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Protocol

Connecting Smartphone and Wearable Fitness Tracker Data with a Nationally Used Electronic Health Record System for Diabetes Education to Facilitate Behavioral Goal Monitoring in Diabetes Care: Protocol for a Pragmatic Multi-Site Randomized Trial

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Abstract

Background: Mobile and wearable technology have been shown to be effective in improving diabetes self-management; however, integrating data from these technologies into clinical diabetes care to facilitate behavioral goal monitoring has not been explored.

Objective: The objective of this paper is to report on a study protocol for a pragmatic multi-site trial along with the intervention components, including the detailed connected health interface. This interface was developed to integrate patient self-monitoring data collected from a wearable fitness tracker and its companion smartphone app to an electronic health record system for diabetes self-management education and support (DSMES) to facilitate behavioral goal monitoring.

Methods: A 3-month multi-site pragmatic clinical trial was conducted with eligible patients with diabetes mellitus from DSMES programs. The Chronicle Diabetes system is currently freely available to diabetes educators through American Diabetes Association–recognized DSMES programs to set patient nutrition and physical activity goals. To integrate the goal-setting and self-monitoring intervention into the DSMES process, a connected interface in the Chronicle Diabetes system was developed. With the connected interface, patient self-monitoring information collected from smartphones and wearable fitness trackers can facilitate educators' monitoring of patients' adherence to their goals. Feasibility outcomes of the 3-month trial included hemoglobin A_{1c} levels, weight, and the usability of the connected system.

Results: An interface designed to connect data from a wearable fitness tracker with a companion smartphone app for nutrition and physical activity self-monitoring into a diabetes education electronic health record system was successfully developed to enable diabetes educators to facilitate goal setting and monitoring. A total of 60 eligible patients with type 2 diabetes mellitus were randomized into either group 1) standard diabetes education or 2) standard education enhanced with the connected system. Data collection for the 3-month pragmatic trial is completed. Data analysis is in progress.

Conclusions: If results of the pragmatic multi-site clinical trial show preliminary efficacy and usability of the connected system, a large-scale implementation trial will be conducted.

Trial Registration: ClinicalTrials.gov NCT02664233; https://clinicaltrials.gov/ct2/show/NCT02664233 (Archived by WebCite at http://www.webcitation.org/6yDEwXHo5)

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KEYWORDS

wearable devices; connected health; mobile health; diabetes; randomized clinical trial; goal setting; lifestyle intervention; electronic health record; self-monitoring; behavior modification

Introduction

Obesity and type 2 diabetes mellitus (T2DM) are serious chronic illnesses in the US. Compared to a standard diabetes education, behavioral lifestyle interventions were found to be more effective in weight loss and diabetes control among overweight or obese patients with T2DM [1,2]. Self-monitoring and goal setting are two essential components of a behavioral lifestyle intervention [3,4]. Self-monitoring of healthy eating and physical activity play a key role in weight management and diabetes control in T2DM patients. Previous studies have shown that self-monitoring with an electronic diary is as effective as monitoring with a paper diary while being less burdensome and time-consuming [5,6]. Smartphones are now gaining attention for their use in facilitating patient self-monitoring of healthy eating and physical activity.

Research supports diabetes education as a cost-effective way to coordinate diabetes care. Diabetes self-management education and support (DSMES) programs located throughout the US are integrated within the existing health care system. Thus, DSMES programs present an ideal setting for testing the implementation of an evidence-based self-monitoring intervention. Chronicle Diabetes is a Web-based electronic health record (EHR) system designed to facilitate behavioral goal monitoring for the American Diabetes Association (ADA)–recognized DSMES Programs [7,8]. Chronicle Diabetes enables educators and their patients to set collaborative goals for their diet and physical activity; however, the lack of an interface to attach a diary was perceived to be one of the barriers by educators [9]. Directly connecting patient's goal-setting and self-monitoring information collected through smartphones to Chronicle Diabetes can facilitate education processes so that educators can better coordinate with care plans and efficiently deliver a potentially more effective and tailored intervention.

We used the Chronicle Diabetes system currently freely available to diabetes educators through ADA–recognized DSMES programs to set patients' diet and physical activity goals and to integrate patients' self-monitoring information collected from smartphones and wearable fitness trackers to improve educators' ability to monitor patients' adherence to goals. Moreover, using a central location for tracking patients' behaviors and progress enables long-term self-management support for sustained behavior change. A system with good usability should foremost have a functionality design that matches the work domain and a user interface that supports efficient task performance by the users. We used a usability framework developed to ensure high usability of connected health systems to guide the development of our proposed connected system [10].

Our study developed such an interface and tested its usability, acceptability, and feasibility in a multi-site randomized clinical trial. The objective of this paper is to report on a study protocol for a pragmatic multi-site trial and the intervention components, including the detailed connected health interfaces.

Methods

Sample

Eligibility was assessed prior to participant enrollment. To participate in the study, individuals had to have been diagnosed with T2DM, be 18 years or older, own a smartphone compatible with the Jawbone UP24 fitness tracker, and be overweight or obese as classified by their body mass index >25kg/m^2. A list available on the Jawbone website was used to determine whether participants' smartphones were compatible with the Jawbone fitness tracker. Research assistants also searched the smartphones' respective app stores to determine whether the companion app to the Jawbone UP24, *UP*, could be downloaded and whether the fitness band could be synced to the phone. Individuals whose smartphones were not compatible with the *UP* app or Jawbone fitness tracker were ineligible for participation in the study. Overweight or obesity status was assessed using self-reported height and weight. In addition, individuals undergoing treatment for severe psychiatric illness were not eligible to participate in the study; however, no potential participants were deemed ineligible based on this criterion.

Sample Size Justification

We enrolled 60 patients for the study: 30 in Houston and 30 in Pittsburgh. In a national study testing the behavioral lifestyle intervention in a nontranslational setting [2], hemoglobin A_{1c} (HbA_{1c}; %) levels dropped from 7.29 to 7.15 after one year in the standard intervention group, whereas the levels dropped more sharply, from 7.25 to 6.61, in the intensive intervention group. The standard deviations were 1 in each group and each repeated measurement. Assuming a correlation of 0.8 between repeated measurements and alpha=.05, we estimated that enrollment of at least 27 patients per group would result in power > 80% to detect the interaction between group and time (pre- and postintervention). The power was estimated by simulating 1000 normal samples based on observed means and variances of the trial. Allowing for 10% attrition at the end of the 3-month follow-up, we sought to enroll 30 patients in each group.

Recruitment, Screening and Enrollment

Individuals were recruited from ADA–recognized DSMES programs in Houston, Texas and Pittsburgh, Pennsylvania. Patients were asked if they had a smartphone and whether they would be interested in participating in a research study in which they would monitor their diet and physical activity using a fitness tracker and smartphone app. Those who expressed interest were provided with more detailed information about

the study and screened for eligibility. Informed consent was provided by all eligible patients. This study was approved by the Institutional Review Boards of The University of Texas Health Science Center at Houston and the University of Pittsburgh.

Randomization

Eligible patients were randomly assigned to the intervention program or a standard diabetes education program in a 1:1 allocation ratio. The study statistician created a randomization sheet to randomly assign the patients at the time of enrollment after written informed consent was obtained.

Treatment Procedures

Standard Diabetes Education Group

The recruiting sites all offer ADA–recognized diabetes education programs. During the study, patients in the standard diabetes education group saw their diabetes educators at baseline and for the follow-up data collection visit at 3 months. The patients' interaction with their diabetes educators included setting and modifying patients' goals related to nutrition, physical activity, risk prevention, self-monitoring of blood glucose, and medication based on their self-report of their progress. Additional visits could be scheduled as usual care based on patients' conditions. These visits were recorded as confounding factors that would indicate any treatment or patient condition changes during the study period.

Connected Group

Participants in the connected group received standard diabetes education as described above. In addition, participants randomly assigned to this group were exposed to the following intervention components and procedures:

- *Goal Setting:* Diabetes educators and patients mutually set nutrition and physical activity goals and established plans for achieving the goals they documented in the Chronicle Diabetes system, in addition to the DSMES content that diabetes educators typically deliver, depending on participants' conditions.
- *Self-Monitoring:* During the baseline visit, each study participant received a Jawbone UP24 wristband with a companion smartphone app for monitoring their diet and physical activity behaviors according to the goals set during the education visit. The study team assisted patients with creating user accounts for device use. In addition, patients received printed instruction manuals and access to YouTube tutorial videos to orient them to the Jawbone device and the companion app. Participants received hands-on training on how to self-monitor their diet and physical activity habits using the Jawbone UP24 at the beginning of the study. Specifically, patients were instructed to record their physical activity and foods eaten using the Jawbone UP24 app and asked to wear the Jawbone wristband for step tracking on a daily basis for 3 months. Participants practiced entering a meal and a workout into the smartphone app, as well as editing each of these entries. Food intake was to include all items and portion sizes consumed in a given meal, including any condiments used. The smartphone app automatically calculated calories, grams of fat, and carbohydrates for each meal, given the portions sizes entered were correct. Any exercise, including the type, duration, and level of intensity, was to be recorded daily as well. Using participants' height and weight data, calories burned were automatically calculated, given the type, duration, and intensity of exercise were entered correctly. Participants were encouraged to log their dietary behaviors and physical activity in real-time whenever possible so that calorie totals would be accurate and so that they could make adjustments to their food choices and level of physical activity throughout the day.

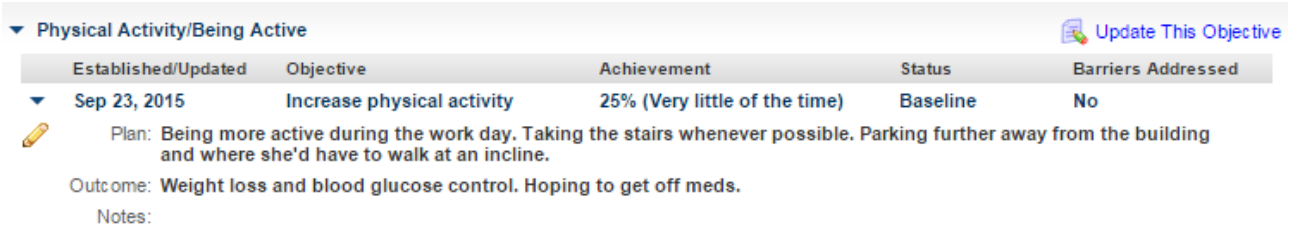
Jawbone UP24 fitness tracker and its Companion Smartphone App

The Jawbone UP24 smartphone app, *UP*, offers several ways to enter dietary behaviors and physical activity. For example, food items can be logged by searching for popular foods in the food database, scanning the barcodes on packaged items, and selecting from a restaurants' menu. *UP* stores nutritional information for thousands of foods and gives each food item a score (1-10) to help users know which foods are most and least healthy. In addition, the fitness tracker has a recognition feature to automatically detect whether an individual is doing some type of exercise. When exercise is detected, the smartphone app asks whether a workout was completed. However, if a workout is not detected, the user can still log an exercise session. Regardless of if a workout is detected or entered into the smartphone app, the fitness tracker wristband that the user is wearing is continually tracking the number of steps that the user is taking. All data from the fitness tracker wristband are wirelessly synced to the smartphone app using Bluetooth technology.

Chronicle Diabetes System

According to the national standards for DSMES, diabetes educators are expected to establish and track patients' behavioral goals [11]. Chronicle Diabetes (http://www.chronicle diabetes.com) is a Health Insurance Portability and Accountability Act (HIPAA)–compliant Web-based electronic diabetes education system developed by the University of Pittsburgh and adopted for reporting outcomes for the ADA–recognized diabetes education programs. All ADA–recognized diabetes education programs have free access to Chronicle Diabetes. During an education session, the patients and diabetes educators can mutually initiate behavioral goals and diabetes educators can use the Chronicle Diabetes system to document the goals by selecting from one of the seven self-care goal categories: healthy eating, being active, monitoring, taking medication, problem-solving, reducing risks, and healthy coping. Patients' goal achievement can be scored at 0%, 25%, 50%, 75%, and 100% at baseline. In addition, diabetes educators and their patients can choose to continue, modify, or discontinue the goals at follow-up visits. This allows for a patient's progress towards meeting a goal to be tracked over time (Figure 1). In our previous evaluation of the Chronicle Diabetes system, the preliminary analysis showed that the diabetes educators favored the feature of setting behavioral goals, the majority of which were focused on nutrition and physical activity [7,8].

Figure 1. A partial snapshot of the Chronicle Diabetes system with goal setting function.



While educators found Chronicle Diabetes useful for setting and tracking behavioral goals, one of the major barriers they identified was the lack of a feature to attach a food diary for educators to evaluate patients' adherence to the prescribed goals. Thus, in this study, we developed a connected interface in the Chronicle Diabetes System to connect data from the Jawbone UP24 fitness tracker and its companion smartphone app for patient diet and physical activity data. Within each patient's documentation record in Chronicle Diabetes, two new sections (tabs) of the record were added: "Self Monitoring–Nutrition" and "Self Monitoring–Activity." These two tabs were used by educators to navigate to two pages showing self-monitored diet and activity information. When educators click the "Self Monitoring–Nutrition" tab in the navigation panel for a patient for the first time, a link to connect to the patient's account will appear. In the beginning of the study, educators needed to click a link in this page to connect the patient's Jawbone account to their account in the Chronicle Diabetes system. The link took the educator into a page to select what they wanted to connect to from a list of the devices or apps that were supported by Validic, an intermediary platform that provides connection to data from a wide variety of devices and apps. In our study, educators were instructed to select Jawbone and enter their account information to complete the connection process. The link can also be sent to participants via a previously generated email template. The educator can encourage the patient to complete the connection process during the first visit after enrolling in the study. Once the connection process is complete, a monthly calendar view will appear in the "Self Monitoring–Nutrition" page with cells for calories, carbs, saturated and unsaturated fat, fiber, and protein for each day (See Figure 2). The weekly average of these macronutrients is also available in the far-right column of this calendar. Educators can click on any single day to view the food types, macronutrient information broken down by meal, and time of the meal.

The "Self Monitoring–Activity" page has the same monthly calendar view as the "Self Monitoring–Nutrition" page once connected: calories burned, steps, and planned exercise duration for each day (Figure 3), along with the weekly total and average for these 3 activity parameters. Educators can click on each day for more details about patients' activity, including the time, type, and intensity levels of the activities (Figure 3). In this connected interface, educators can switch between the nutrition and physical activity pages easily by clicking on the two tabs on the left (the month being viewed on one tab is automatically displayed on the other tab, allowing for easy correlation between the two months). Also, they can use the "Jump to date" function to select a particular date of interest and can go forward and back one month in the calendar view to quickly review data over a few months and see trends.

Figure 2. Partial Screenshot of Monthly Calendar View of Diet Monitoring in Chronicle Diabetes.

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Week Averages
	Sep 13	Sep 14	Sep 15	Sep 16	Sep 17	Sep 18	Sep 19	Sep 13 - Sep 19
Calories:	661	847	756	1188	230	No Data	No Data	736.4
Carbs:	72g	115g	128g	148g	36g	No Data	No Data	99.8g
Saturated Fat:	5g	15g	4g	10g	4g	No Data	No Data	7.6g
Unsaturated Fat:	23g	9g	8g	31g	2g	No Data	No Data	14.6g
Fiber:	12g	7g	17g	10g	0	No Data	No Data	9.2g
Protein:	23g	32g	19g	33g	5g	No Data	No Data	22.4g

Figure 3. Partial Screenshot of Monthly Calendar View of Activity Monitoring in Chronicle Diabetes.

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Week Totals (Averages)
	Sep 13	Sep 14	Sep 15	Sep 16	Sep 17	Sep 18	Sep 19	Sep 13 - Sep 19
Calories Burned:	2560	1294	1412	181	1159	194	107	6907 (987)
Steps:	8441	9721	10914	3506	8438	3708	1990	46718 (6674)
Exercise:	108min	50min	57min	-	48min	-	-	263min (37min)

Validic as an Intermediary Platform Between Mobile Apps and Devices and the Chronicle Diabetes System

We used Validic as an intermediary platform to connect the Jawbone UP24 diet and physical activity data to the Chronicle Diabetes system. We adopted this approach rather than directly connecting mobile data and Chronicle Diabetes owing to 1) the flexibility of connecting to additional fitness tracking systems in the future, 2) robust screening of data and high-level security through Validic, and 3) Validic's experience working with large EHR systems. We believe the incorporation of Validic not only enables a seamless transition for national dissemination of our developed connected interface but also enables its future integration with EHRs seamlessly to make connected technology available to any health care system using an EHR system.

