be used to describe all participants. These will be compared between treatment groups using *t* tests or Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables. To test for intervention efficacy, we will conduct primary analyses of our primary outcomes (HIV testing, STI testing, and PrEP awareness and willingness) using regression analyses to compare our treatment and control groups using the appropriate link function (identity for continuous outcome, logit for binary outcome, and natural log for count outcomes). Interactions between group assignment and these characteristics will be tested to explore the potential moderators of treatment effect. We will repeat these analyses for the secondary outcomes (eg, theoretical mediators, sexual risk behaviors, sexual risk behaviors, PrEP uptake).

We will use the general framework of generalized linear mixed models (GLMM) to test for intervention effects over time. Note that some of our outcomes are binary, some are count, and some continuous traits and thus need to be treated differently. The general form of GLMM will be $g(\mu_{ij}) = \beta_{0i} + \beta_{cov}$ Covariates$_{ij}$ + β_{Time} Times$_j$ + $\beta_{Arm \times Time}$, where μ_{ij} is the mean response

corresponding to subject *i* at Time *j (baseline and 4 follow-ups)*, with its appropriate link function (identity for continuous outcome, logit for binary outcome, and natural log for count outcomes); Trt_i=1 if the i^{th} subject is in the intervention group, and Trt_i=0 if the i^{th} subject is in the control group. The interaction coefficients $\beta_{Trt \times Time}$ are of interest here, measuring the difference in the rate of change in outcome across the 2 treatment groups over time. The subject-specific random intercepts β_{0i} are assumed to be normally distributed with a common variance and they account for within-person correlation. We will also explore if we need a subject-specific random slope corresponding to visit in the above model. Maximum likelihood estimation will be used for fixed effect parameters.

Models will be compared according to the information criteria such as Akaike Information Criterion and Bayesian Information Criterion. For some binary outcomes, such as HIV testing, we will perform an aggregate analysis after collapsing across the repeated measures using simple logistic regression, comparing whether the probability of having tested at least once over the entire follow-up period is different across treatment groups, after adjusting for baseline values. To ensure robustness, we will also apply an exchangeable working correlation structure to its corresponding generalized estimating equation model. We will conduct exploratory regression analyses to examine regional differences. These regressions will be run with group assignment and region in the model, controlling for sociodemographic characteristics. Interactions between group assignment and region will be tested to explore potential site-specific moderators of treatment effect.

As a secondary analysis, we will build on our GLMM framework to examine whether the intervention effects in the theoretical mediators (eg, attitudes, norms, and self-efficacy) are associated with our outcomes. We will also test whether these relationships vary as a function of YMSM's varying engagement with the intervention (intervention acceptability, use of intervention over time). Interactions between group assignment and these characteristics will test for potential moderators of treatment effect.

Cost Analysis

In order to inform the eventual scale-up of GC, we will also conduct a cost analysis of GC and control conditions to inform discussions of sustainability and roll out of the GC intervention. We will collect information on costs associated with the delivery of the intervention. No costs associated with research data collection will be included. These components of cost will be summed over the 12-month study period for each participant to generate an estimated per person cost. Effectiveness will be measured by examining HIV-related outcomes reported by YMSM over the 12-month period. Incremental cost effectiveness ratio (ICER) across treatment arms will be defined as delta C or delta E, where delta C denotes the estimated difference in mean cost of the intervention and delta E reflects the estimated difference in mean effectiveness between the intervention and control groups. Nonparametric bootstrap resampling will be used to estimate the 95% CI of incremental cost effectiveness ratio [62]. Analysis will be performed on participants with complete data. Sensitivity analysis will be conducted by including all participants with multiple imputations for those with missing data.

Qualitative Assessment of Testing Sites' Satisfaction

We will qualitatively assess testing sites' satisfaction with the biannual performance assessments and their improvements in service delivery when working with YMSM across the 3 regions. Ten site directors will be randomly selected from testing sites in each city. Eligible participants will be able to read and speak English and serve as the site director of an HIV or STI testing site in Philadelphia, Atlanta, or Houston. We will conduct semistructured qualitative in-depth interviews (60-90 minutes) that focus on 4 domains: (1) existing prevention services used and promoted by the agency, (2) agency (internal) resources currently missing, that if identified and addressed, could improve the delivery of HIV, STI, and PrEP services to YMSM, (3) feedback on the biannual performance assessments and their use for service delivery improvements, and (4) the advantages and disadvantages of GC rollout within AIDS Service Organizations.

Interviews will occur via teleconference to maximize candidness and privacy while decreasing travel-related costs. We will use VSee, a simple and low-cost video chat platform that requires no server infrastructure to set up or maintain and allows providers to be HIPAA-compliant. Interviews will be audio-recorded to allow for verbatim transcription, and then checked for accuracy and completion. Initial reading and coding of the transcripts will be reviewed, compared, and refined in team meetings. This systematic process will lead to the creation of a coding structure that includes a hierarchical set of constructs seen in the data. We will analyze several transcripts jointly to establish intercoder reliability. The team will then code all transcripts using our coding structure and add inductive codes during the iterative analysis process. Throughout, we will discuss emerging themes, resolve difficulties or concerns that may arise, and adapt the codebook as necessary.

Since we seek to gain a multilevel understanding of the structural, organizational, and interpersonal barriers and facilitators of implementing GC, our analysis will utilize a phenomenological framework [63]. Although our analysis will rely primarily on a phenomenological inductive approach, we will also employ aspects of deductive analysis that consider our guiding conceptual framework. This combination of analytic strategies will enable us to conduct a phenomenological analysis (inductive) that was initially informed by existing research and theory via the conceptual framework (deductive). We will analyze the qualitative data using thematic analysis until we have reached saturation [64-66].