Data Security in Smartphone Use, Transit, and the Chronicle Diabetes System

The security features are based on the premise that any data at rest or in motion must be encrypted and unreadable to outsiders. User profile, clinical data, and progress stored in the local SQL lite database on the smartphones are encrypted using Advanced Encryption Standard/Rivest-Shamir-Aldeman algorithms. When the data are sent to the server, the data are encrypted using the session ID received from the server in its initial authorization token. This encrypted data is sent over HTTPS, thus allowing 2 levels of security. When the data reach the server, they are decrypted using the session identification and stored in the database by encryption again using a server-specific encryption algorithm. Thus, the basic premise is satisfied and the data are completely secure when collected through smartphones, in transit, and when accessed from the Chronicle Diabetes system. All data from the Chronicle Diabetes system are stored securely in an HIPAA–compliant manner and restricted based on access privileges. An HIPAA Business Associates Agreement is signed with each facility using this system. All data access is recorded and a full audit trail can be produced.

Outcome Measures

Feasibility

Feasibility of the study was evaluated through participant attrition rates and qualitative and quantitative assessments of the usability of the connected system. Usability of the connected interface technology was measured using the System Usability Scale [12]. The System Usability Scale measures patients' and educators' acceptability, satisfaction, and perceived usefulness of the intervention that is the focus of the study (that is, the connected interface technology within Chronicle Diabetes). Patients and educators were asked to rate each usability item in the scale from 0 to 100.

Preliminary Efficacy

Preliminary efficacy was measured by changes in patients' HbA_{1c} levels and weight from baseline to 3 months. HbA_{1c} levels were measured using the *A1cNOW* self-check system via a finger stick or extracted from clinical visit data. Participants' weight was measured via a weight scale in the clinic or self-report.

Additional Baseline and Follow-Up Measures

At baseline, a sociodemographic and medical history questionnaire is used to collect study participants' socio-demographic information, diabetes treatment plan, and other medical history. At 3 months, we asked patients how many medical, emergency, and diabetes education visits were made in between the 2 study visits and recorded this information as potential confounding factors of the study outcome.

Data Analysis Plan

SAS (version 9.2, SAS Institute, Inc, Cary, NC) was used for data screening and analyses. All the statistical tests were performed at 5% level-of-significance. The outcome variables HbA_{1c} (%) level and weight change were used to measure the preliminary efficacy of this study. Qualitative thematic analysis was used to analyze interview data.

Results

We recruited 30 patients from Houston, Texas and 30 patients from Pittsburgh, Pennsylvania, through various diabetes education programs recognized by the ADA. At each site, 30 enrolled patients were randomly assigned to the intervention group or standard diabetes education group. Data collection is completed. Data analysis is in progress. The study results will be reported in mid-2018.

Discussion

This study leveraged existing DSMES programs, resources, and diabetes educators to deliver the technology-based program. Although mobile health interventions were developed to improve patient self-management in various research efforts [13-15], none of these efforts focused on using data from mobile devices for clinicians to use in clinical practice. The implementation of the evidence-based behavioral goal setting and monitoring program in the diabetes education setting using technology provides an opportunity to secure reimbursement for delivering the program in a practice setting. This study helped us test the implementation of the evidence-based behavior intervention using a newly developed interface-connected technological assistance built on an existing EHR system used by diabetes educators to facilitate the long-term implementation in a diabetes education setting in a 3-month randomized controlled trial with ADA–recognized diabetes education programs.

Using smartphones and connected wearable fitness trackers not only reduces the burden of patient self-monitoring but also enables the connection of daily patient information to the Chronicle Diabetes clinical information system, where educators can track patients' behaviors between visits in a graphical format and prepare for the next intervention session. This connection could also serve as an interactive platform to deliver intervention and provide feedback from diabetes educators in real time in the future. Connection to a national recognition data base through Chronicle Diabetes also offers the potential to collect behavioral and clinical information on unique populations and practices nationwide. Connecting patients' self-monitoring information collected through smartphones to Chronicle Diabetes can facilitate education processes by allowing

educators to more efficiently coordinate care plans with patients and ensure delivery of effective and tailored interventions. Moreover, using a central location for tracking patients' behaviors and progress enables long-term self-management support for sustained behavior change. A system with good usability should foremost have good design of functionality that matches the work domain and a user interface that supports efficient task performance by the users [10]. The usability evaluation conducted in this study could also provide scientific evidence and support for other noncommunicable diseases that may benefit from continuous behavior monitoring. The interface developed in this study could also be used for more interactive designs in future studies, such as enabling educators to send tailored feedback to patients' smartphones.

This study could be easily and widely disseminated in future studies and practice. There are increasing numbers of smartphone users in the United States, including minority populations. As ADA–recognized education programs with access to the Chronicle Diabetes system are located throughout the US, this study could be widely disseminated. We anticipated that diabetes educators would use this connected tool to engage diabetes patients in lifestyle changes in between diabetes education visits and facilitate conversation on meeting or changing behavioral goals at follow-up diabetes education visits, rather than use data from the connected tool as a stand-alone piece of information to make treatment changes. The smartphone and wearable tracker usage in this study is only a tool to assist with diabetes educators, not to replace the role of a diabetes educator. The wearable fitness tracker and its companion smartphone app are not approved by the US Food and Drug Administration and their accuracy on measuring physical activity levels and dietary information is not guaranteed. Thus, the data connected from these devices and smartphone apps to Chronicle Diabetes system should be used with caution.

In summary, if proven effective, the study will not only advance nursing and behavioral science by leveraging existing resources to disseminate an evidence-based behavior intervention via emerging technology, but it will also provide theoretical and methodological guidance for other researchers conducting usability evaluations connecting mobile device information collection with EHR systems for managing diabetes and other chronic conditions.

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Conflicts of Interest

BU is the President of Flipside Media. Flipside Media was the contractor that originally developed Chronicle Diabetes for the University of Pittsburgh Medical Center. Flipside Media is currently the contractor that maintains Chronicle Diabetes for the American Diabetes Association. Neither BU nor Flipside Media have any financial interest in Chronicle Diabetes.

References

1. Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med 2010 Sep 27;170(17):1566-1575 [FREE Full text] [doi: 10.1001/archinternmed.2010.334] [Medline: 20876408]
2. Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care 2007 Jun;30(6):1374-1383 [FREE Full text] [doi: 10.2337/dc07-0048] [Medline: 17363746]
3. Look AHEAD Research Group, Wadden TA, West DS, Delahanty L, Jakicic J, Rejeski J, et al. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. Obesity (Silver Spring) 2006 May;14(5):737-752 [FREE Full text] [doi: 10.1038/oby.2006.84] [Medline: 16855180]
4. Ryan DH, Espeland MA, Foster GD, Haffner SM, Hubbard VS, Johnson KC, Look AHEAD Research Group. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Control Clin Trials 2003 Oct;24(5):610-628. [Medline: 14500058]
5. Burke LE, Wang J, Sevick MA. Self-monitoring in weight loss: a systematic review of the literature. J Am Diet Assoc 2011 Jan;111(1):92-102 [FREE Full text] [doi: 10.1016/j.jada.2010.10.008] [Medline: 21185970]
6. Burke LE, Conroy MB, Sereika SM, Elci OU, Styn MA, Acharya SD, et al. The effect of electronic self-monitoring on weight loss and dietary intake: a randomized behavioral weight loss trial. Obesity (Silver Spring) 2011 Feb;19(2):338-344 [FREE Full text] [doi: 10.1038/oby.2010.208] [Medline: 20847736]

7. Wang J, Siminerio L. Chronicle Diabetes: A Web-Based Tool to Document Behavioral Goals. Poster presentation at the CDC's 34th Annual Diabetes Translation Conference, Minniapolis, MN 2011.
8. Wang J, Siminerio L. Using a web-based system for behavioral goal monitoring in diabetes education. Diabetes. (Suppl 1) 2011;60:0755.
9. Wang J, Siminerio LM. Educators' insights in using chronicle diabetes: a data management system for diabetes education. Diabetes Educ 2013;39(2):248-254. [doi: 10.1177/0145721713475844] [Medline: 23427239]
10. Wang J, Zhang J. Adapting A Unified Electronic Health Record Usability Framework for Evaluation of Connected Health Care Technologies Linking Mobile Data. iproc 2015;1(1):e20.
11. Beck J, Greenwood DA, Blanton L, Bollinger ST, Butcher MK, Condon JE, et al. 2017 National Standards for Diabetes Self-Management Education and Support. Diabetes Care 2017 Jul 28;40(10):1409-1419. [doi: 10.2337/dci17-0025] [Medline: 28754780]
12. Brooke J. : SUS - a quickdirty usability scale. Jordan, P., Thomas, B., Weerdmeester, B., McClelland, A. (eds.) Usability Evaluation in Industry. Taylor Francis, London (1996) 1996.
13. Osborn CY, van Ginkel JR, Rodbard D, Heyman M, Marrero DG, Huddleston B, et al. One Drop | Mobile: An Evaluation of Hemoglobin A1c Improvement Linked to App Engagement. JMIR Diabetes 2017 Aug 24;2(2):e21. [doi: 10.2196/diabetes.8039]
14. Fukuoka Y, Gay CL, Joiner KL, Vittinghoff E. A Novel Diabetes Prevention Intervention Using a Mobile App: A Randomized Controlled Trial With Overweight Adults at Risk. Am J Prev Med 2015 Aug;49(2):223-237 [FREE Full text] [doi: 10.1016/j.amepre.2015.01.003] [Medline: 26033349]
15. Sevick MA, Zickmund S, Korytkowski M, Piraino B, Sereika S, Mihalko S, et al. Design, feasibility, and acceptability of an intervention using personal digital assistant-based self-monitoring in managing type 2 diabetes. Contemporary Clinical Trials 2008 May;29(3):396-409. [doi: 10.1016/j.cct.2007.09.004]

Abbreviations

ADA: American Diabetes Association
DSMES: diabetes self-management eucation and support
EHR: electronic health record
HIPPA: Health Insurance Portability and Accountability Act
T2DM: type 2 diabetes mellitus

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Protocol

Epic Allies, a Gamified Mobile Phone App to Improve Engagement in Care, Antiretroviral Uptake, and Adherence Among Young Men Who Have Sex With Men and Young Transgender Women Who Have Sex With Men: Protocol for a Randomized Controlled Trial

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Abstract

Background: In the United States, young men who have sex with men (YMSM) and transgender women who have sex with men (YTWSM) bear a disproportionate burden of prevalent and incident HIV infections. Once diagnosed, many YMSM and YTWSM struggle to engage in HIV care, adhere to antiretroviral therapy (ART), and achieve viral suppression. Computer-based interventions, including those focused on behavior change, are recognized as effective tools for engaging youth.

Objective: The purpose of the study described in this protocol is to evaluate the efficacy of Epic Allies, a theory-based mobile phone app that utilizes game mechanics and social networking features to improve engagement in HIV care, ART uptake, ART adherence, and viral suppression among HIV-positive YMSM and YTWSM. The study also qualitatively assesses intervention acceptability, perceived impact, and sustainability.

Methods: This is a two-group, active-control randomized controlled trial of the Epic Allies app. YMSM and YTWSM aged 16 to 24 inclusive, with detectable HIV viral load are randomized 1:1 within strata of new to care (newly entered HIV medical care ≤12 months of baseline visit) or ART-nonadherent (first entered HIV medical care >12 months before baseline visit) to intervention or control conditions. The intervention condition addresses ART adherence barriers through medication reminders and adherence monitoring, tracking of select adherence-related behaviors (eg, alcohol and marijuana use), an interactive dashboard that displays the participant's adherence-related behaviors and provides tailored feedback, encouragement messages from other users, daily HIV/ART educational articles, and gamification features (eg, mini-games, points, badges) to increase motivation for behavior change and app engagement. The control condition features weekly phone-based notifications to encourage participants to view educational information in the control app. Follow-up assessments are administered at 13, 26, and 39 weeks for each arm. The primary outcome measure is viral suppression. Secondary outcome measures include engagement in care, ART uptake, ART adherence, and psychosocial barriers to engagement in care and ART adherence, including psychological distress, stigma, and social support.

Results: Baseline enrollment began in September 2015 and was completed in September 2016 (n=146), and assessment of intervention outcomes continued through August 2017. Results for primary and secondary outcome measures are expected to be reported in ClinicalTrials.gov by April 30, 2018.

Conclusions: If successful, Epic Allies will represent a novel adherence intervention for a group disproportionately impacted by HIV in the United States. Adherent patients would require less frequent clinic visits and experience fewer HIV-related secondary infections, thereby reducing health care costs and HIV transmission. Epic Allies could easily be expanded and adopted for use among larger populations of YMSM and YTWSM, other HIV-positive populations, and for those diagnosed with other chronic diseases such as diabetes and hypertension.

Trial Registration: ClinicalTrials.gov NCT02782130; https://clinicaltrials.gov/ct2/show/NCT02782130 (Archived by Webcite at http://www.webcitation.org/6yGODyerk)

(JMIR Res Protoc 2018;7(4):e94) doi:10.2196/resprot.8811

KEYWORDS

mHealth; mobile apps; HIV; medication adherence; youth; men who have sex with men; transgender persons; games; randomized controlled trial

Introduction

Background

Men who have sex with men (MSM) account for nearly two-thirds of all new HIV infections in the United States and young MSM (YMSM) are the only risk group experiencing an increase in HIV incidence [1-3]. Regional studies suggest that HIV prevalence among transgender women is among the highest of all risk groups, especially among transgender women of color, and African American transgender women in particular [4-6]. Although likely underestimated, HIV prevalence among young transgender women, including young transgender women who have sex with men (YTWSM), ranges from 4.5% to 15.9% [7]. Youth diagnosed with HIV must adjust to living with a highly stigmatized health condition that requires lifelong medical management. Due to structural, developmental, and psychosocial barriers, many youth struggle to enter medical care, initiate antiretroviral therapy (ART), adhere to ART, or achieve viral suppression (VS) [8,9]. For YMSM and YTWSM who may already be ostracized from families and friends because of their sexual identity, receiving an HIV diagnosis can lead to an increase in social isolation, as well as negative affective states such as depression and anxiety, which may create additional barriers to HIV treatment [10-13]. Interventions for YMSM and YTWSM that increase engagement in care, ART uptake, ART adherence, and VS are needed to maximize the individual and public health benefits of treatment [14].

Computer-based interventions (CBIs), particularly those delivered online, can address some of the barriers that HIV-positive youth face in engaging in traditional face-to-face interventions, such as stigma, lack of social support, time, and transportation [15,16]. A growing body of scientific literature demonstrates equivalent outcomes from in-person and CBIs across a range of health behaviors [17-27]. Youth in particular are highly receptive to CBIs and as a result, CBIs have been widely advocated in the fields of adolescent health education and prevention [21,22,28-33].

As of January 2017, 88% of US adults are online, 95% have a cell phone, and 77% have a smartphone [34,35]. Youth (ages 18-29 years) have the highest levels of smartphone ownership at 92% [35]. US lesbian, gay, bisexual, and transgender individuals under the age of 35 years have had consistently higher rates of smartphone ownership than their general population counterparts [36,37]. In addition to increased smartphone ownership, the use of mobile phone apps is on the rise [38].

Serious games (games designed to accomplish a purpose, such as influencing learning, civic engagement, or health behavior change) are increasingly being used to address behavioral and psychological factors that inhibit adherence to medical treatment regimens [39-41]. Such games are intended to be goal-oriented, immersive, challenging, and motivating [42]. Games designed to improve health can influence health attitudes and improve behavior change self-efficacy [43-46]. As a result, games are an ideal platform to engage youth in behavior change as they have the ability to attract and maintain attention, avoiding the development of boredom and attrition [42]. The ability to add “fun” into design and game play serves to enhance overall motivation.

Social networking sites are also extremely popular among young adults. As of July 2015, 90% of black and 95% of white youth aged between 18 and 29 years use social networking sites [47]. MSM and transgender women have high rates of social networking use [6], in part, because online venues often represent one of a limited number of venues for connecting with one another. Social networking has been used successfully to change behaviors, increase social support, and reduce social isolation in HIV prevention and care interventions [48,49].

Epic Allies was developed based on the information, motivation, and behavioral (IMB) skills model [50] to address the urgent need for interventions that improve engagement in care, ART uptake, and ART adherence among YMSM and YTWSM. The app was created using an iterative process with input from the target population at each stage of development to ensure acceptability, relevance, and appeal [16]. We anticipate that the gaming features will enhance motivation for behavior changes related to engagement in care and ART adherence. Furthermore, social networking features will increase motivation by providing users with a sense of community and social support. Funded by the National Institutes of Health, we worked with programmers

and designers at Caktus Consulting Group, LLC to develop and test the Epic Allies prototype and found it to be acceptable among a sample of HIV-positive YMSM [16].

Aims and Objectives

The aim of this paper is to describe the study protocol for the randomized controlled trial (RCT) of the Epic Allies intervention. The first objective of the study is to test the efficacy of the Epic Allies intervention among HIV-positive YMSM and YTWSM by conducting a two-arm RCT. The primary outcome measure is VS. Secondary outcomes include engagement in HIV care (ie, completion of HIV-related care clinic visit in last 3 months), ART uptake (ie, initiation of ART in the last 3 months), ART adherence (ie, >90% of doses taken in previous week), and psychosocial barriers to engagement in care and ART adherence such as psychological distress, stigma, and social support.

The second objective is to qualitatively assess intervention acceptability, perceived impact, and potential for long-term sustainability. In-depth interviews with a subset of intervention arm participants conducted after the intervention period will evaluate acceptability of Epic Allies and examine participants' perspectives on the relationship between app use and study outcomes and potential for long-term sustainability of app use.

Methods

Trial Design

This study is a two-arm parallel RCT that will test the 26-week Epic Allies intervention against a control condition that includes weekly phone-based notifications to encourage participants to view educational information in the control app (Figure 1). Approximately 200 YMSM and YTWSM will be enrolled from 5 participating sites that provide HIV medical care for youth. Participants will be randomized 1:1 to intervention or control arms that are balanced by new to care (newly entered HIV medical care within 12 months of baseline visit) or ART-nonadherent status (first entered HIV medical care more than 12 months before baseline visit). Outcomes of interest will be measured at baseline, week 13 (during intervention phase), week 26 (end of intervention phase), and week 39 (postintervention phase). In-depth qualitative app satisfaction interviews will be conducted with approximately 20 intervention arm participants at the end of intervention use at week 26 to assess intervention experiences, acceptability, perceptions of associations between app use and study outcomes, and potential for long-term sustainability of using the app to support ART adherence.

Ethics

The study protocol was approved by the institutional review boards (IRB) at the University of North Carolina at Chapel Hill and all participating study sites, including University of South Florida, Tampa, FL; Stroger Hospital of Cook County, Chicago, IL; Montefiore Medical Center, Bronx, NY; Tulane Medical Center, New Orleans, LA; and University of North Carolina Hospital, Chapel Hill, NC (also includes Regional AIDS Interfaith Network, Charlotte, NC). Individuals who express interest in the study will be required to provide signed informed consent before medical records are abstracted to confirm eligibility or study procedures are performed. The informed consent documents will describe all study procedures in detail. During the informed consent process, site study staff will go over the consent documents and answer any questions that may arise. A waiver of parental consent for individuals younger than 18 years has been obtained for all sites given that this is a minimal-risk study.

Participants

Individuals participating in this study must meet the following eligibility criteria: (1) HIV-1 infected; (2) aged from 16 to 24 years; (3) assigned male sex at birth, of any gender identity, and self-reports a desire to engage or is engaging in sex with men; (4) at least one VL collected within the 12 weeks before the baseline visit, and the VL collected closest to the baseline visit is greater than the lower limit of detection for the site-specific assay used to test the specimen; (5) reliable daily access to an Android- or iOS-based mobile phone with a data plan; and (6) able to speak and read English. Self-reported eligibility criteria will be verified through an in-person screening with site study staff. Medical eligibility criteria will be verified through medical chart abstraction by site study staff. Individuals who cannot provide consent due to active substance use or psychological condition will be considered ineligible.

Recruitment and Enrollment

Potential study participants will be identified through medical chart reviews and/or medical provider referrals at participating sites. Identified individuals will be informed of the nature of the study, the information to be collected, and the evaluations and assessments that are involved. For individuals interested in study participation, self-reported eligibility criteria will be verified. Before confirmation of medical eligibility criteria, a signed informed consent will be obtained. Individuals who provide informed consent and meet all study eligibility criteria will be enrolled in the study and complete a baseline computer-assisted self-interviewing (CASI) survey.

Randomization

Study participants will be classified as either new to care (newly entered HIV medical care within the 12 months before the baseline visit) or ART nonadherent (first entered HIV medical care more than 12 months before the baseline visit). Randomization will occur in a 1:1 ratio within each of the 2 classification strata separately, with an equal number of participants assigned to the intervention and control arms. Due to rolling enrollment, block randomization will be used to help ensure balance within strata. Status as new to care vs nonadherent (eg, eligibility group) will be chosen as the primary stratum and randomized separately in blocks of 4 participants. Study statisticians will not be blinded to study arm assignment because they will be involved in data quality control and quality assurance.

Incentives

The amount of participant compensation for study participation is determined separately by each site and approved by each site's IRB. Participants will receive US $40 to $60 for completion of each RCT assessment at baseline, week 13, week

26, and week 39. Intervention arm participants who log on to the Epic Allies app 12 out of the first 14 days after the baseline visit will receive US $20 as a one-time sign-on bonus and those who log on at least once in each 30-day period will receive US $10 to help defray costs associated with smartphone data usage during that period. Participants in the intervention arm who are selected for and complete the in-depth qualitative interview will receive US $20 to $50.

Intervention Theoretical Model and Features

The design of Epic Allies was informed by the IMB skills model, which conceptualizes health behavior change (eg, medication adherence) as a product of mediators, including information about the behavior, motivation to change, and the skills needed to achieve change [50]. Studies testing the IMB model of ART adherence support relationships between information, motivation, and behavioral skills and medication adherence [51-55]. Group- and individual-level IMB-based interventions improve ART adherence [56-59], though none have been designed specifically for YMSM and YTWSM. Epic Allies' features (see Multimedia Appendix 1) address numerous elements of the IMB model (Figures 2-11). For example, the gaming features are designed to enhance sustained app use and motivate patterning new adherence behaviors [60]. The social networking features allow users to give and receive support, a relevant need for many YMSM and YTWSM who experience social isolation due to HIV-related stigma and homophobia [61-63].

Intervention and Control Conditions

At baseline visit, participants assigned to the intervention arm will download and install Epic Allies, create a 4-digit app password, and receive a guided tour of the app by site study staff. Intervention arm participants will have full access to all features of Epic Allies during the 26-week intervention period. Participants assigned to the control group will download and install the Epic Allies control app (phone notification messages only), create a 4-digit app password, and be provided with instructions on using the app. During the 26-week trial, control participants will receive weekly phone notifications that inform users that new content is available and one brief informational article will be provided. Control group articles are a subset of Daily Dose articles focused on ART adherence and HIV disease self-management.

Figure 1. Epic Allies study schema. CASI: computer-assisted self-interviewing.

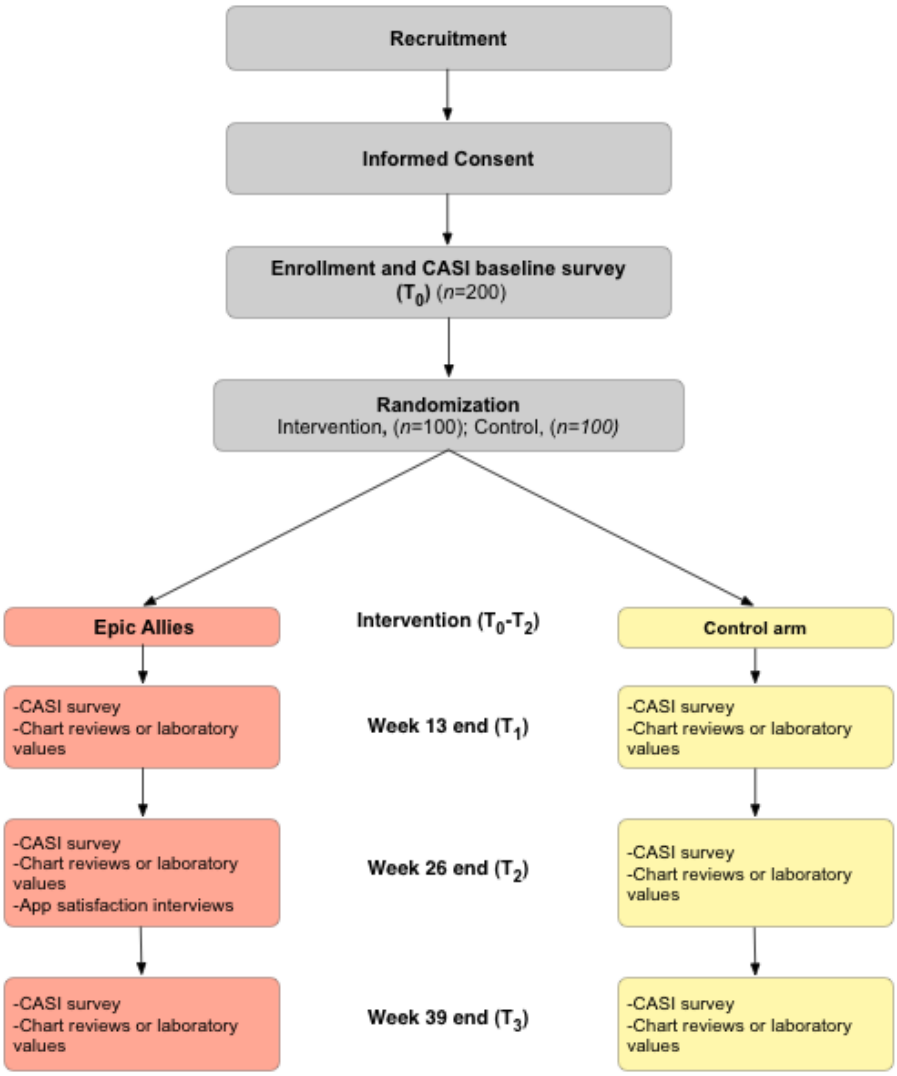

Figure 2. Medication reminder setup. ART: antiretroviral therapy.

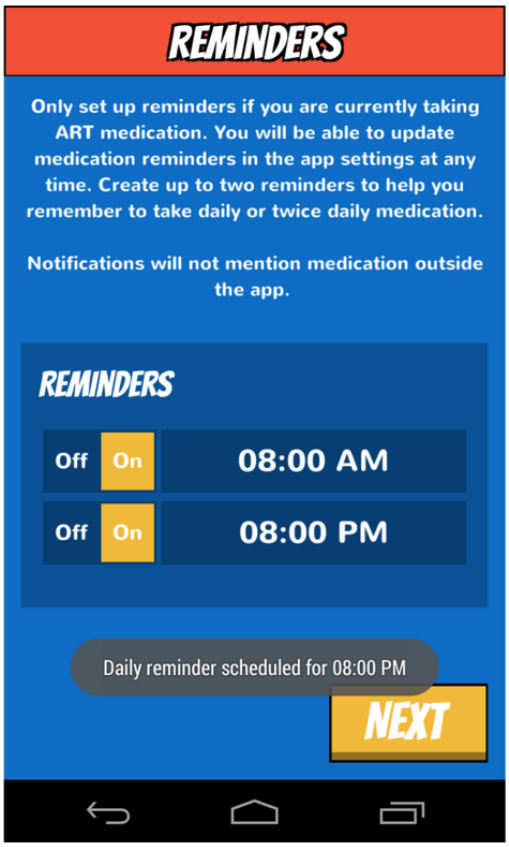

Figure 3. Profile.

Figure 4. Profile: Customizable avatar.

Figure 5. Profile: Readiness badge.

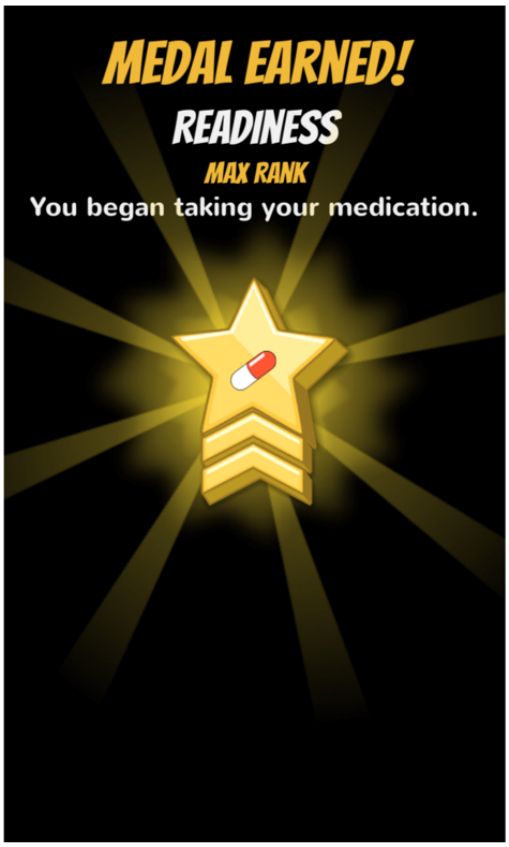

Figure 6. Health Center: Visual representation of adherence.

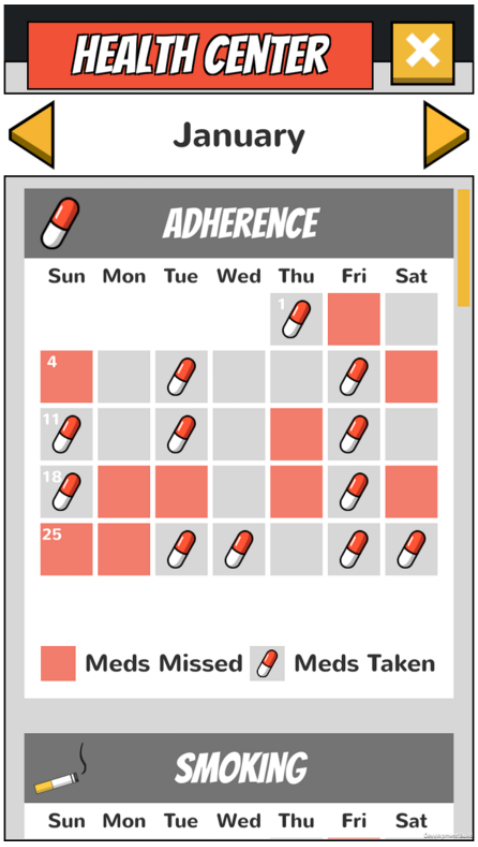

Figure 7. Health Center: Weekly tailored feedback.

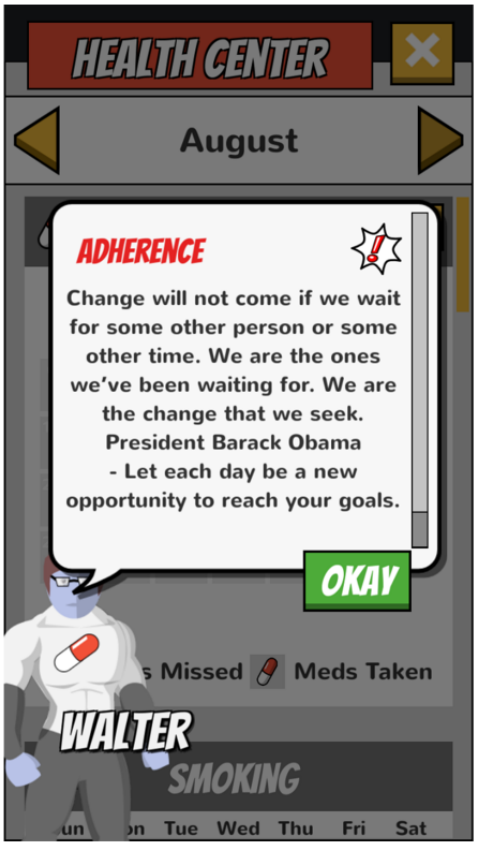

Figure 8. Ally interactions.

Figure 9. The Daily Dose.