Results

GC research activities began in September 2016 and are ongoing. Institutional review board (IRB) submission is complete, with IRB authorization agreements being finalized across the participating universities and SRVs.

Discussion

There are several potential challenges and limitations to the proposed clinical trial. First, we will rely on self-reported outcomes. We will not include biological measures (eg, presence of HIV or STI), as we would have to dramatically increase our sample size to detect significant effects in biomarkers among newly diagnosed HIV or STI cases and it would be inefficient to collect biomarkers in a Web-based study. We will frame the presentation of results as self-reported outcomes. Second, we propose to recruit a diverse (in terms of race or ethnicity and age) sample of 15-24 year-old participants. It is possible that we may experience more success in recruiting older YMSM (those aged >18 years). To counteract this, we will include a broad range of social media outlets in our recruitment, allowing us the potential to recruit our full age range. Collectively, the team has a vast experience of recruiting youth into HIV research efforts and substantial experience in recruiting online samples of urban race or ethnic minority YMSM. Third, we are unable to untangle race from Latino ethnicity, as it would require a much larger sample size to examine race by ethnicity subgroup differences. Because we propose to quota sample across race or ethnicity in each of the regions, the breakdown of Latino race would create some small sample sizes. Fourth, we recognize that socioeconomically disadvantaged participants may require access to a computer or secure Wi-Fi connection to participate fully in the study. YMSM who are interested in participating but require access or who prefer to complete assessments at a study location will be able to complete intervention activities at their local iTech SRV. Finally, to minimize potential risks, all iTech SRVs have specific policies governing the treatment of human participants, including the referral to medical and psychological services in the event a participant should report a need for these services or experience any adverse reactions resulting from study procedures.

With increasingly promising evidence of the efficacy of biomedical prevention tools, such as PrEP, for reducing the risk of HIV infection among MSM [38,39,67-70], there is increased attention to the potential for HIV testing to act as a gateway to other HIV prevention tools and care efforts [71,72]. Many of the cognitive and behavioral risk factors that contribute to the high rates of HIV infection among MSM are established during adolescence and the transition into young adulthood. This age should be considered a priority time for intervening on cognitive and behavioral risks for HIV, while also introducing YMSM to HIV testing as a gateway to other HIV prevention options.

Efforts to encourage and motivate YMSM to engage in repeat HIV or STI testing or to adopt other prevention efforts (eg, PrEP [38,39,67]) may be diminished if structural barriers (eg, medical mistrust, lack of insurance or transportation) and cultural insensitivity to YMSM's needs (eg, racial or ethnic and sexual orientation stigma) lead to delays or avoidance of HIV or STI services [10,73,74]. HIV prevention tools must be designed to help YMSM overcome a series of multilevel barriers at the individual (eg, risk awareness), systems (eg, costs, lack of culturally competent care), and structural (eg, homelessness, stigma) levels. Developing strategies to promote the use of HIV prevention services among YMSM requires the creation of interventions such as GC that are culturally sensitive to their psychosocial needs [13] and facilitate access to comprehensive sexual health services [14]. If proven efficacious, GC has the potential to fill a gap in HIV prevention by providing a Web-based, tailored intervention that allows YMSM to learn about local prevention services and to build the skills necessary for successful adoption of prevention.

Acknowledgments

This work was supported by the National Institutes of Health Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN 139; MPI: Bauermeister & Stephenson) as part of and the UNC/Emory Center for Innovative Technology (iTech; PIs: Drs Hightow-Weidman/Sullivan, 1U19HD089881). The content is solely the responsibility of the authors and does not represent the official views of the funding agencies. The authors would like to thank Adi Ferrara, MS, ELS, for help in the preparation of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ATOD: alcohol, tobacco, and other drug
CDC: Centers for Disease Control and Prevention
ES: effect sizes
GC: Get Connected
GLMM: generalized linear mixed models
IRB: institutional review board
LGBTQ: lesbian, gay, bisexual, transgender, questioning or queer
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SRV: subject recruitment venues
STI: sexually transmitted infection
YMSM: young men who have sex with men

Edited by A Pettifor, B Mustanski, S Allison, I Holloway, R Schnall; submitted 19.03.18; peer-reviewed by P Dittus, S Ramsey; comments to author 01.05.18; revised version received 07.05.18; accepted 08.05.18; published 02.08.18.

Please cite as:
Bauermeister JA, Golinkoff JM, Horvath KJ, Hightow-Weidman LB, Sullivan PS, Stephenson R
A Multilevel Tailored Web App–Based Intervention for Linking Young Men Who Have Sex With Men to Quality Care (Get Connected): Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2018;7(8):e10444
URL: http://www.researchprotocols.org/2018/8/e10444/
doi:10.2196/10444
PMID:30072358

Protocol

University of North Carolina/Emory Center for Innovative Technology (iTech) for Addressing the HIV Epidemic Among Adolescents and Young Adults in the United States: Protocol and Rationale for Center Development

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Abstract

Background: Over a fifth of all new HIV infections in the United States occur among persons aged 13 24 years, with most of these diagnoses occurring among gay and bisexual males (81%). While the epidemic of HIV in the United States has leveled off for many age groups, the annual number of new HIV diagnoses among young men who have sex with men (YMSM; 13-24 years old) remains high. Traditional approaches to continuum improvement for youth have been insufficient, and targeted interventions are urgently needed for young people at risk for or infected with HIV. Interventions delivered through mobile health technology represent a promising approach for improving outcomes in this population. Mobile phones have nearly reached saturation among youth, making mobile technology a particularly promising tool for reaching this population.