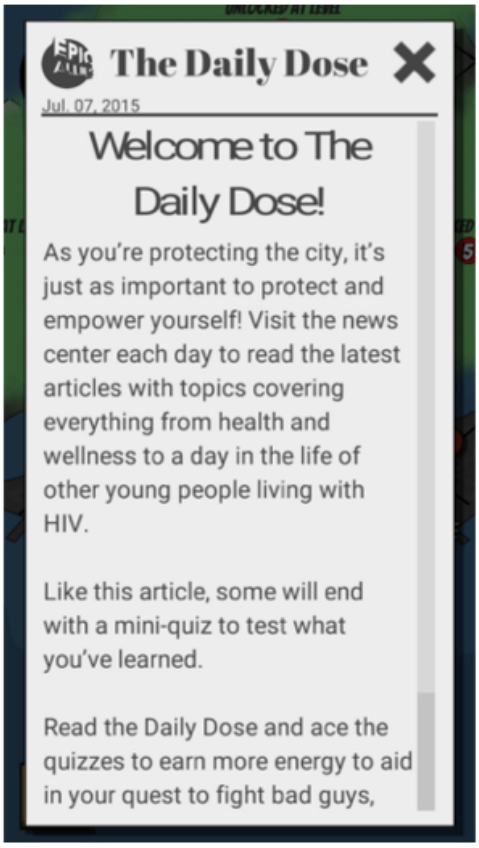

Figure 10. Mini-games: Social game leaderboard.

Figure 11. Mini-games: Mind Mine.

Data Collection Study Objective 1: Efficacy

Baseline, week 13, week 26, and week 39 assessments will be conducted in person. At each time point, participants will complete a CASI survey. Clinical data will include data collected via chart abstraction and/or laboratory values (VL only). If a participant does not have a VL value recorded in their chart in the 6-week window before the study visit, VL testing will be conducted on the day of the study visit as part of standard of care (ie, participant is scheduled for a medical care visit that includes VL testing) or by the study (ie, the study visit does not coincide with a medical care visit with VL testing). Table 1 lists primary and secondary outcomes and the source, collection points, and a description of each measure.

App usage data will be transmitted from the participant's smartphone to a secure server any time the participant is connected to the Internet via broadband or Wi-Fi. App data metrics include log-ins/log-outs, use of app features, and app progress.

Data Collection Study Objective 2: Acceptability

In-depth qualitative app satisfaction interviews will be conducted via Skype with approximately 20 intervention arm participants at the end of the intervention. We will attempt to enroll equal numbers of participants into one of four cells in Table 2 based on their ART status at study entry and app usage during the intervention. As each participant finishes the 26-week intervention period, they will be asked if they are willing to participate in the in-depth app qualitative satisfaction interview. Once a given care-usage cell has reached its quota, that cell will be "closed," and interviews will be offered to only those participants who fall within the remaining open cells.

The in-depth qualitative app satisfaction interview will last between 45 and 60 min and will be recorded with the participant's consent. Participants who prefer can opt to use video during the interview, but there will be no video recording. All interviews will be conducted by one of 3 trained qualitative interviewers from the study team using a semistructured interview guide. Following each interview, the recording will be transcribed by Verbal Ink (a division of Ubiqus, Los Angeles, California), checked for accuracy by study staff, and uploaded to the UNC-CH secure server. The transcripts of the first three interviews will be reviewed by the study team to assess for quality and content before completing the remaining interviews.

Table 1. Primary and secondary outcomes. "X" indicates that this outcome was assessed at the time point indicated in the column above. VS: viral suppression. VL: viral load. CASI: computer-assisted self-interviewing. ART: antiretroviral therapy.

Outcome	Source	13 weeks	26 weeks	39 weeks	Description
Primary study outcomes					
VS defined as VL below the lower limit of detection in the 6-week window before the scheduled study visits	Chart review (any value in 6-week window before scheduled visit) OR laboratory value collected at study visit	X	X		<40 copies/mL or lower limit of detection for site-specific assay used to test the specimen
Secondary study outcomes					
VL suppression defined as VL below the lower limit of detection in the 6-week window before the scheduled study visits	Chart review (any value in 6-week window before scheduled visit) OR laboratory value collected at study visit			X	<40 copies/mL or lower limit of detection for site-specific assay used to test the specimen
Engagement in care	CASI survey	X	X	X	Completion of HIV-related care clinic visit in last 3 months
ART uptake (for participants not on ART)	CASI survey	X	X	X	"Are you currently taking medication to treat your HIV (Y/N)?"
ART adherence[a] (for participants on ART)	CASI survey	X	X	X	(1) "How many times during the day has your doctor told you to take a dose of medicine (pills or other medicines) to treat your HIV?" and (2) "Thinking about the last 7 days, how many times did you miss taking a dose of pills?"[64]

[a]Outcome of >90% adherence is comprised 2 components (1) is the denominator, indicating the frequency of doses prescribed (multiplied x7 to represent total weekly doses); (2) is the numerator, indicating the number of times, total, a dose was missed.

Table 2. In-depth qualitative app satisfaction interview enrollment.

Antiretroviral therapy (ART) experience at entry	New to care	ART nonadherent	Total
App utilization pattern			
Intervention low users (uses app <4 days/week)	5	5	10
Intervention users (uses app ≥4 days/week)	5	5	10
Total	10	10	20

Follow-Up and Retention

Tracking Participant Follow-Up

All participants will be contacted before each follow-up study visit (ie, 13, 26, and 39 weeks after baseline). Multiple contact methods will be used for youth who are difficult to reach (eg, mail, alternate phone numbers, email, text message, Facebook). Participants will be asked whether or not messages can be left for each of the phone numbers that they provide. They will be informed that messages will not contain any information regarding the nature of the project.

Study Visit Management

The preferred time frame for all follow-up visits is within 4 weeks before or after the target study visit date. If the participant is unable to attend a visit within this time frame, the site staff will work with the participant to identify a day closest to the scheduled visit to perform the visit.

Participants in the intervention arm will be reminded by the Epic Allies app via a discreet phone notification (eg, "Your allies need you–log in to Epic Allies") to log on to the app every week. If a participant does not log on for 4 weeks, study staff will notify site staff and ask that they reach out to the participant.

Completing Web-Based Computer-Assisted Self-Interviewing Surveys

CASI surveys will ideally be completed at the clinic site during each study visit. Participants will be provided with a quiet, private area to complete the survey. The survey may be completed on the participant's smartphone, but a computer with Wi-Fi connection should be made available in case the participant prefers to complete the survey on a computer.

If a participant is unable to attend a follow-up study visit, the participant may complete the survey on his or her own. The survey should be completed within 4 weeks before or after the study visit target date. If a participant is unable to complete the survey within this window due to extenuating circumstances, the window may be lengthened to 7 weeks.

Data Security

Epic Allies App Data

Caktus Consulting Group will store app usage data on a secure Web server for the duration of the study. At the end of the study, Caktus Consulting Group will send app usage data to the study team, destroy the data on the server, and then shut down the server. Protected health information is neither collected nor stored on the Web server.

In-Depth Qualitative App Satisfaction Interview

For the in-depth qualitative app satisfaction interview with intervention arm participants, the audio recording as well as the transcript will be marked with the participant's study ID only. Any identifying information mentioned in the interviews will be redacted in the transcripts, thus the transcripts will be deidentified. Both files will be uploaded and stored on a secure server.

Data Analysis Study Objective 1: Efficacy

Sample Size and Power Estimates

We estimated a sample size of 200 as feasible enrollment. Power calculations are estimated to detect between-group differences in the primary outcome (viral suppression) in a parallel two-group repeated measures design with equal allocation, based on a generalized estimating equation (GEE) framework assuming an exchangeable covariance structure, measurements at 3 follow-up points, and correlation among same participant repeat measures (rho) of .4. For all estimates, we used a two-sided test of significance and an alpha level of .05. Assuming a 20% loss to follow-up, we will have 80% power to detect absolute differences in viral suppression of 16.3% between the intervention and control groups in the proportion of participants with viral suppression when the proportion in the control group is 27%.

Quantitative Data Analysis

We will compare within- and between-group differences in primary and secondary outcomes for each follow-up time period. The 13- and 26-week follow-up will be considered our primary endpoint for the primary outcome, thus *P* values will only be computed for these time periods for the primary outcome. *P* values will be adjusted for multiple comparisons using the Benjamini-Hochberg procedure [65]. Estimates for all outcomes will be presented with 95% CI. Intervention and control groups will be compared on baseline characteristics to assess balance. Patterns of missing data for our primary outcome of VS will be examined and baseline characteristics of participants with complete vs incomplete follow-up will be compared with assess nonresponse and attrition biases.

Intervention effects will be evaluated using an intention-to-treat (ITT) approach. The primary study outcome (VS, defined as the lower limit of detection of site assay) will be compared at 13, 26, and 39 weeks in the intervention and control groups using generalized linear models (GLM), which can be used for dependent variables with normal, binary, poisson, and negative binomial distributions. Link functions will be selected as appropriate based on the distribution of the dependent variable. We will apply the GEE extension of GLM to account for within-participant correlation associated with repeated measures. GEEs allow for inclusion of categorical and count-dependent variables and appropriate specification of working covariance structures for observations that are correlated within groups and across time. Fixed main effects parameters for study site and eligibility group will be fitted to data to account for the nature of the randomized design. Intervention efficacy will be assessed in terms of the main effect for overall group differences. Use of a GEE framework means that inference will be made to the marginal effect of the Epic Allies treatment on the outcome, averaged across the study population. Secondary analyses will be performed similar to the methods described above to identify potential mediators and moderators of the intervention impact on primary outcome.

Missing, Unused, and Spurious Data

Several procedures will be used to conduct data analysis when data for either outcomes or baseline covariates are missing. The

first step will be to assess the extent and pattern of missing data. If data are missing for only a few cases, then data analysis will be conducted only on study participants with complete data. If the pattern of missing outcome data is monotone, then inverse probability weighting will be performed to adjust the available data for loss to follow-up [66]. If substantial nonmonotone missing outcome data are present, then a multiple imputation approach will be used. Unused or spurious data will be documented and discussed when disseminating results of this study. Baseline covariates will be compared between participants with complete follow-up vs those who have incomplete follow-up in order to assess the presence of informative missingness.

Data Analysis Study Objective 2: Acceptability, Perceived Impact, and Sustainability

Qualitative Approach

The interview and analysis structure will follow a phenomenological approach to optimize our ability to capture and understand the study's experience-based topics of interest (eg, experience of HIV diagnosis and acceptance, experience of engaging with Epic Allies intervention and participants). Phenomenology is an ideal theoretical approach for this component as it is focused on describing both *what* a given group of participants experience and *how* they experience this particular phenomenon [67-69]. Data are presented through textual descriptions of the phenomena based on summaries of the experiences described by respondents. The composite descriptions offer an explanation of the underlying structure which exists across the participants' experiences [69,70]. This will focus on individual and shared experiences and meanings.

Qualitative Data Analysis

For the analysis, process interviews will be transcribed and then we will begin with our a priori list of themes (experience using Epic Allies, recent ART adherence challenges, etc). Study team members will read all transcripts and identify emergent themes from participants' experiences. These themes will be discussed as a group, and a final list of themes will be developed with brief descriptions, relationships between themes, and supporting quotes. For the qualitative research component, the Atlas.ti qualitative data analysis software (version 8, Scientific Software Development, Berlin, Germany) will be used to assist with theme identification and building, as well as coding textual data [69,71]. Coding and analytic activities will be discussed during weekly team meetings.

Interim Analysis

No interim analysis will be performed for this study. The study team determined that this study does not involve greater than minimal risk (45 CFR Part 46.404 and 21 CFR Part 50.51). Participation in this study poses no more harm or discomfort to participants than they may experience in normal daily life or during routine physical or psychological examinations or tests.

Protection Against Harms

All sites have specific policies governing the treatment of human subjects. These policies specify that medical and psychological assistance will be available in the immediate environment in the event a participant should experience any adverse reactions resulting from study procedures.

Results

A total of 146 YMSM and YTWSM were enrolled in Epic Allies between September 2015 and 2016. Demographic characteristics of study participants are shown in Table 3. Although we estimated 200 as feasible for enrollment, study sites had fewer individuals eligible for participation in the study than expected. As a result, our ability to detect differences in our primary outcome (viral suppression) with 80% power assuming 20% loss to follow-up and the proportion of viral suppression in the control group is 27%, decreases by 3.1% (>16.3% to >19.4%).

Table 3. Sample characteristics of Epic Allies study population by intervention arm. Q1: 25th percentile. Q3: 75th percentile.

Characteristic	Intervention (N=74)	Control (N=72)	Total (N=146)
Classification strata, n (%)			
New to care	36 (49)	38 (53)	74 (50.7)
Antiretroviral therapy nonadherent	38 (51)	34 (47)	72 (49.3)
Study site, n (%)			
University of South Florida	19 (26)	11 (15)	30 (20.5)
Stroger Hospital	9 (12)	14 (19)	23 (15.8)
Montefiore Medical Center	15 (20)	15 (21)	30 (20.5)
Tulane Medical Center	9 (12)	17 (24)	26 (17.8)
University of North Carolina	22 (30)	15 (21)	37 (25.3)
Age <18 years, n (%)			
No	71 (96)	66 (92)	137 (94.0)
Age			
Median	22.0	21.0	21.5
Q1, Q3	20.0, 23.0	20.0, 23.0	20.0, 23.0
Gender identity, n (%)			
Male	69 (93)	67 (93)	136 (93.2)
Transgender female	5 (7)	3 (4)	8 (5.5)
Other	0 (0)	2 (3)	2 (1.4)
Sexual identity, n (%)			
Gay	55 (74)	58 (81)	113 (77.4)
Bisexual	16 (22)	11 (15)	27 (18.5)
Other	3 (4)	3 (4)	6 (4.1)
Hispanic or Latino ethnicity, n (%)			
Yes	17 (23)	12 (17)	29 (19.9)
No	57 (77)	60 (83)	117 (80.1)
Black or African American race, n (%)			
Yes	60 (81)	60 (83)	120 (82.2)
No	14 (19)	12 (17)	26 (17.8)
White race, n (%)			
Yes	10 (14)	6 (8)	16 (11.0)
No	64 (86)	66 (92)	130 (89.0)
Other race, n (%)			
Yes	5 (7)	8 (11)	13 (8.9)
No	69 (93)	64 (89)	133 (91.1)
Highest level of education completed, n (%)			
<12th grade	17 (23)	11 (15)	28 (19.2)
Completed high school/General Equivalency Diploma, some technical school/college	48 (65)	58 (81)	106 (72.6)
College/technical degree or more	9 (12)	3 (4)	12 (8.2)
Annual income, n (%)			
<US $11,999	56 (76)	52 (72)	108 (74.0)
US $12,000+	10 (14)	13 (18)	23 (15.8)

Characteristic	Intervention (N=74)	Control (N=72)	Total (N=146)
Don't know/Refuse	8 (11)	7 (10)	15 (10.3)
Employment, n (%)			
Yes	51 (69)	44 (61)	95 (65.1)
No	23 (31)	28 (39)	51 (34.9)
Health insurance, n (%)			
Medicaid	24 (32)	26 (36)	50 (34.2)
Private health insurance (eg, Blue Cross Blue Shield, parent's)	7 (9)	15 (21)	22 (15.1)
AIDS Drug Assistance Program	21 (28)	17 (24)	38 (26.0)
Other	6 (8)	0 (0)	6 (4.1)
I do not have health insurance	16 (22)	14 (19)	30 (20.5)
Homelessness in past 3 months, n (%)			
Yes	24 (32)	18 (25)	42 (28.8)
No	50 (68)	54 (75)	104 (71.2)
Lifetime incarceration, n (%)			
Yes	21 (28)	18 (25)	39 (26.7)
No	53 (72)	54 (75)	107 (73.3)

Discussion

Epic Allies Summary

Epic Allies addresses ART uptake and adherence, a critical need among a disproportionately affected patient population via familiar technologies using engaging, theory-based components. The app targets the most common ART adherence barriers among youth, addresses specific behavior outcomes, and is tailored for the target population and customizable for individual users. The social support, encouragement, and informational features listed above are designed to help youth overcome barriers to adherence across various stages of engagement in HIV care, ranging from lack of understanding and low health literacy, coping with side effects and drug toxicities, to the impact of drug and alcohol use on ART adherence.

This novel intervention app, Epic Allies, targets HIV-positive YMSM and YTWSM, aged between 16 and 24 years (inclusive), with a detectable HIV VL. Epic Allies utilizes self-management tools, social support, and gamification to increase ART information, motivation, and behavioral skills and improve ART adherence, including (1) real-time data tracking of adherence with graphic visualizations; (2) tailored reminders and motivational messages; (3) connection to a network of other HIV-positive YMSM and YTWSM; and (4) a gaming approach engineered to reinforce daily adherence tracking, promote social networking support among users, encourage learning and skill building, and maintain user engagement.

Limitations

As with all longitudinal studies, a loss of participants to follow-up may induce a selection bias if missingness is informative and is related to both treatment arm and the study outcome. Furthermore, if compliance with the treatment assignment is less than 100% in either study arm, the ITT estimate, the study's primary estimate, will differ from the compliance-averaged causal estimate [72,73]. In this case, the ITT estimate will still validly measure the efficacy of being randomized to the treatment arm but may not estimate the efficacy of the treatment itself. Data for secondary outcomes will be collected primarily from self-report survey, which is prone to both exposure and outcome misclassification. This misclassification could bias our study results either toward or away from the null hypothesis. Contamination may also be an issue, as participants at each of the study sites can be randomized to the intervention or control arm, and participants in the intervention arm may show Epic Allies to those in the control arm. All study participants are recruited from sites that provide HIV medical care and have procedures to monitor and address poor retention in care. Although many study participants were not regularly engaged in care at enrollment, retention in care outcomes among the study sample may be inflated when compared with a community-recruited sample. Thus, caution should be exercised regarding generalizability of retention in care outcomes. Finally, a modest sign-on bonus for regular use of the app in the first 2 weeks of the study and nominal monthly data use reimbursements are offered to those in the intervention group but not to those in the control group. The purpose of the sign-on bonus is to encourage regular use of the app early in the study to try to increase the likelihood that app use becomes a daily habit. The bonus is intentionally modest and time-limited to decrease the likelihood that money alone influences differences in study outcomes between the arms. Reimbursement for data use is intended to ensure that intervention arm participants do not intentionally avoid the app due to concerns about data usage. This is only warranted for intervention participants because the amount of data used for the control app is extremely low. While it is important to acknowledge the differences in incentives for the intervention and control groups,

we believe they are unlikely to explain differences in outcomes between the arms.

Conclusions

If successful, Epic Allies will represent a novel adherence intervention for a group disproportionately impacted by HIV in the United States. Epic Allies would be clinically attractive, as adherent patients would require less frequent clinic visits and experience fewer HIV-related secondary infections [74-76]. Reducing clinic visits and secondary infections could make the intervention financially attractive by reducing health care costs. Epic Allies could also greatly impact public health as ART adherence reduces HIV infectivity and subsequently reduces HIV transmission [74]. Epic Allies could be used during times of adherence vulnerability (eg, when initiating ART or changing medication regimens) and could easily be expanded and adopted for use among larger populations of YMSM and YTWSM, other HIV-positive populations, and for those diagnosed with other chronic diseases such as diabetes and hypertension.

Conflicts of Interest

Caktus Consulting Group, LLC partially owns the Epic Allies app. TM is a co-owner of the company. NN is a former Caktus employee who worked on the Epic Allies team.

Multimedia Appendix 1

Features of Epic Allies.

[PDF File (Adobe PDF File), 50KB - resprot_v7i4e94_app1.pdf]

References

1. Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, HIV Incidence Surveillance Group. Estimated HIV incidence in the United States, 2006-2009. PLoS One 2011;6(8):e17502 [FREE Full text] [doi: 10.1371/journal.pone.0017502] [Medline: 21826193]
2. CDC. 2011 Aug. Estimates of new HIV infections in the United States, 2006-2009 URL: https://www.cdc.gov/nchhstp/newsroom/docs/HIV-Infections-2006-2009.pdf [accessed 2017-08-11] [WebCite Cache ID 6xvRAMXxO]
3. An Q, Prejean J, Hall HI. Racial disparity in U.S. diagnoses of acquired immune deficiency syndrome, 2000-2009. Am J Prev Med 2012 Nov;43(5):461-466. [doi: 10.1016/j.amepre.2012.07.040] [Medline: 23079167]
4. Herbst JH, Jacobs ED, Finlayson TJ, McKleroy VS, Neumann MS, Crepaz N, HIV/AIDS Prevention Research Synthesis Team. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. AIDS Behav 2008 Jan;12(1):1-17. [doi: 10.1007/s10461-007-9299-3] [Medline: 17694429]
5. Clements-Nolle K, Marx R, Guzman R, Katz M. HIV prevalence, risk behaviors, health care use, and mental health status of transgender persons: implications for public health intervention. Am J Public Health 2001 Jun;91(6):915-921. [Medline: 11392934]
6. Sevelius JM, Keatley J, Gutierrez-Mock L. HIV/AIDS programming in the United States: considerations affecting transgender women and girls. Womens Health Issues 2011 Nov;21(6 Suppl):S278-S282 [FREE Full text] [doi: 10.1016/j.whi.2011.08.001] [Medline: 22055679]
7. Poteat T, Scheim A, Xavier J, Reisner S, Baral S. Global epidemiology of HIV infection and related syndemics affecting transgender people. J Acquir Immune Defic Syndr 2016 Aug 15;72(Suppl 3):S210-S219. [Medline: 27429185]
8. Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. AIDS Patient Care STDS 2014 Mar;28(3):128-135 [FREE Full text] [doi: 10.1089/apc.2013.0345] [Medline: 24601734]
9. Ryscavage P, Anderson EJ, Sutton SH, Reddy S, Taiwo B. Clinical outcomes of adolescents and young adults in adult HIV care. J Acquir Immune Defic Syndr 2011 Oct 01;58(2):193-197. [doi: 10.1097/QAI.0b013e31822d7564] [Medline: 21826014]
10. Hosek SG, Harper GW, Lemos D, Martinez J. An ecological model of stressors experienced by youth newly diagnosed with HIV. J HIV AIDS Prev Child Youth 2008;9(2):192-218 [FREE Full text] [doi: 10.1080/15538340902824118] [Medline: 20216916]
11. Hosek SG, Harper GW, Domanico R. Psychological and social difficulties of adolescents living with HIV: a qualitative analysis. J Sex Educ Ther 2015 Jan 21;25(4):269-276. [doi: 10.1080/01614576.2000.11074360]
12. Lam PK, Naar-King S, Wright K. Social support and disclosure as predictors of mental health in HIV-positive youth. AIDS Patient Care STDS 2007 Jan;21(1):20-29. [doi: 10.1089/apc.2006.005] [Medline: 17263655]
13. Murphy DA, Durako SJ, Moscicki AB, Vermund SH, Ma Y, Schwarz DF, Adolescent Medicine HIV/AIDS Research Network. No change in health risk behaviors over time among HIV infected adolescents in care: role of psychological distress. J Adolesc Health 2001 Sep;29(3 Suppl):57-63. [Medline: 11530304]
14. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis 2011 Mar 15;52(6):793-800 [FREE Full text] [doi: 10.1093/cid/ciq243] [Medline: 21367734]

15. Lall P, Lim SH, Khairuddin N, Kamarulzaman A. Review: an urgent need for research on factors impacting adherence to and retention in care among HIV-positive youth and adolescents from key populations. J Int AIDS Soc 2015 Feb 26;18(2 Suppl 1):19393 [FREE Full text] [Medline: 25724503]
16. LeGrand S, Muessig KE, McNulty T, Soni K, Knudtson K, Lemann A, et al. Epic Allies: Development of a Gaming App to Improve Antiretroviral Therapy Adherence Among Young HIV-Positive Men Who Have Sex With Men. JMIR Serious Games 2016 May 13;4(1):e6 [FREE Full text] [doi: 10.2196/games.5687] [Medline: 27178752]
17. Feil EG, Noell J, Lichtenstein E, Boles SM, McKay HG. Evaluation of an Internet-based smoking cessation program: lessons learned from a pilot study. Nicotine Tob Res 2003 Apr;5(2):189-194. [Medline: 12745491]
18. Lenert L, Muñoz RF, Stoddard J, Delucchi K, Bansod A, Skoczen S, et al. Design and pilot evaluation of an internet smoking cessation program. J Am Med Inform Assoc 2003;10(1):16-20 [FREE Full text] [Medline: 12509354]
19. Napolitano MA, Fotheringham M, Tate D, Sciamanna C, Leslie E, Owen N, et al. Evaluation of an internet-based physical activity intervention: a preliminary investigation. Ann Behav Med 2003;25(2):92-99. [Medline: 12704010]
20. Newman MG, Kenardy J, Herman S, Taylor CB. Comparison of palmtop-computer-assisted brief cognitive-behavioral treatment to cognitive-behavioral treatment for panic disorder. J Consult Clin Psychol 1997 Feb;65(1):178-183. [Medline: 9103747]
21. Schinke SP, Schwinn TM, Di Noia J, Cole KC. Reducing the risks of alcohol use among urban youth: three-year effects of a computer-based intervention with and without parent involvement. J Stud Alcohol 2004 Jul;65(4):443-449 [FREE Full text] [Medline: 15376818]
22. Schinke SP, Di Noia J, Glassman JR. Computer-mediated intervention to prevent drug abuse and violence among high-risk youth. Addict Behav 2004 Jan;29(1):225-229 [FREE Full text] [Medline: 14667434]
23. Sciamanna CN, Lewis B, Tate D, Napolitano MA, Fotheringham M, Marcus BH. User attitudes toward a physical activity promotion website. Prev Med 2002 Dec;35(6):612-615. [Medline: 12460529]
24. Selmi PM, Klein MH, Greist JH, Sorrell SP, Erdman HP. Computer-administered therapy for depression. MD Comput 1991;8(2):98-102. [doi: 10.1176/ajp.147.1.51] [Medline: 2038242]
25. Tate DF, Wing RR, Winett RA. Using Internet technology to deliver a behavioral weight loss program. JAMA 2001 Mar 7;285(9):1172-1177. [Medline: 11231746]
26. Tate DF, Jackvony EH, Wing RR. Effects of Internet behavioral counseling on weight loss in adults at risk for type 2 diabetes: a randomized trial. JAMA 2003 Apr 9;289(14):1833-1836. [doi: 10.1001/jama.289.14.1833] [Medline: 12684363]
27. Woodruff SI, Edwards CC, Conway TL, Elliott SP. Pilot test of an Internet virtual world chat room for rural teen smokers. J Adolesc Health 2001 Oct;29(4):239-243. [Medline: 11587907]
28. Hightow-Weidman LB, Pike E, Fowler B, Matthews DM, Kibe J, McCoy R, et al. HealthMpowerment.org: feasibility and acceptability of delivering an internet intervention to young Black men who have sex with men. AIDS Care 2012;24(7):910-920 [FREE Full text] [doi: 10.1080/09540121.2011.647677] [Medline: 22272759]
29. Lightfoot M, Comulada WS, Stover G. Computerized HIV preventive intervention for adolescents: indications of efficacy. Am J Public Health 2007 Jun;97(6):1027-1030. [doi: 10.2105/AJPH.2005.072652] [Medline: 16670219]
30. Noar SM, Black HG, Pierce LB. Efficacy of computer technology-based HIV prevention interventions: a meta-analysis. AIDS 2009 Jan 2;23(1):107-115. [doi: 10.1097/QAD.0b013e32831c5500] [Medline: 19050392]
31. Noar SM. Computer technology-based interventions in HIV prevention: state of the evidence and future directions for research. AIDS Care 2011 May;23(5):525-533 [FREE Full text] [doi: 10.1080/09540121.2010.516349] [Medline: 21287420]
32. Paperny DM. Computerized health assessment and education for adolescent HIV and STD prevention in health care settings and schools. Health Educ Behav 1997 Feb;24(1):54-70. [doi: 10.1177/109019819702400107] [Medline: 9112098]
33. Schinke SP, Orlandi MA. Skills-Based, Interactive Computer Interventions to Prevent HIV Infection Among African-American and Hispanic Adolescents. Comput Human Behav 1990;6(3):235-246 [FREE Full text] [doi: 10.1016/0747-5632(90)90020-H] [Medline: 20589223]
34. Pew Research Center. 2017. Internet/Broadband Fact Sheet URL: http://www.pewinternet.org/fact-sheet/internet-broadband/ [WebCite Cache ID 6xvUNUXrU]
35. Pew Research Center. 2017. Mobile Fact Sheet URL: http://www.pewinternet.org/fact-sheet/mobile [WebCite Cache ID 6xvUYqfEx]
36. Community Marketing Inc. 2012. 2012 LGBT Community Survey URL: https://communitymarketinginc.com/wp-content/uploads/2016/01/BisexualCommunitySurvey2012_Final.pdf [accessed 2018-03-15] [WebCite Cache ID 6xvUkX10N]
37. Community Marketing Inc. 2011. 16th Annual Gay & Lesbian Tourism Report: Exploring tourism and hospitality opportunities in the gay and lesbian marketplace URL: https://www.communitymarketinginc.com/documents/temp/CMI_16thLGBTTourismStudy.pdf [accessed 2018-03-15] [WebCite Cache ID 6xvUrb95i]
38. Pew Research Center. 2015. App permissions in the Google Play Store URL: http://www.pewinternet.org/2015/11/10/apps-permissions-in-the-google-play-store/ [WebCite Cache ID 6xvUzH8HS]
39. Kato PM. Video games in health care: Closing the gap. Rev Gen Psychol 2010;14(2):113-121. [doi: 10.1037/a0019441]
40. Ritterfeld U, Cody M, Vorderer P, editors. Serious Games: Mechanisms and Effects. New York, NY: Taylor & Francis; 2009.