Objective: The University of North Carolina/Emory Center for Innovative Technology (iTech) is a National Institutes of Health cooperative agreement as part of the Adolescent Medicine Trials Network for HIV/AIDS Interventions. iTech aims to impact the HIV epidemic by conducting innovative, interdisciplinary research on technology-based interventions across the HIV prevention and care continuum for adolescents and young adults in the United States, particularly YMSM, by providing the following: (1) evaluation of novel approaches to identifying youth with undiagnosed HIV infections; (2) evaluation of multilevel, combination prevention approaches, particularly relevant to gender- and sexual-minority youth facing co-occurring health risks; (3) evaluation of uptake of and adherence to biomedical prevention modalities; and 4) evaluation of interventions designed to promote or optimize engagement in care and antiretroviral therapy adherence in HIV-positive youth, to optimize viral load suppression.

Methods: iTech brings together multidisciplinary experts in the fields of adolescent HIV treatment and prevention, development and evaluation of technology-based interventions, HIV surveillance and epidemiology, and intervention design and evaluation. This initiative will support 8 efficacy trials and 2 exploratory projects, each led by 2 principal investigators. Taken together, the studies address all of the key steps of the HIV prevention and care continuum for youth in the United States. Each proposal uses technology in a scientifically rigorous and innovative way to access, engage, and impact at-risk or infected youth. Nine iTech subject recruitment venues are spread across 8 US cities. Three cores (management, analytic, and technology) support all iTech activities and form the research network's infrastructure, facilitating all aspects of study implementation and evaluation.

Results: Formative work has already begun on many of the above-mentioned iTech trials. We expect the first randomized controlled trials to begin in mid-2018. Additional details can be found in the individual intervention protocol papers in this issue.

Conclusions: Through its comprehensive research portfolio, iTech aims to effectively advance HIV prevention and care for youth through technology-based, youth-relevant interventions that maximize adaptability and sustainability.

Registered Report Identifier: RR1-10.2196/10365

(JMIR Res Protoc 2018;7(8):e10365) doi:10.2196/10365

KEYWORDS

adolescent; HIV; care continuum; technology; mobile app

Introduction

Over a fifth (22%) of all new HIV infections in the United States occur among persons aged 13-24 years, with most of these diagnoses occurring among gay and bisexual males (81%) [1]. While the epidemic of HIV in the United States has leveled off for many age groups, the annual number of new HIV diagnoses among young men who have sex with men (YMSM; 13-24 years old) remains high. Though it fell by 18% between 2008 and 2014, in 2015, YMSM accounted for 92% of new infections among people aged 13-24 years and 27% of all new infections among MSM [2].

Advances in HIV prevention tools can effectively reduce new HIV infections among youth. Antiretroviral therapy (ART) is a powerful tool and can be used among HIV-negative youth to reduce susceptibility to infection (pre-exposure prophylaxis, PrEP) or among youth living with HIV infection (in the form of treatment as prevention) to reduce infectiousness [3-6]. The effectiveness of ART for reducing HIV transmission requires successes at multiple steps of the HIV prevention and care continuum (HIV testing, PrEP or ART treatment initiation, and treatment adherence), which may prove challenging for youth due to individual, structural, and societal barriers [7-10]. Comprehensive, evidence-based behavioral, psychosocial, and structural interventions are needed to optimize PrEP and treatment as prevention among youth.

HIV testing is the critical first component to facilitate entry into HIV prevention and care. Individuals who are aware of their infection can begin treatment, thus reducing the likelihood of onward transmission and improving clinical outcomes [11]. Those individuals testing negative can engage in interventions to prevent HIV acquisition, such as behavioral counseling and PrEP initiation. Due to the high HIV incidence among YMSM, routine HIV testing is particularly important and represents an ongoing prevention activity that requires strategies for continued engagement [12]. Access to and uptake of HIV testing is suboptimal, even among YMSM who report behaviors that place them at high risk for infection [13,14]. Data from the 2015 Youth Risk Behavior Surveillance System, which collects data from high school students (9th-12th grade), found that among sexually debuted YMSM, only 21% had ever been tested for HIV [1]. Further, at the end of 2013, an estimated 60,900 youth were living with HIV in the United States. Of these, 51% (31,300/60,900) were living with undiagnosed HIV, the highest rate of undiagnosed HIV in any age group [1].

Although PrEP has demonstrated high efficacy in clinical studies, uptake has been low among YMSM, especially YMSM of color [8,15,16]. There have been a number of challenges to increasing PrEP uptake in the United States, including low awareness of PrEP among youth and providers, only recent FDA approval of PrEP for those aged <18 years, concerns about potential side effects or safety, low risk perception, and PrEP stigma [17-19]. Efficacy of PrEP is highly correlated with adherence, and evidence suggests there may be worse adherence rates among younger populations and racial and ethnic minority populations [20-23].

For youth diagnosed with HIV, engagement in care and treatment with ART to achieve viral suppression are critical components for reaching the goals of improved individual health and prevention of onward transmission. In the United States, only approximately 44% of young people aged 13-24 years diagnosed with HIV have achieved viral suppression [1]. One recent study of 1548 youths [24], conducted within the Adolescent Trials Network for HIV/AIDS Interventions (ATN), showed that only 7% of diagnosed adolescents and young adults achieved undetectable viral loads. Among participants with baseline biomedical data (N=733), 81.0% (594/733) were male, 72.0% (528/733) were black, and 70.0% (513/733) were gay or bisexual. This was substantially lower than the estimated 50% of persons achieving viral suppression for all age groups combined [24,25].