41. Hightow-Weidman LB, Muessig KE, Bauermeister JA, LeGrand S, Fiellin LE. The future of digital games for HIV prevention and care. Curr Opin HIV AIDS 2017 Sep;12(5):501-507. [doi: 10.1097/COH.0000000000000399] [Medline: 28692490]
42. McGonigal J. Reality is broken: Why games make us better and how they can change the world. New York, NY: Random House; 2011.
43. Baranowski T, Baranowski J, Cullen KW, Marsh T, Islam N, Zakeri I, et al. Squire's Quest! Dietary outcome evaluation of a multimedia game. Am J Prev Med 2003 Jan;24(1):52-61. [Medline: 12554024]
44. Brown SJ, Lieberman DA, Germeny BA, Fan YC, Wilson DM, Pasta DJ. Educational video game for juvenile diabetes: results of a controlled trial. Med Inform (Lond) 1997;22(1):77-89. [Medline: 9183781]
45. Kato PM, Cole SW, Bradlyn AS, Pollock BH. A video game improves behavioral outcomes in adolescents and young adults with cancer: a randomized trial. Pediatrics 2008 Aug;122(2):e305-e317 [FREE Full text] [doi: 10.1542/peds.2007-3134] [Medline: 18676516]
46. Lieberman DA. Interactive video games for health promotion: Effects on knowledge, self-efficacy, social support, and health. In: Street Jr RL, Gold WR, Manning TR, editors. Health promotion and interactive technology: Theoretical applications and future directions. Mahwah, NJ, US: Lawrence Erlbaum Associates; 1997:103-120.
47. Pew Research Center: Internet and Technology. 2015. Gaming, Jobs and Broadband URL: http://www.pewinternet.org/datasets/2015/ [WebCite Cache ID 6xvVr9tkT]
48. Hightow-Weidman LB, Muessig KE, Pike EC, LeGrand S, Baltierra N, Rucker AJ, et al. HealthMpowerment.org: Building Community Through a Mobile-Optimized, Online Health Promotion Intervention. Health Educ Behav 2015 Aug;42(4):493-499. [doi: 10.1177/1090198114562043] [Medline: 25588932]
49. Young SD, Cumberland WG, Lee SJ, Jaganath D, Szekeres G, Coates T. Social networking technologies as an emerging tool for HIV prevention: a cluster randomized trial. Ann Intern Med 2013 Sep 03;159(5):318-324 [FREE Full text] [doi: 10.7326/0003-4819-159-5-201309030-00005] [Medline: 24026317]
50. Fisher JD, Fisher WA, Amico KR, Harman JJ. An information-motivation-behavioral skills model of adherence to antiretroviral therapy. Health Psychol 2006 Jul;25(4):462-473. [doi: 10.1037/0278-6133.25.4.462] [Medline: 16846321]
51. Amico KR, Toro-Alfonso J, Fisher JD. An empirical test of the information, motivation and behavioral skills model of antiretroviral therapy adherence. AIDS Care 2005 Aug;17(6):661-673. [doi: 10.1080/09540120500038058] [Medline: 16036253]
52. Amico KR, Barta W, Konkle-Parker DJ, Fisher JD, Cornman DH, Shuper PA, et al. The information-motivation-behavioral skills model of ART adherence in a Deep South HIV+ clinic sample. AIDS Behav 2009 Feb;13(1):66-75 [FREE Full text] [doi: 10.1007/s10461-007-9311-y] [Medline: 17876697]
53. Kalichman SC, Rompa D, DiFonzo K, Simpson D, Austin J, Luke W, et al. HIV treatment adherence in women living with HIV/AIDS: research based on the Information-Motivation-Behavioral Skills model of health behavior. J Assoc Nurses AIDS Care 2001;12(4):58-67. [doi: 10.1016/S1055-3290(06)60217-3] [Medline: 11486721]
54. Rongkavilit C, Naar-King S, Kaljee LM, Panthong A, Koken JA, Bunupuradah T, et al. Applying the information-motivation-behavioral skills model in medication adherence among Thai youth living with HIV: a qualitative study. AIDS Patient Care STDS 2010 Dec;24(12):787-794 [FREE Full text] [doi: 10.1089/apc.2010.0069] [Medline: 21091238]
55. Starace F, Massa A, Amico KR, Fisher JD. Adherence to antiretroviral therapy: an empirical test of the information-motivation-behavioral skills model. Health Psychol 2006 Mar;25(2):153-162. [doi: 10.1037/0278-6133.25.2.153] [Medline: 16569106]
56. Kalichman SC, Cherry J, Cain D. Nurse-delivered antiretroviral treatment adherence intervention for people with low literacy skills and living with HIV/AIDS. J Assoc Nurses AIDS Care 2005;16(5):3-15. [doi: 10.1016/j.jana.2005.07.001] [Medline: 16433105]
57. Margolin A, Avants SK, Warburton LA, Hawkins KA, Shi J. A randomized clinical trial of a manual-guided risk reduction intervention for HIV-positive injection drug users. Health Psychol 2003 Mar;22(2):223-228. [Medline: 12683743]
58. Parsons JT, Golub SA, Rosof E, Holder C. Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. J Acquir Immune Defic Syndr 2007 Dec 1;46(4):443-450 [FREE Full text] [Medline: 18077833]
59. Wagner GJ, Kanouse DE, Golinelli D, Miller LG, Daar ES, Witt MD, et al. Cognitive-behavioral intervention to enhance adherence to antiretroviral therapy: a randomized controlled trial (CCTG 578). AIDS 2006 Jun 12;20(9):1295-1302. [doi: 10.1097/01.aids.0000232238.28415.d2] [Medline: 16816559]
60. Naar-King S, Kolmodin K, Parsons JT, Murphy D, ATN 004 Protocol Team, Adolescent Trials Network for HIV/AIDS Interventions. Psychosocial factors and substance use in high-risk youth living with HIV: a multi-site study. AIDS Care 2010 Apr;22(4):475-482 [FREE Full text] [doi: 10.1080/09540120903220279] [Medline: 20146112]
61. Balaji AB, Oster AM, Viall AH, Heffelfinger JD, Mena LA, Toledo CA. Role flexing: how community, religion, and family shape the experiences of young black men who have sex with men. AIDS Patient Care STDS 2012 Dec;26(12):730-737. [doi: 10.1089/apc.2012.0177] [Medline: 23134543]
62. Lewis LJ, Kertzner RM. Toward improved interpretation and theory building of African American male sexualities. J Sex Res 2003 Nov;40(4):383-395. [doi: 10.1080/00224490209552204] [Medline: 14735412]

63. Stokes JP, Peterson JL. Homophobia, self-esteem, and risk for HIV among African American men who have sex with men. AIDS Educ Prev 1998 Jun;10(3):278-292. [Medline: 9642425]
64. MacDonell KK, Jacques-Tiura AJ, Naar S, Fernandez MI, ATN 086/106 Protocol Team. Predictors of Self-Reported Adherence to Antiretroviral Medication in a Multisite Study of Ethnic and Racial Minority HIV-Positive Youth. J Pediatr Psychol 2016 May;41(4):419-428. [doi: 10.1093/jpepsy/jsv097] [Medline: 26498724]
65. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate - A Practical and Powerful Approach to Multiple Testing. J Royal Stat Soc 1995;57(1):289-300.
66. Fitzmaurice GM, Laird NM, Ware JH. Missing Data and Dropout: Overview of Concepts and Methods. In: Applied Longitudinal Analysis, 2nd Edition. Hoboken, NJ: John Wiley & Sons, Inc; Aug 2011:489-513.
67. Patton MQ. Qualitative evaluation and research methods, 2nd edition. Thousand Oaks, CA: Sage Publications, Inc; Feb 01, 1990.
68. Schutz A. In: Wagner HR, editor. On Phenomenonology and Social Relations. Chicago, IL: University of Chicago Press; 1970.
69. Lewis S. Qualitative inquiry and research design: Choosing among five approaches. Health Promot Pract 2015 Apr 02;16(4):473-475.
70. Moustakas C. Phenomenological research methods. Thousand Oaks, CA: Sage Publications, Inc; 1994.
71. Miles MB, Huberman AM. Qualitative Data Analysis: An Expanded Sourcebook. Thousand Oaks, CA: Sage Publications, Inc; 1994.
72. Yau LHY, Little RJ. Inference for the Complier-Average Causal Effect From Longitudinal Data Subject to Noncompliance and Missing Data, With Application to a Job Training Assessment for the Unemployed. J Am Stat Assoc 2001 Dec;96(456):1232-1244. [doi: 10.1198/016214501753381887]
73. Toh S, Hernán MA. Causal inference from longitudinal studies with baseline randomization. Int J Biostat 2008 Oct 19;4(1):Article 22 [FREE Full text] [doi: 10.2202/1557-4679.1117] [Medline: 20231914]
74. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011 Aug 11;365(6):493-505 [FREE Full text] [doi: 10.1056/NEJMoa1105243] [Medline: 21767103]
75. Levy A, Johnston K, Annemans L, Tramarin A, Montaner J. The impact of disease stage on direct medical costs of HIV management: a review of the international literature. Pharmacoeconomics 2010;28(Suppl 1):35-47. [doi: 10.2165/11587430-000000000-00000] [Medline: 21182342]
76. Strategies for Management of Antiretroviral Therapy (SMART) Study Group, Lundgren JD, Babiker A, El-Sadr W, Emery S, Grund B, et al. Inferior clinical outcome of the CD4+ cell count-guided antiretroviral treatment interruption strategy in the SMART study: role of CD4+ Cell counts and HIV RNA levels during follow-up. J Infect Dis 2008 Apr 15;197(8):1145-1155. [doi: 10.1086/529523] [Medline: 18476293]

Abbreviations

ART: antiretroviral therapy
CASI: computer-assisted self-interviewing
CBIs: computer-based interventions
GEE: generalized estimating equation
GLM: generalized linear models
RCT: randomized controlled trial
VL: viral load
VS: viral suppression
YMSM: young men who have sex with men
YTWSM: transgender women who have sex with men

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Protocol

Application of Behavior Change Techniques in a Personalized Nutrition Electronic Health Intervention Study: Protocol for the Web-Based Food4Me Randomized Controlled Trial

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Abstract

Background: To determine the efficacy of behavior change techniques applied in dietary and physical activity intervention studies, it is first necessary to record and describe techniques that have been used during such interventions. Published frameworks used in dietary and smoking cessation interventions undergo continuous development, and most are not adapted for Web-based delivery. The Food4Me study (N=1607) provided the opportunity to use existing frameworks to describe standardized Web-based techniques employed in a large-scale, internet-based intervention to change dietary behavior and physical activity.

Objective: The aims of this study were (1) to describe techniques embedded in the Food4Me study design and explain the selection rationale and (2) to demonstrate the use of behavior change technique taxonomies, develop standard operating procedures for training, and identify strengths and limitations of the Food4Me framework that will inform its use in future studies.

Methods: The 6-month randomized controlled trial took place simultaneously in seven European countries, with participants receiving one of four levels of personalized advice (generalized, intake-based, intake+phenotype–based, and intake+phenotype+gene–based). A three-phase approach was taken: (1) existing taxonomies were reviewed and techniques were identified a priori for possible inclusion in the Food4Me study, (2) a standard operating procedure was developed to maintain consistency in the use of methods and techniques across research centers, and (3) the Food4Me behavior change technique framework was reviewed and updated post intervention. An analysis of excluded techniques was also conducted.

Results: Of 46 techniques identified a priori as being applicable to Food4Me, 17 were embedded in the intervention design; 11 were from a dietary taxonomy, and 6 from a smoking cessation taxonomy. In addition, the four-category smoking cessation framework structure was adopted for clarity of communication. Smoking cessation texts were adapted for dietary use where

necessary. A posteriori, a further 9 techniques were included. Examination of excluded items highlighted the distinction between techniques considered appropriate for face-to-face versus internet-based delivery.

Conclusions: The use of existing taxonomies facilitated the description and standardization of techniques used in Food4Me. We recommend that for complex studies of this nature, technique analysis should be conducted a priori to develop standardized procedures and training and reviewed a posteriori to audit the techniques actually adopted. The present framework description makes a valuable contribution to future systematic reviews and meta-analyses that explore technique efficacy and underlying psychological constructs. This was a novel application of the behavior change taxonomies and was the first internet-based personalized nutrition intervention to use such a framework remotely.

Trial Registration: ClinicalTrials.gov NCT01530139; https://clinicaltrials.gov/ct2/show/NCT01530139 (Archived by WebCite at http://www.webcitation.org/6y8XYUft1)

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KEYWORDS

behavior; behavior change technique; personalized nutrition; dietary management; nutrition; health; Web-based

Introduction

Emergence of Web-Based e-Resources

Improvement of health behavior relating to diet and lifestyle (eg, physical activity [PA]) is a key goal of studies aiming to reduce the incidence and progression of noncommunicable diseases (NCD). Chronic NCD such as cardiovascular disease (CVD), type II diabetes, and obesity carry heavy health care costs and are predicted to account for nearly three-quarters of global deaths in 2020 [1], with at least 2 million deaths each year currently associated with CVD in Europe alone [2]. Dietary and lifestyle factors play a key role in the progression and prognosis of many chronic NCD [3-5], and there is a continuing need to develop successful strategies to facilitate positive health-related behavior change. With the emergence of Web-based e-resources in electronic health initiatives, which offer cost-effective and fast delivery of health services [6], it is important to understand what drives behavior change in the context of these new digital environments.

Evaluation of Web-Based Behavior Change Science

The science of health-related behavior change is complex and now requires reviewing owing to the large amount of research that has been conducted of late. Study designs are highly variable, and some interventions are more effective than others. New technologies such as mobile phones and other communication technologies are increasingly being used to deliver interventions, and this may influence behavior change technique (BCT) efficacy in ways we cannot yet predict. For instance, some meta-analyses have suggested that studies testing dietary and PA interventions that targeted fewer BCTs per individual were most effective [7].

In contrast, a meta-analysis conducted on computerized Web-based studies has suggested that the application of a greater number of BCTs to individuals was associated with greater effect sizes in successful interventions [8], although associations were not tested in the same individuals in Web-based versus face-to-face interventions, making comparison difficult. It may be the case that computerized studies offering less face-to-face support may benefit from the inclusion of greater numbers of BCTs that individuals can potentially pick and choose as appropriate. As Web-based studies offer access to greater numbers of individuals and are quicker and more cost-effective to deliver [6], it is likely that they will become increasingly popular with public health practitioners in the future. So it may also be necessary to formulate BCT strategies specifically for Web-based delivery methods.

In meta-analyses of dietary, PA, and smoking cessation (SC) interventions, the lack of or ambiguous recording of BCTs was highlighted, which hinders comparison and replication of different methodologies [7,8]. Until BCTs are properly recorded and BCT taxonomies are developed and used as a standard practice in studies seeking to change health behaviors, it will be difficult to assess BCT efficacy and to understand the psychological mechanisms underpinning intervention efficacy. BCT taxonomic frameworks are still being developed to enable a better understanding of dietary and other behavior changes to enable standardization of reporting, thereby providing a suitable basis for comparison, replication, and evaluation [9,10]. However, given the increase in Web-based delivery of health services, it is important to consider the development, use, and specification of BCTs in their design.

Theory-Driven Application of a Web-Based Behavior Change Methodology

The taxonomy of BCT outlined in dietary and PA research by Susan Michie and her colleagues [9,10] was developed from earlier work by Abraham and Michie in 2008 [11]. An initial 26-item BCT taxonomy was derived from 72 intervention studies targeting diet and lifestyle behavior change. Michie et al developed well-validated BCT taxonomies for dietary behavior change, for example, the *Coventry, Aberdeen, and London-Refined*, or CALO-RE study [9], PA, and SC [10]. Michie et al's BCT selection was derived from a number of theoretical standpoints [11] where BCTs were analyzed in terms of their deemed level of congruency or association with different important theoretical stances. These stances included control theory [12], which assumes that behavior is optimally changed by goal setting, self-monitoring, and evaluation; the Information-Motivation-Behavioral Skills model [13] and Theory of Planned Behavior [14], which focus on the provision of information on the link between behavior and health, health consequences of behavior, and others' approval to bring about an intention to change; Social Cognitive Theory [15], where

use of the social context is deemed necessary to understand barriers to change, provide support and encouragement for behavior change, and to learn from others; and Operant Theory [16], where reward-based learning occurs by identifying and using prompts and cues and by establishing routines to bring about good habit formation. Thus, the pan-European Food4Me study (N=1607) [17] provided an opportunity to use validated theory-driven BCT taxonomies to develop a BCT framework targeted at changing dietary and PA behaviors in an internet-based randomized controlled trial (RCT), with BCT selection for Food4Me being guided by this earlier theoretically driven work.

The overall aim of this paper was to articulate and describe the BCT Web-based methodology embedded in the structure and design of the Food4Me study and to explain why the BCT techniques were selected and for what purpose. Specifically, we aim to:

- Describe measurable BCTs embedded in the Food4Me study design from a validated BCT framework
- Demonstrate how the BCT framework was used in the development of standard operating procedures (SOPs) and training to maintain consistency across seven European countries
- Hypothesize as to the strengths and limitations of the BCT framework in the context of the Food4Me proof of principle (PoP) RCT
- Inform the use of this BCT framework in future studies of similar nature

Although psychological theories are described here briefly in terms of taxonomic development in general, it is beyond the scope of this methods paper to link BCTs to psychological theory.

Methods

Study Sample

The Food4Me PoP study was a 6-month, internet-based, 4-arm parallel, randomized controlled dietary intervention trial that took place in seven European countries (Germany, Greece, Ireland, the Netherlands, Poland, Spain, and the United Kingdom) from August 2012 to February 2014. Participants aged 18 to 80 years were recruited through their national recruitment center and undertook the study in the local language. Volunteers were excluded if they had no internet access, were suffering from chronic disease, were pregnant, lactating, or otherwise had special dietary requirements.

All participants signed Web-based consent forms at each of two screening stages, which were then returned electronically to the local study investigators for countersigning and archiving. Ethical approval for the Food4Me study (registered at Clinicaltrials.gov, NCT01530139) was granted by the local research ethics committee at each center.

Study Design

Participants were randomized to one of four arms (see Figure 1):

- Controls (level 0, L0) received currently accepted public health guidelines at months 0 and 3
- Levels 1, 2, and 3 (L1, L2, and L3, respectively) received personalized nutrition (PN) dietary advice at months 0 and 3 based on self-reported intake via Food Frequency Questionnaires (FFQs)

This PN advice took the form of three or four target nutrients to change and PA goals. L1 received dietary advice based on FFQ data alone, L2 on FFQ + phenotypic data from blood sampling, and L3 on FFQ + phenotypic + genotypic data. In addition, the frequency of advice was varied within each PN condition: low-intensity L1 to L3 participants received feedback at months 0 and 3 months, whereas high-intensity participants received additional feedback at months 1 and 2. Low-intensity L1 to L3 participants received basic PA advice and targets based on PA questionnaires collected at 0 and 3 months, whereas high-intensity participants also received feedback based on their PA monitor (TracmorD tri-axial accelerometer, Philips Consumer Lifestyle, The Netherlands [17]) data at months 0, 1, 2, and 3. All participants were required to use home kits to provide DNA samples at month 0 and blood samples at months 0, 3, and 6. Instructions for anthropometric measurements, DNA and blood sampling, and use of PA monitors were provided in hard copy form and were also available via video clips at the Food4me [18] website.