Thus, traditional approaches to continuum improvement for youth have been insufficient. Targeted interventions are urgently needed to improve the knowledge of undiagnosed HIV infection, access to and retention in prevention and care, medication adherence, and long-term viral load outcomes among youth at risk for or infected with HIV. Interventions delivered through mobile health (mHealth) technology represent a promising approach for improving outcomes among youth at risk for or infected with HIV. Mobile phones have nearly reached saturation among youth, making mobile technology a particularly promising tool to reach this population. As of 2015, 78% of those aged 18-29 years in the United States own a desktop or laptop computer and 98% report having a mobile phone of some kind, and 86% of these devices are smartphones [26]. Although white teens (91%) are more likely than black or Latino teens to report owning a desktop or laptop computer (~80% each), black teens are more likely to own a mobile phone (85%) and go online through a mobile device (100%) than white teens (71% ownership, 90% access) [27].

Although a number of apps related to HIV and other sexually transmitted infections (STIs) are available via commercial sites (Apple iTunes, Google Play), there are limited data to support the design of these apps or rigorous evaluations of their impact [28,29]. Of note, there are no current mHealth interventions targeting access to, uptake of, and adherence to PrEP. Further, youth face unique barriers to care at multiple levels including individual, social, and structural. Thus, technology (including app-based) interventions for youth must be specifically tailored based on their developmental stage and should include factors beyond individual-level behaviors and barriers to care. Additionally, once developed, these interventions must be rigorously evaluated and include the estimation of both overall cost and cost-effectiveness (compared with standard of care).

To effectively advance HIV prevention for youth, technology-based, youth-relevant interventions that maximize adaptability and sustainability need to be developed, heeding lessons learned from successes and failures of in-person interventions. A more efficient and potentially more scalable process for developing and testing these interventions would be to collate interventions that share common principles, design elements, data collection, and evaluation approaches. Moving forward, it is imperative that we build upon and enhance successful platforms to develop sustainable technology-based solutions that represent the highest standards of usability, affordability, accessibility, and large-scale dissemination.

The University of North Carolina (UNC)/Emory Center for Innovative Technology (iTech) is a National Institutes of Health cooperative agreement as part of the ATN (see Eunice Kennedy Shriver National Institute of Child Health and Human Development ATN overview, also submitted for this special issue). iTech aims to impact the HIV epidemic by conducting innovative, interdisciplinary research on technology-based interventions across the HIV prevention and care continuum for adolescents and young adults in the United States. The overall goals of iTech seek to decrease the impact of HIV on the lives of adolescents and young adults in the United States, particularly YMSM, by providing the following: (1) evaluation of novel approaches to identifying youth with undiagnosed HIV infection; 2) evaluation of multilevel, combination prevention approaches, particularly relevant to gender and sexual-minority youth facing co-occurring health risks (eg, substance use, mental illness, homelessness; 3) evaluation of uptake of and adherence to biomedical prevention modalities; and 4) evaluation of interventions designed to promote or optimize engagement in care and ART adherence in HIV-positive youth, to optimize viral load suppression.

Methods

iTech Structure

iTech will support 8 efficacy trials of interventions and 2 exploratory projects, each of which will be led by 2 principal investigators (PIs). Taken together, the studies address all of the key steps of the HIV prevention and care continuum for youth in the United States. Each proposal uses technology in a scientifically rigorous and innovative way to access, engage, and impact at-risk or infected youth. Nine iTech subject recruitment venues (SRVs) are spread across 8 US cities (Boston, MA; Philadelphia, PA; Chicago, IL; New York City, NY, 2 sites; Houston, TX; Tampa, FL; Atlanta, GA; and Los Angeles, CA). Three cores (management, analytic, and technology) support all iTech activities and form the research network's infrastructure that supports all aspects of study implementation and evaluation.

iTech Cores

iTech is composed of three cores (management, analytic, and technology) that function in a coordinated and complementary manner to achieve overall objectives (Figure 1). Authors LBH-W and PSS oversee all activities. A project management plan provides rules for iTech Core governance.

The *Management Core* (MC) provides the organization and structure necessary to maximize the potential of the research projects within iTech. MC provides infrastructure, regulatory, and operational support and ensures communication and collaboration among the research studies within iTech and with the funders. It is responsible for the project management plan and overall and study-specific timelines, ensuring the project remains within cost and scope, and overseeing and monitoring the iTech SRVs.

The *iTech Analytic Core* (AC) provides expertise and data systems for the conduct of formative research, usability testing, pilot studies, randomized controlled trials (RCTs) and economic analyses to support the aims of the iTech and its research protocols. Throughout the development, execution, analysis, and dissemination phases of each iTech study activity, AC provides guidance on implementing cross-site collaborative research, maintaining scientific rigor, and ensuring timely research completion. Activities of AC are supported by data analytic staff at Emory and UNC with skills in 4 primary areas: data management, qualitative data analysis, quantitative data analysis, and costing analyses. Lead statisticians assemble and supervise teams comprising AC data management and analytic staff for each RCT and complete the design and execution of primary analyses for each iTech study. AC also leads efforts to ensure study tools and measures are harmonized wherever possible across iTech studies and the broader ATN to facilitate pooled and large-scale secondary data analyses projects. Network-wide measures encompass 5 domains: demographics or socioeconomic characteristics, sexual behavior and risk, substance use or abuse, HIV-positive cascade, and HIV-negative cascade. In addition, other survey measures specifically for use within iTech were developed: additional demographic or socioeconomic characteristics, technology items (technology use, eHealth literacy, intervention usability, and intervention acceptability), mental health, and social supports. Further details on ATN data harmonization can be found in a companion manuscript in this eCollection (will be cited once available).

Economic analyses are planned for five of iTech's current studies (COMPARE, P3, Get Connected, ePrEP, and YouTHrive). Cost data will be collected by input type and activity. Standardized tools and harmonized measures will be used across studies wherever possible. The study staff will develop the inventory of inputs for each activity for each intervention (eg, inputs for the initial screening visit and app

setup) and standard definitions of each input and unit of measure. Each study site will use a standard data collection instrument that lists all the inputs, the time frame for collection, and the primary source of cost data. We will use activity-based (also called "bottom-up") costing to assess the cost of the respective interventions. Cost data will be collected by site. The average of the site-specific costs will be used, and the variation in site-specific costs will be examined and reported. Total cost results will be presented by cost per participant using the intervention and cost per percent increase in primary study outcome(s) (eg, HIV testing, PrEP uptake), referent to the control arm.

The iTech Technology Core (TC) provides services for technology-related fields, including mobile technologies, Web-based platforms, laboratory monitoring platforms that collect samples through mailed-out testing kits, social media- and Web-based recruitments, and technology-related ethics issues. TC provides a secure, HIPPA (Health Insurance Portability and Accountability Act of 1996)-compliant Web-based system for participant management and retention that is used across all SRVs and studies. TC assists with the measurement of *paradata*, auxiliary data that capture details about the process of interaction with the Web-based intervention, including website and app analytics, and creates an infrastructure to share and disseminate best practices in technology-delivered HIV interventions. To date, paradata have been underexamined and underreported in research among youth at risk for or infected with HIV [30]. Paradata can be used to help understand what components of the intervention led to behavior change and which components are not useful and should not be continued in future iterations of the technology. Finally, TC provides support for scaling and dissemination, including planning for eventual implementation at all stages of protocol development.

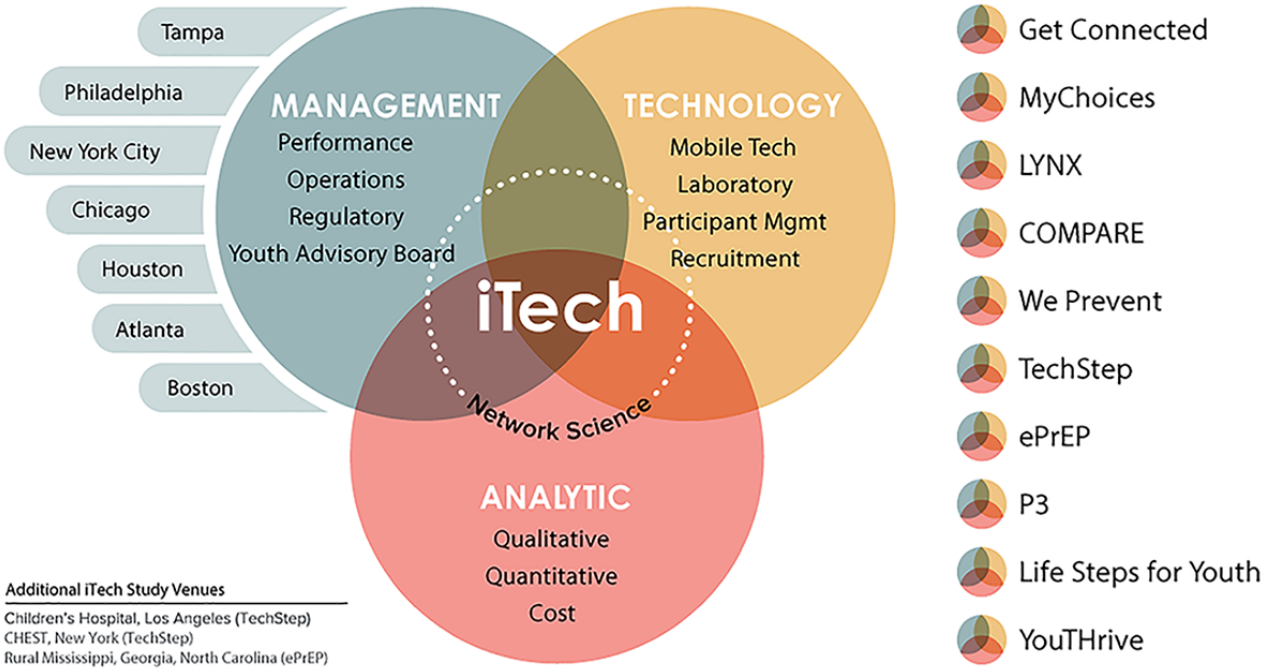
Commitment to Adolescent Research

Through a developed and centralized management and analytic framework, iTech supports a network of multidisciplinary scientists, researchers, clinicians, and public health professionals who work collaboratively to support iTech's diverse research portfolio. The network science team is made up of all research study PIs, SRV PIs, plus members of iTech's scientific leadership cores. This team meets monthly to talk about cross-cutting issues, brainstorm new concepts, review new scientific research, and leverage cross-protocol opportunities. iTech also supports a collaborative training and educational mission that crosses all cores and disciplines. iTech provides a nurturing environment to foster new junior investigators into adolescent HIV or AIDS research and builds collaborations to create new and innovative research in this area. We have deliberately built mentoring relationships into each of the research studies, pairing junior investigators with more experienced investigators.