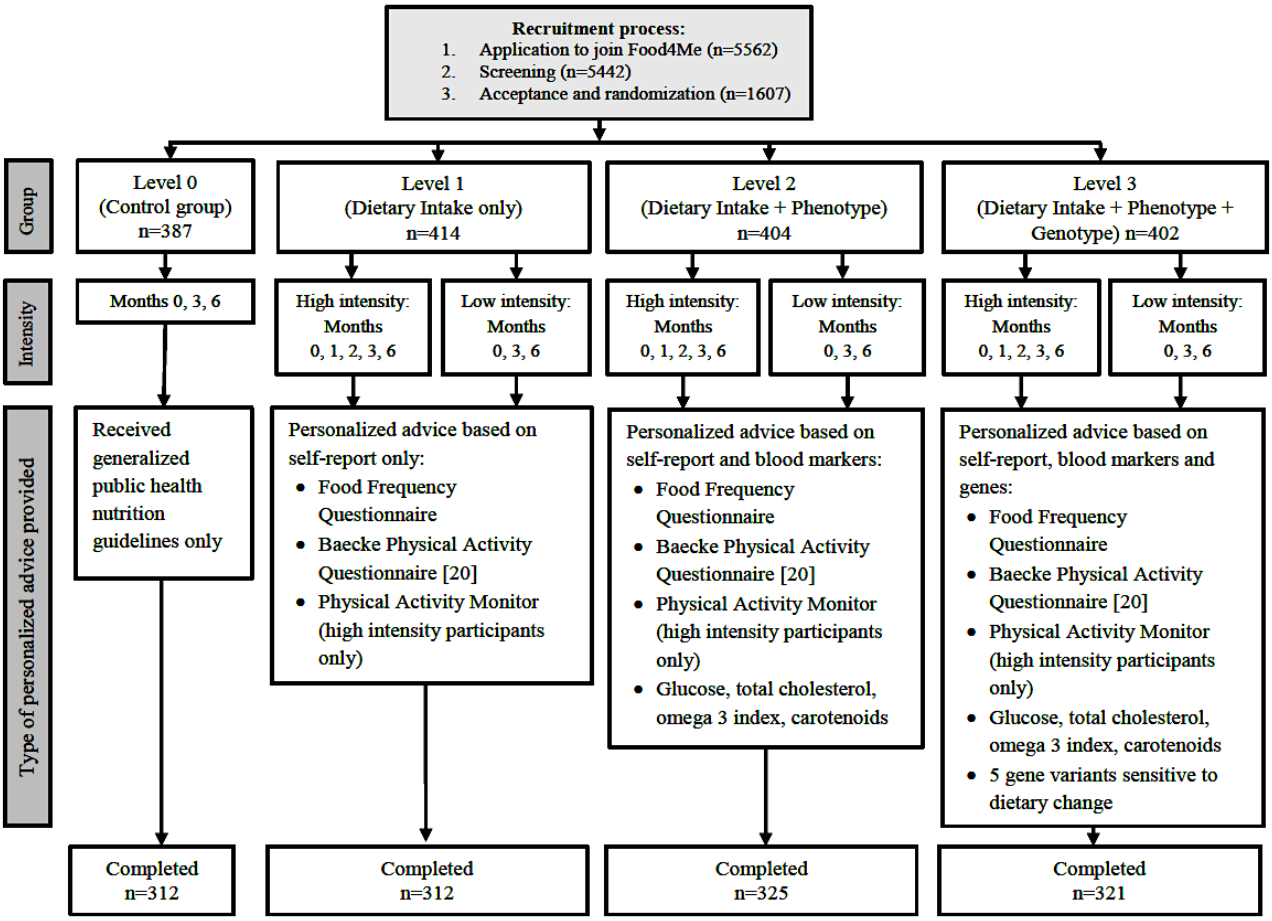
All participants completed a bespoke Dietary Change Questionnaire, designed to determine intention to change dietary behaviors [19], at their first measurement time point. The Baecke PA Questionnaire [20], a validated 16-item self-report tool to determine differences in three PA dimensions (habitual PA for work, sport PA during leisure time, and leisure time PA excluding sport), was administered at all data collection time points. The study design is described in full elsewhere [17].

All participants received a fully personalized report at the end of the study at month 6 in acknowledgment of their participation, which included their top three or four nutrient targets, PA goals, and blood and DNA results. This complex study design enabled comparisons over time between provision of general public health advice and personalized advice, between types of personalized advice delivered, and between high and low frequency (eg, intensity) of personalized advice provision [21].

Behavior Change Technique Analysis

The analysis of BCTs used in the Food4Me study was carried out in three phases: (1) phase I (a priori): conduct a scoping review to identify theoretically appropriate BCT well-described in previous work [9,10] that could be applied to dietary and PA behaviors, in a remote or internet-based intervention context, for potential use in the Food4Me study; (2) phase II: develop a working BCT SOP for use by researchers in the PoP study, and train researchers at all Food4Me centers; and (3) phase III (a posteriori): review the BCT list on completion of the intervention study, and include any additional BCT utilized in the Food4Me study. Analyses for all three phases were carried out by Food4Me BCT researchers.

Figure 1. Process flow diagram for the Food4Me Proof of Principle study.



BCTs were reviewed for inclusion on the basis of their perceived capacity to support and promote change in dietary and other healthy behaviors utilizing the individual's own motivations, capacity, and ability to change; the provision and delivery of dietary advice; and the quality of interactions supporting this provision.

BCTs were finally selected on the basis of how closely they aligned with the dietary and health goals of the study (for instance, in terms of the type, nature, and frequency of feedback to participants), on the basis of practicality (for instance, how far and how robustly they could be used remotely), and in terms of how easily they could be embedded in the provision of feedback, information, and advice.

Results

Behavior Change Technique Analysis Phase I—Food4Me Behavior Change Technique Identification

Phase I was carried out during the design phase of the Food4Me PoP dietary intervention study. Michie et al's CALO-RE [9] and SC BCT [10] taxonomies were used to develop the Food4Me BCT framework. CALO-RE contains 40 uncategorized items, whereas the SC framework includes 43 items categorized into four functions, namely (1) motivation behaviors, (2) self-regulatory capacity or skill-related behaviors, (3) promotion of adjuvant (supporting) activities (eg, dietary advice), and (4) general aspects of interaction (eg, information gathering, delivery, and communication). Six BCTs from the SC BCT list that were not included in the 40-item CALO-RE BCT list were identified as being potentially useful for adaptation to the Food4Me dietary intervention, making 46 BCTs in total. The list of 46 BCTs was reviewed and agreed by six members of the Food4Me BCT research team based at Food4Me study centers at the universities of Reading, Ulster, Newcastle, and Wageningen.

Behavior Change Technique Analysis Phase II—Food4Me Behavior Change Technique Development

On completion of the phase I analysis, the combined 46-item BCT framework was assessed to determine which BCTs were to be used in the Food4Me RCT (see Multimedia Appendix 1). At this stage, 11 items from the CALO-RE BCT list were judged appropriate when considering the constraints of a Web-based study in a remote setting.

Six items were adapted from the SC BCT list [10]: "emphasize choice," "tailor interactions appropriately," "assess current and past dietary behavior," "assess current readiness and ability to change," "assess past history of dietary change attempts," and "assess adverse reactions." These 6 items did not appear in the CALO-RE list; however, the research team considered that these BCTs were particularly appropriate for Web-based study designs and for studies conducted in remote settings. For instance, volunteers (1) received different types of advice depending on group allocation (tailor interactions appropriately); (2) were

provided with choices of healthier foods (emphasize choice); (3) were assessed, and responses compared, at a number of time points (assess current and past dietary behavior), with readiness and ability measured by the Dietary Change Questionnaire (assess current readiness and ability to change); and (4) their adverse reactions were recorded throughout in line with clinical best practice (assess adverse reactions). Attempts were made to adapt the SC BCT texts for a dietary intervention where necessary and to align the adapted BCT text to reflect the commonality and underlying purpose of the BCT. For instance, "tailor interactions appropriately" [10] suited the Food4Me design where feedback was based on personal characteristics such as self-reported dietary intake, blood markers and genotype, and the text was included unchanged, whereas "assess current and past smoking behavior: assess amount smoked, age when started, pattern of smoking behavior" [10] was adapted to "Assess current and past dietary behavior: assess amount of food eaten and current and past patterns of food eaten," as this was measured during the intervention. Multimedia Appendix 2 shows the changes made with rationales for the adapted text. The finalized revised list was then used to develop an SOP for use in all participating countries.

BCTs requiring more individualized or additional training resources and not in effect representing one single BCT but a set of them, such as BCT items 15 (prompting generalization of a target behavior), 36 (stress management or emotional control training), and 37 (motivational interviewing), were excluded. Items judged to require more in-depth or face-to-face interaction or resources beyond the scope of the study were excluded. Examples of excluded items are 23 (teach to use prompts or cues), 28 (facilitate social comparison), and 33 (prompt self-talk). BCTs with a negative inference, for instance, items 31 (prompting anticipated regret) and 32 (fear arousal) were excluded, as advice was designed to emphasize the benefits of following recommendations (eg, increasing intake of fruits and vegetables has been shown to reduce your risk of CVD) rather than focus on risk per se (eg, if you don't eat enough fruits and vegetables you may be at greater risk of CVD). In this internet-based study, it was possible that the Web-based interface and associated lack of face-to-face support could have exacerbated any negative emotions on the part of the participant that the researchers would have been unable to monitor, control, or manage effectively. The rationale used for excluding BCT items is shown in Multimedia Appendix 3.

In summary, of the 46 BCT items previously identified, a total of 17 items were initially deemed appropriate to use when designing the Food4Me RCT and were included in the SOP during phase II. For practical reasons, it was decided to adopt the categorization framework developed for the SC program, as this was judged to be easier to communicate to all researchers and easier to use in practice in the SOP. The 17-item Food4Me BCT SOP was reviewed and agreed by the 6-strong Food4Me BCT research team.

Behavior Change Technique Analysis Phase III—Food4Me Behavior Change Technique Poststudy Review

At the end of the study, the Food4Me SOP BCT was reviewed within the context of the intervention delivery. The 17 SOP BCT had initially been adopted across all centers, as these had been embedded in the design and implementation of the intervention study. A further 9 CALO-RE BCT had been adopted during the course of the study owing to the development of interim reports containing various types and levels of participant feedback for diet and PA. The interim report development had occurred in parallel with, or after, publication of the BCT SOP. This phase III analysis indicated that 26 BCTs were actually being used in the Food4Me dietary and lifestyle intervention, of which 20 came from the CALO-RE BCT list, and 6 were adapted from the SC BCT list (see Multimedia Appendix 1).

Discussion

Principal Findings and Comparison With Other Work

The identification of BCTs used in the Food4Me PoP study took place over three phases: identification of possible BCT for use in the Food4Me study (phase I: identification), development of an SOP (phase II: development), and review of the BCT used in the intervention (phase III: review). Initially, 46 BCTs were selected from validated BCT taxonomies [9,10] for possible inclusion, and 17 BCTs were selected for inclusion in the Food4Me PoP study SOP. At the end of the study, a further 9 BCTs were identified from the CALO-RE list in the final review as having actually been used by researchers after the development of the feedback reports. BCTs were largely embedded in the study design, which lent itself well to the development of a BCT SOP for use across all seven European study centers. This approach, for example, of a priori BCT review taking into account important contextual constraints on the delivery format and ad hoc a posteriori revision, is another form of approaching intervention development for adoption by future multicenter intervention studies where SOP may undergo further iterations and refinements in response to unanticipated needs emerging during the study.

In comparison with other dietary studies, the Food4Me PoP study had a higher number of BCTs embedded in its design. In Michie et al's meta-analysis of interventions targeting improvements in smoking-related behaviors, dietary intake, and PA [7], dietary interventions included four to 19 BCTs, and the most successful interventions had fewer BCTs. This conclusion has been supported elsewhere [22]. However, the meta-analysis carried out by Thomas Webb et al on internet-delivered health interventions reported that more effective interventions were associated with greater numbers of BCTs [8]. There is still much work to be done to determine the exact nature of the relationship between the number of BCTs and efficacy of an intervention, which may be driven by any number of other factors, the assessment of which is beyond the scope of the current analysis.

Previous studies have usefully attempted to categorize the BCT taxonomy in terms of type of BCT category. For instance, the

SC taxonomy [10] distinguished between motivation-based BCT, self-regulatory BCT, BCT providing adjuvant (supporting) activities, and BCT relating to general interactions (delivery, information gathering, and communication). This framework was crucial in helping us to describe the Food4MePOP study BCT framework and for identifying BCTs suitable for delivery of an internet-based intervention. For example, the SC BCT taxonomy included "before" and "after" comparisons, which have formed the basis of previous intervention studies, where feedback has been based on outcomes measured during the study. The SC taxonomy also included a BCT to monitor adverse reactions (eg, nicotine withdrawal). Reporting of adverse events (AEs) is considered the best clinical practice and is mandatory in clinical trials [23]. Dietary trials, including the Food4Me study, which include invasive measurements such as blood sampling in the home, should ideally aim to meet similar standards, even if recording of AEs is not compulsory. Finally, the categorization framework was particularly useful when communicating the BCT SOP to study researchers and for researcher training.

Three CALO-RE BCTs and five SC BCTs were subjected to varying degrees of adaptation for use in the Food4Me study; further scrutiny may be required to determine if altered BCTs are essentially the same as the original BCTs, or if the revised BCTs are distinct concepts in their own right. For instance, reporting of adverse *reactions* (eg, nicotine withdrawal) in the SC BCT may relate only to cause and effect as a direct result of the intervention target outcomes (eg, stopping smoking), whereas reporting of AEs appears broader and may relate to intervention outcomes (eg, excessive weight loss and reactions to recommended foods) and measurement factors (eg, blood-sampling in the home), both of which may hinder trial completion and prevent target outcomes from being achieved. Clinical best practice dictates that any study impacting on an individual's health and well-being should include an overarching BCT for reporting AEs (including reactions), although this could be in addition to, or instead of, the adverse reactions to BCTs. BCTs were excluded if they were considered to be more appropriate for face-to-face interventions, which were beyond the scope of the study, or required additional resources that were incompatible with the original study design. In particular, BCTs that were thought to instigate negative emotions (eg, fear arousal and prompt anticipated regret) were avoided, in case they brought about adverse reactions that would be difficult to monitor or manage in an internet-based study.

Although some researchers have started to define BCT frameworks for use in intervention design (conceptual BCT-based design), many do not consider doing so in this way, with some key exceptions [24-26]. BCT analysis is still at an early stage with respect to dietary intervention studies and is not yet in a state where BCT descriptions may be linked to psychological constructs and its mechanisms [27,28]. The development of meta-analysis methodologies is ongoing and will not only contribute greatly to an understanding of the psychological mechanisms underpinning BCTs but also to an observable linkage with intervention efficacy [27]. However, such work is hampered by inadequate descriptions of study designs, failure to identify BCT a priori, or to monitor actual BCT use in interventions [9]. It is therefore recommended that future intervention design should incorporate a priori BCT identification, especially to aid the development of SOPs, and a posteriori BCT review, to ensure that all relevant BCTs have been captured and identified for future analysis in meta-analyses designed to determine such links, as the initially proposed BCT might change to better fit the context and individual needs. In this study, we are confident that the Food4Me study BCT framework has been well defined and categorized and will enable replication in the future.

To our knowledge, BCTs have not previously been described and categorized a priori for use in an internet-based PN intervention study of this nature, where participants were required to provide samples using home testing kits. Neither have they been used in the development of SOP for European multicenter research for a PN intervention study on this scale. As such, this a priori categorization combined with an a posteriori review of BCT in an internet-based, pan-European PN or PA RCT intervention is a novel use of the BCT framework taxonomy [9-11] and the first of its kind to do so.