Community Engagement

iTech has purposefully partnered with clinical care sites that have well-established community collaborations, including established youth advisory boards (YABs). We will work closely with each SRV to ensure sustained YAB involvement at each venue and within the larger iTech network. iTech's leadership will also work closely with YABs and other community stakeholders and advisors to help evaluate tools and programs, ensuring age appropriateness and readability, cultural sensitivity and linguistic appropriateness, gender and sexual orientation sensitivity, and minimal burden of intervention strategies. In addition, iTech has proposed involvement of at least one YAB member from each SRV in monthly Web-based Youth Advisory Council meetings to allow input on local as well as cross-iTech issues.

Figure 1. Overall iTech organizational structure.



Regulatory and Ethics

All research conducted within iTech will be centrally reviewed and approved by the institutional review board (IRB) of the University of North Carolina at Chapel Hill, acting as the IRB of record in accord with National Institutes of Health policies [31]. Local IRBs for participating institutions and SRVs sign reliance agreements with the UNC IRB and receive regular updates and notices of continuations or changes in protocol, as well as are informed of any adverse or serious adverse events that may occur at their site. A waiver of parental consent or assent is obtained for participants who are 15-17 years old. All studies have (5 studies) or will be (5 studies) registered on ClinicalTrials.gov (Table 1).

iTech Projects

The iTech scientific agenda is translated through 8 efficacy trials and 2 exploratory projects, all designed to address 4 primary objectives. Each study includes qualitative formative research to develop or adapt the intervention and an RCT of the intervention(s) versus standard of care. Many new or substantially adapted interventions are also conducting technical pilots in which the intervention is tested for a short period of time and qualitative exit interview data are used to finalize the intervention for RCT. This standardization of the research process across iTech studies is a key aspect of the network. Below, we outline each of the 4 objectives and briefly describe the interventions currently in place to address these objectives; note that all iTech interventions address multiple components of the care and prevention cascades and cross-cutting issues (Figure 2). Additional details can be found in the individual intervention protocol papers (will be cited once available or under review).

Evaluation of Novel Approaches for Identifying Youth With Undiagnosed HIV Infection

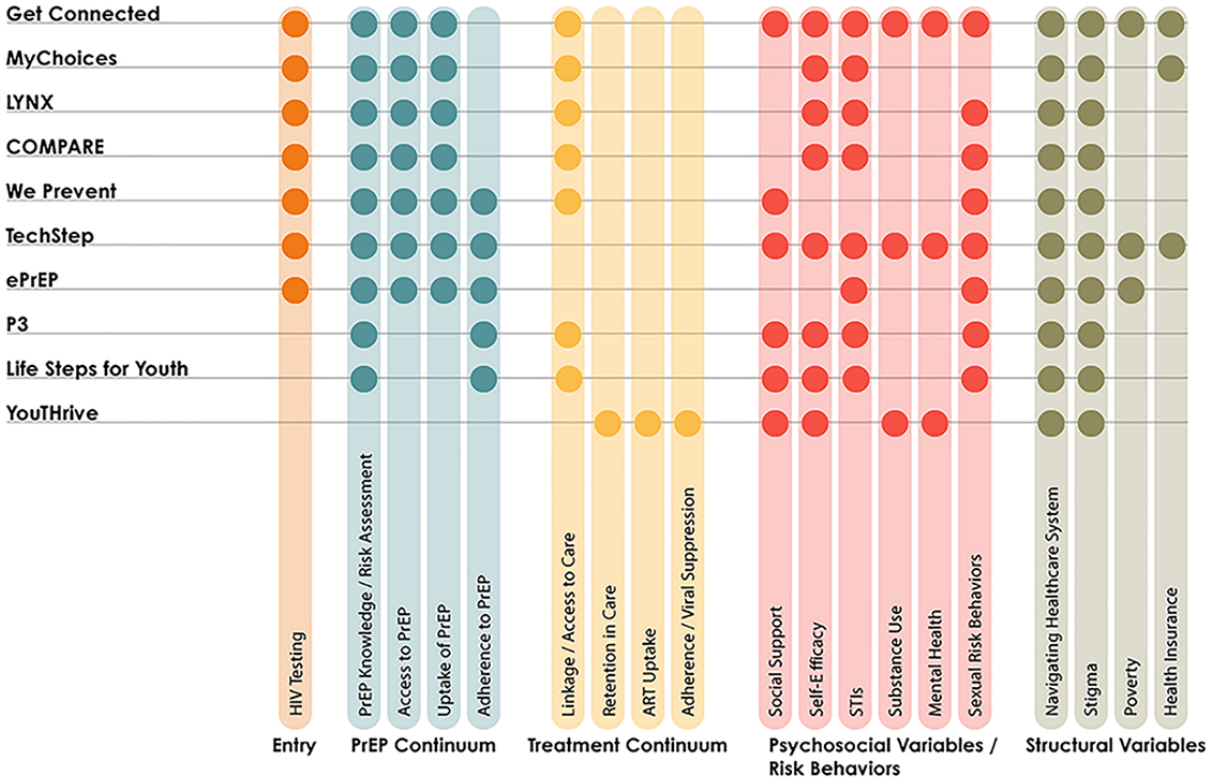
Despite Centers for Disease Control and Prevention and American Academy of Pediatrics recommendations that high-risk youth receive an HIV test at least annually [32], many sexually active YMSM have either never been tested or have not been tested in the last year. More than half of youth living with HIV (51%) are unaware of their infection [1,14,33,34]. Barriers to testing among youth, including YMSM, include misperception of individual risk, fear of testing positive, concerns about confidentiality, access to healthcare services, and provider reluctance to discuss sexual risk behaviors among adolescent patients and offer routine testing to those at risk [35]. Four iTech studies have a primary focus on HIV testing:

- *LYNX*: LYNX is a novel mobile app designed to increase HIV or STI testing and support PrEP uptake among YMSM. In this study, the investigators will expand their current mobile app, designed primarily to increase HIV or STI testing, to include components to increase the uptake and linkage to PrEP for YMSM, and then evaluate the feasibility and acceptability of this app in a pilot RCT. The key components addressed by the integrated LYNX app will be information, motivation, and behavioral skill needs [36-38] for increasing HIV or STI testing frequency and PrEP uptake.
- *MyChoices*: MyChoices is a youth-optimized version of a mobile app designed to increase HIV or STI testing and support PrEP uptake among YMSM [39]. In this study, the investigators will expand and enhance their current mobile app through theater testing with youth and then evaluate the feasibility and acceptability of this app in a pilot RCT. The key components of MyChoices address constructs of social cognitive theory, including self-regulation, self-efficacy, and environmental influences [40].
- *COMPARE*: If either app described above (or both) is shown to be feasible and acceptable, the app(s) will be tested in this follow-on research study to evaluate for efficacy. If both are deemed feasible and acceptable, YMSM in this 3-year study will be randomized to receive either MyChoices or LYNX or standard of care information about HIV testing and PrEP.
- *We Prevent*: This project aims to develop and test a relationship skills-focused HIV prevention intervention for YMSM and their partners. The intervention consists of two telemedicine sessions: the first focuses on relationship skills, and the second consists of HIV testing and counseling for couples and prevention planning [41]. Both sessions are attended by both members of the dyad.

Table 1. iTech studies' registration status.

Study name	ClinicalTrials.gov identifier or anticipated date of registration
Get Connected	NCT03132415
LYNX	NCT03177512
MyChoices	NCT03179319
P3 (Prepared, Protected, emPowered)	NCT03320512
YouthThrive	NCT03149757
LifeSteps for PrEP for Youth	Mid-2018
We Prevent	Mid-2018
ePrEP	Mid-2018
TechStep	Mid-2018
COMPARE	Late 2018

Figure 2. iTech research studies and intended continuum of prevention and care targets. ART: antiretroviral therapy; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.



Evaluation of Multilevel, Combination Prevention Approaches

Structural factors, such as lack of access to or prior negative experiences with prevention and care services may impede HIV or STI testing and PrEP uptake among YMSM and transgender youth, particularly among youth with co-occurring health risks and comorbidities (eg, substance use, mental illness, homelessness) [42-44]. It is critical to provide developmentally and culturally appropriate services and tailored short message service (SMS) text messaging for YMSM and transgender youth, to increase their engagement in risk reduction activities, routine uptake of HIV or STI testing, and awareness of PrEP. Two iTech studies primarily focus on combination prevention approaches that address structural factors:

- *Get Connected*: Get Connected! is a motivationally based, brief Web-based intervention that employs individual and system-level tailoring technology to reduce barriers to linkage into competent prevention care (eg, HIV or STI testing, PrEP) for YMSM [45,46]. YMSM receive personalized and theory-driven content regarding HIV or STI prevention, and structural factors are addressed through linkage to prevention and care services known to serve YMSM populations competently.
- *TechStep*: The rates of HIV infection among transgender youth (including transfeminine, transmasculine, and gender-nonconforming youth) are extremely high, particularly among transwomen [47,48] and transmen who have sex with men [49]. Furthermore, engagement in routine health care has been problematic due to structural barriers (eg, housing instability, unemployment or underemployment, limited educational attainment), provider attitudes, and perceived or actual experiences of stigma and discrimination [50]. TechStep is a two-condition, technology-based RCT, with a stepped care approach, among high-risk HIV-negative transgender youth for reducing sexual risk behaviors and increasing PrEP uptake. The stepped care approach includes increasing intervention intensity from SMS text messaging or a Web app to e-coaching.

Evaluation of Uptake of and Adherence to Biomedical Prevention Modalities

PrEP provides a strong preventive benefit to youth at risk for HIV infection and there is overwhelming evidence supporting its efficacy [20,21,51-53]. Although oral PrEP adherence is highly correlated with its efficacy in clinical trials, adherence rates are variable [52,54-56]. In real-world practice settings, PrEP adherence may even be lower, particularly among youth [21,23]. As such, interventions are needed to improve and sustain adherence to PrEP, thereby maximizing its preventive benefits in at risk populations. Three iTech interventions primarily address PrEP uptake and adherence:

- *LifeSteps for PrEP for Youth (LSPY)*: LifeSteps is an evidence-based HIV medication adherence intervention for HIV infected individuals, which was developed by Safren et al [57-59] and has been adapted for diverse populations [60-62], including adolescents [63]. It consists of four, weekly, nurse-delivered sessions with weekly SMS. In this study, investigators will tailor LSPY to meet the unique

needs of YMSM and then conduct a pilot two-arm RCT of the modified version of LSPY to test feasibility, acceptability, and preliminary efficacy.

- *P3 (Prepared, Protected, emPowered)*: P3 is an interactive mobile phone app for HIV-uninfected YMSM. The app utilizes social networking and game-based mechanics, as well as a comprehensive understanding of what constitutes "best practices" in app development to improve PrEP adherence and retention in preventive care. An enhanced arm (P3+) will deliver in-app adherence counseling based on the integrated Next Step Counseling model [64,65]. A three-arm RCT will be conducted.
- *ePrEP*: Rural and periurban areas across the Southeast do not have extensive access to PrEP providers. A tailored approach for rural YMSM, addressing known structural barriers of transportation, access to providers, and privacy, is likely to yield high levels of PrEP initiation and persistence in care. The study will finalize the development of a unified rural telemedicine system with a standalone mobile phone app interface and then conduct an RCT of the ePrEP intervention to determine if there is higher PrEP adherence compared with a control condition, which gives access to a Web-based PrEP locator.

Evaluation of Interventions Designed to Promote or Optimize Engagement in Care, ART Adherence, and Viral Load Suppression in HIV-Positive Youth

Poor adherence among youth is multifactorial and includes medical (eg, side effects, dissatisfaction with medical team), logistical (eg, forgetting, inconvenience), and psychological (eg, depression, lack of support, perceived stigma) barriers [66,67]. Sufficient and sustained ART adherence reduces excess morbidity and mortality among people living with HIV [68] and lowers the probability of forward transmission to sexual partners [69]. Advancing targeted and innovative ART adherence interventions for youth with HIV is an urgent priority; one iTech intervention primarily targets ART adherence:

- *YouTHrive*: YouTHrive (pronounced "youth thrive") is a Web app intervention to improve ART adherence among youth living with HIV that has the following components: (1) enhanced peer-to-peer interaction, (2) engagement SMS text messages, (3) mood and ART adherence self-monitoring, (4) goal setting, and (5) tailored ART and HIV informational content. Gamification techniques (eg, leveling) are used to promote sustained engagement.

Results

Formative work has already begun on a number of the iTech trials detailed above. We expect the first RCTs to begin in mid-2018. iTech is anticipating preliminary findings from the first randomized control trials (LYNX and MyChoices) to be presented by early 2019. Additional preliminary findings from TechStep and P3 are expected mid to late 2020, with YouTHrive, Get Connected, and ePrEP presenting preliminary RCT findings by late 2021. We expect additional findings as we add new interventions focused within each of our four iTech objectives.

Discussion

iTech brings together multidisciplinary experts in the fields of adolescent HIV treatment and prevention, development and evaluation of technology-based interventions, HIV surveillance and epidemiology, and intervention design and evaluation. Fostered by an MC that prioritizes communication and collaboration, this robust team will work collaboratively to respond to emerging issues and promote continued advancements in the field.

Technology-delivered interventions are well-suited for youth given their modality, the common use of technology in the population, the platform's suitability to deliver tailored content specific to each user's HIV or AIDS risk behaviors and context, and the platform's unique capability to diffuse HIV or AIDS prevention programs to large numbers of youth residing in numerous geographic locations. Youth, including YMSM, are receptive to internet- and mobile phone-delivered interventions [29,70,71].

Using the internet to recruit, engage, and retain youth in interventions is not only possible but also necessary. Youth may lack the social capital or resources to access in-person interventions, may be dependent on adults for money or transportation, or may need permission to attend programs. These barriers are particularly problematic for YMSM who, due to anticipated or actual stigma, are unable or unwilling to talk to adults about their same-sex attractions, behavior, sexual identity, and need to receive prevention and care services [72-75]. Traditional face-to-face formats thus create difficulties for youth when they cannot easily access these interventions in their communities, are not able to attend the sessions when they are offered, and cannot choose to engage with the interventions' content when most convenient. In addition, in a world where so much content is available online, there is an appeal (and perhaps even an expectation) to interventions that can be accessed online, in the privacy of one's home, viewed alone or with friends, and when best suits the young person. However, while in-person interventions may be costlier, some youth may benefit from face-to-face interactions with culturally responsive providers. Thus, costing analyses are critically important with regard to technology-based interventions that are resource intensive to develop but have a great potential to be scalable and cost-effective, with high public health impact [76]. We have integrated sophisticated methodologies to translate findings into HIV prevention recommendations for youth in the United States.

Acknowledgments

This work was supported by the National Institutes of Health Adolescent Medicine Trials Network for HIV/AIDS Interventions and the University of North Carolina/Emory Center for Innovative Technology (1U19HD089881, PIs: LBH-W and PSS). This work was also supported by the Center for AIDS Research at Emory University (P30AI050409) and the University of North

Carolina at Chapel Hill Center for AIDS Research (P30AI50410). The content is solely the responsibility of the authors and does not represent the official views of the funding agencies. The authors would like to thank Adi Ferrara, MS, ELS, for help with the preparation of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AC: Analytic Core
ART: antiretroviral therapy
ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions
HIPPA: Health Insurance Portability and Accountability Act of 1996

IRB: institutional review board
iTech: University of North Carolina/Emory Center for Innovative Technology
LSPY: LifeSteps for PrEP for Youth
MC: Management Core
mHealth: mobile health
NIH: National Institutes of Health
PI: principal investigator
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SMS: short message service
SRV: subject recruitment venue
STI: sexually transmitted infection
TC: Technology Core
UNC: University of North Carolina
YAB: youth advisory board
YMSM: young men who have sex with men

Edited by B Mustanski, S Allison, I Holloway, A Pettifor, R Schnall; submitted 11.03.18; peer-reviewed by L Kuhns, M Kipke; comments to author 15.04.18; revised version received 02.05.18; accepted 08.05.18; published 03.08.18.

Please cite as:
Hightow-Weidman LB, Muessig K, Rosenberg E, Sanchez T, LeGrand S, Gravens L, Sullivan PS
University of North Carolina/Emory Center for Innovative Technology (iTech) for Addressing the HIV Epidemic Among Adolescents and Young Adults in the United States: Protocol and Rationale for Center Development
JMIR Res Protoc 2018;7(8):e10365
URL: http://www.researchprotocols.org/2018/8/e10365/
doi:10.2196/10365
PMID:30076126

Publisher:
JMIR Publications
130 Queens Quay East.
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