Strengths and Limitations

The process of defining the Food4Me BCT framework revealed a number of key strengths in our methodology. First, it enabled a clear understanding of the complex nature of the BCT framework used in an intervention where behavior change was the primary outcome. This is important: behavior change is poorly understood and difficult to predict in dietary and lifestyle interventions, so consistent and comparable use of methods that may contribute to our ability to determine drivers of behavior change is invaluable. A second important strength was that the development of the Food4Me BCT framework enabled us to use and test two established, evidence-based, theory-derived BCT taxonomies. CALO-RE and SC were found to be user-friendly and helpful in identifying target BCT and informing intervention design, development, and evaluation, although as Michie et al have acknowledged [9], there is still work to be done to develop these taxonomies further. Indeed, by combining the two taxonomies, the Food4Me study researchers were able to identify gaps in the CALO-RE taxonomy. These gaps were addressed by revisiting the SC taxonomy and by additional use of the SC categories. A third major strength of the Food4Me study approach was the creation and dissemination of a BCT SOP to be used by all recruiting centers, which helped to maintain consistency across seven European countries and provided the basis for researcher training. To our knowledge, this is a novel use of the BCT framework in a complex, pan-European, internet-based study. A final key strength was the incorporation of a three-phase process to define the Food4Me BCT framework, enabling a complete audit of BCTs at the study design, development, and completion stages. This mapping of the evolution of the decision-making process for the selection of BCTs, from conception and design through to execution, has the added advantage that it will contribute to the BCT meta-analysis process, as documentation does not always occur satisfactorily in this way, with either a priori or, in most cases, a posteriori recording and determination [7].

Some limitations were encountered. The BCT SOP was developed in parallel with other key aspects of the study (eg, interim reports) and was distributed before completion of the interim report piloting. This resulted in the choice of SOP BCT being dependent on design choices previously made in other elements of the study (for instance, blood collection processes and type or availability of other information on which advice was based), and this may have limited our ability to choose the most effective BCTs. Future researchers should attempt to design elements of the study likely to influence behavioral outcomes in advance of BCT analysis and before the start of the study. However, as we have demonstrated here, this is not always possible in practice, especially in complex multidisciplinary and multicenter experimental interventions with competing parameters. Second, in addition to the CALO-RE BCT, we used some SC-specific BCT to meet the needs of the Food4Me BCT framework; in some instances, we made alterations to existing BCT texts where the existing BCT did not fully apply to the specific needs of Food4Me. As a consequence of this, the meaning of the BCT may be slightly different from applications elsewhere, making comparison with other intervention studies difficult. Third, a number of elements of the Food4Me study, such as the interim report, incorporate several BCTs, which makes it difficult to assess the impact of a single BCT on study outcomes. Future research should investigate the effects of both single BCTs and BCT combinations, as combinations will typically be used in practice. The Food4Me results may provide insight into the latter.

Future Recommendations

Our research has shown that BCTs can be usefully incorporated into the development of a complex dietary and PA Web-based RCT. It is recommended that literature-based lists, and possibly exploratory research, are used to provide clear justification for the inclusion or exclusion of BCTs in research designs. However, it should also be noted that a degree of pragmatism, which in this case was based upon study complexity, might be required in determining the number of BCTs to measure, especially where there is a lack of clear guidance within the literature about a recommended range of BCTs to measure. Finally, particularly in complex study designs, there should be sufficient flexibility to allow for additional BCT measures where necessary. Routine explicit description of BCTs used in research studies will help to enhance our understanding of BCTs for use in both specific and generalized situations and enable us to determine the optimal number and range of BCTs to incorporate into RCTs.

Conclusions

Validated BCT taxonomies were helpful in developing the Food4Me BCT framework. Using an existing taxonomy to develop a BCT framework enables replication and comparison in future meta-analyses. The Food4Me framework will contribute to the future determination of psychological constructs and mechanisms underpinning behavior change and intervention efficacy. Categorization and description assisted the development of SOP and promoted consistency in experimental work. All BCT frameworks should be described and evaluated both a priori and a posteriori to aid replication and future analysis.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Coventry, Aberdeen, and London-Refined and smoking cessation behavior change techniques included in the Food4Me study.

[PDF File (Adobe PDF File), 39KB - resprot_v7i4e87_app1.pdf]

Multimedia Appendix 2

Changes made to Coventry, Aberdeen, and London-Refined and smoking cessation Michie et al behavior change technique descriptions adapted for Food4Me on finalization of standard operating procedures.

[PDF File (Adobe PDF File), 39KB - resprot_v7i4e87_app2.pdf]

Multimedia Appendix 3

Coventry, Aberdeen, and London-Refined behavior change techniques excluded from Food4Me, with rationale.

[PDF File (Adobe PDF File), 31KB - resprot_v7i4e87_app3.pdf]

References

1. WHO. Global Strategy on Diet, Physical Activity and Health. Geneva: World Health Organization; 2002.

2. Allender S, Scarborough P, Peto V, Rayner M, Leal J, Luengo-Fernandez R, et al. European Cardiovascular Disease Statistics. London, UK: European Heart Network; 2008.
3. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, Lancet Physical Activity Series Working Group. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012 Jul 21;380(9838):219-229 [FREE Full text] [doi: 10.1016/S0140-6736(12)61031-9] [Medline: 22818936]
4. Waxman A. WHO's global strategy on diet, physical activity and health. Response to a worldwide epidemic of non-communicable diseases. Scand J Nutr 2004;48(2):58-60 [FREE Full text] [doi: 10.1080/11026480410033539]
5. Mbanya JC, Squire SB, Cazap E, Puska P. Mobilising the world for chronic NCDs. Lancet 2011;377(9765):536-537. [doi: 10.1016/S0140-6736(10)61891-0] [Medline: 21074252]
6. Celis-Morales C, Lara J, Mathers JC. Personalising nutritional guidance for more effective behaviour change. Proc Nutr Soc 2015;74(2):130-138. [doi: 10.1017/S0029665114001633] [Medline: 25497396]
7. Michie S, Jochelson K, Markham WA, Bridle C. Low-income groups and behaviour change interventions: a review of intervention content, effectiveness and theoretical frameworks. J Epidemiol Community Health 2009;63(8):610-622. [doi: 10.1136/jech.2008.078725] [Medline: 19386612]
8. Webb TL, Joseph J, Yardley L, Michie S. Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. J Med Internet Res 2010;12(1):e4 [FREE Full text] [doi: 10.2196/jmir.1376] [Medline: 20164043]
9. Michie S, Ashford S, Sniehotta FF, Dombrowski SU, Bishop A, French DP. A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy. Psychol Health 2011;26(11):1479-1498. [doi: 10.1080/08870446.2010.540664] [Medline: 21678185]
10. Michie S, Hyder N, Walia A, West R. Development of a taxonomy of behaviour change techniques used in individual behavioural support for smoking cessation. Addict Behav 2011;36(4):315-319. [doi: 10.1016/j.addbeh.2010.11.016] [Medline: 21215528]
11. Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. Health Psychol 2008;27(3):379-387. [doi: 10.1037/0278-6133.27.3.379] [Medline: 18624603]
12. Carver CS, Scheier MF. Control theory: a useful conceptual framework for personality-social, clinical, and health psychology. Psychol Bull 1982;92(1):111-135. [Medline: 7134324]
13. Fisher JD, Fisher WA, Bryan AD, Misovich SJ. Information-motivation-behavioral skills model-based HIV risk behavior change intervention for inner-city high school youth. Health Psychol 2002;21(2):177-186. [Medline: 11950108]
14. Ajzen I. The theory of planned behaviour. Organ Behav Hum Decis Process 1991;50(2):179-211 [FREE Full text]
15. Bandura A. Health promotion from the perspective of social cognitive theory. Psychol Health 1998;13(4):623-649. [doi: 10.1080/08870449808407422]
16. Skinner BF. Contingencies of Reinforcement: A Theoretical Analysis. Cambridge, MA: BF Skinner Foundation; 2014.
17. Celis-Morales C, Livingstone KM, Marsaux CF, Forster H, O'Donovan CB, Woolhead C, et al. Design and baseline characteristics of the Food4Me study: a web-based randomised controlled trial of personalised nutrition in seven European countries. Genes Nutr 2015;10(1):450 [FREE Full text] [doi: 10.1007/s12263-014-0450-2] [Medline: 25491748]
18. Food4Me. Strategies for Personalised Nutrition (Food4Me). 2013 Aug 23. URL: https://clinicaltrials.gov/show/NCT01530139 [accessed 2015-03-25] [WebCite Cache ID 6XII1QwHz]
19. Forster H, Walsh MC, O'Donovan CB, Woolhead C, McGirr C, Daly EJ, et al. A dietary feedback system for the delivery of consistent personalized dietary advice in the web-based multicenter Food4Me study. J Med Internet Res 2016;18(6):e150 [FREE Full text] [doi: 10.2196/jmir.5620] [Medline: 27363307]
20. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982;36(5):936-942 [FREE Full text] [Medline: 7137077]
21. Celis-Morales C, Livingstone KM, Marsaux CF, Macready AL, Fallaize R, O'Donovan CB, Food4Me Study. Effect of personalized nutrition on health-related behaviour change: evidence from the Food4Me European randomized controlled trial. Int J Epidemiol 2017;46(2):578-588. [doi: 10.1093/ije/dyw186] [Medline: 27524815]
22. Dombrowski SU, Sniehotta FF, Avenell A, Johnston M, MacLennan G, Araújo-Soares V. Identifying active ingredients in complex behavioural interventions for obese adults with obesity-related co-morbidities or additional risk factors for co-morbidities: a systematic review. Health Psychol Rev 2012;6(1):7-32. [doi: 10.1080/17437199.2010.513298]
23. FDA. Silver Spring, MD: US Food and Drug Administration; 2009. Guidance for clinical investigators, sponsors, and IRBs: adverse event reporting to IRBs - Improving human subject protection URL: https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf [accessed 2018-03-17] [WebCite Cache ID 6xzQjc5Ew]
24. Dombrowski SU, Sniehotta FF, Johnston M, Broom I, Kulkarni U, Brown J, et al. Optimizing acceptability and feasibility of an evidence-based behavioral intervention for obese adults with obesity-related co-morbidities or additional risk factors for co-morbidities: an open-pilot intervention study in secondary care. Patient Educ Couns 2012;87(1):108-119. [doi: 10.1016/j.pec.2011.08.003] [Medline: 21907528]
25. Araújo-Soares V, McIntyre T, MacLennan G, Sniehotta FF. Development and exploratory cluster-randomised opportunistic trial of a theory-based intervention to enhance physical activity among adolescents. Psychol Health 2009;24(7):805-822. [doi: 10.1080/08870440802040707] [Medline: 20205028]

26. Godino JG, Merchant G, Norman GJ, Donohue MC, Marshall SJ, Fowler JH, et al. Using social and mobile tools for weight loss in overweight and obese young adults (Project SMART): a 2 year, parallel-group, randomised, controlled trial. Lancet Diabetes Endocrinol 2016;4(9):747-755. [doi: 10.1016/S2213-8587(16)30105-X] [Medline: 27426247]
27. Peters GY, de Bruin M, Crutzen R. Everything should be as simple as possible, but no simpler: towards a protocol for accumulating evidence regarding the active content of health behaviour change interventions. Health Psychol Rev 2015;9(1):1-14 [FREE Full text] [doi: 10.1080/17437199.2013.848409] [Medline: 25793484]
28. Michie S, Johnson BT, Johnston M. Advancing cumulative evidence on behaviour change techniques and interventions: a comment on Peters, de Bruin, and Crutzen. Health Psychol Rev 2015;9(1):25-29. [doi: 10.1080/17437199.2014.912538] [Medline: 25793487]

Abbreviations

AE: adverse event
BCT: behavior change technique
CALO-RE: Coventry, Aberdeen, and London-Refined
CVD: cardiovascular disease
FFQ: Food Frequency Questionnaire
NCD: noncommunicable diseases
PA: physical activity
PN: personalized nutrition
PoP: proof of principle
RCT: randomized controlled trial
SC: smoking cessation
SOP: standard operating procedure

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Protocol

Mobile Phone Support for Diabetes Self-Care Among Diverse Adults: Protocol for a Three-Arm Randomized Controlled Trial

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Abstract

Background: Nonadherence to self-care is common among patients with type 2 diabetes (T2D) and often leads to severe complications. Moreover, patients with T2D who have low socioeconomic status and are racial/ethnic minorities disproportionately experience barriers to adherence and poor outcomes. Basic phone technology (text messages and phone calls) provides a practical medium for delivering content to address patients' barriers to adherence; however, trials are needed to explore long-term and sustainable effects of mobile phone interventions among diverse patients.

Objective: The aim of this study is to evaluate the effects of mobile phone–based diabetes support interventions on self-care and hemoglobin A_{1c} (HbA_{1c}) among adults with T2D using a 3-arm, 15-month randomized controlled trial with a Type 1 hybrid effectiveness-implementation approach. The intervention arms are (1) Rapid Encouragement/Education And Communications for Health (REACH) and (2) REACH + Family-focused Add-on for Motivating Self-care (FAMS).

Methods: We recruited primary care patients with T2D (N=512) from Federally Qualified Health Centers and an academic medical center, prioritizing recruitment of publicly insured and minority patients from the latter. Eligible patients were prescribed daily diabetes medication and owned a cell phone with text messaging capability. We excluded patients whose most recent HbA_{1c} result within 12 months was <6.8% to support detection of intervention effects on HbA_{1c}. Participants were randomly assigned to REACH only, REACH + FAMS, or the control condition. REACH provides text messages tailored to address patient-specific barriers to medication adherence based on the Information-Motivation-Behavioral skills model, whereas FAMS provides monthly phone coaching with related text message content focused on family and friend barriers to diet and exercise adherence. We collect HbA_{1c} and self-reported survey data at baseline and at 3, 6, and 12 months, and again at 15 months to assess sustained changes. We will use generalized estimating equation models to test the effects of REACH (either intervention arm) on HbA_{1c} relative to the control group, the potential additive effects of FAMS, and effects of either intervention on adherence to self-care behaviors and diabetes self-efficacy.

Results: The trial is ongoing; recruitment closed December 2017. We plan to perform analyses on 6-month outcomes for FAMS in July 2018, and project to have 15-month data for REACH analyses in April 2019.

Conclusions: Our study will be one of the first to evaluate a long-term, theory-based text messaging intervention to promote self-care adherence among racially/ethnically and socioeconomically diverse adults with T2D. Moreover, our study will assess the feasibility of a family-focused intervention delivered via mobile phones and compare the effects of text messaging alone versus text messaging plus phone coaching. Findings will advance our understanding of how interventions delivered by phone can benefit diverse patients with chronic conditions.

Trial Registration: ClinicalTrials.gov NCT02409329; https://clinicaltrials.gov/ct2/show/NCT02409329 (Archived by WebCite at http://www.webcitation.org/6yHkg9SSl); NCT02481596; https://clinicaltrials.gov/ct2/show/NCT02481596 (Archived by WebCite at http://www.webcitation.org/6yHkj9XD4)

(JMIR Res Protoc 2018;7(4):e92) doi:10.2196/resprot.9443

KEYWORDS

mobile health; medication adherence; type 2 diabetes; text messaging; self-care; glycated hemoglobin

Introduction

Background

The prevalence of diabetes is rapidly rising at both a global [1] and national level [2]. Individuals with diabetes are at a higher risk of heart disease, stroke, kidney disease, and premature mortality [1,3-5]. Type 2 diabetes (T2D) can be managed and its complications avoided by engaging in self-care, including healthy diet, exercise, self-monitoring of blood glucose (SMBG), and taking medications as prescribed [6]. However, multiple barriers impede self-care adherence for patients with T2D [7-10]. Racial/ethnic minorities and people with low socioeconomic status (SES) tend to experience more barriers to diabetes self-care [11,12] and, in turn, have worse self-care adherence [13,14], more complications [13,15], and worse glycemic control (ie, hemoglobin A_{1c} [HbA_{1c}]) [16,17].

Basic mobile phone technology (text messaging and phone calls) presents viable opportunities to reach and support adults with T2D to improve self-care adherence and HbA_{1c} [18-20]. The vast majority of American adults (95%) own cell phones [21]; however, non-whites and those with less education and income are less likely to own a smartphone [21]. Text messaging and phone calls do not require a smartphone, and text messaging is the most common cell phone activity among all mobile phone users [22]. This ubiquity suggests potential to reach patients with low SES and racially/ethnically diverse patients [23,24]. Moreover, text messages can deliver tailored content and address modifiable barriers to diabetes self-care.

Involving human support as part of a diabetes mobile phone intervention may enhance efficacy [25,26] and improve participant engagement [27], particularly among disadvantaged or vulnerable patients [28]. In a recent 6-month randomized controlled trial (RCT), participants were assigned to receive health coaching along with access to a diabetes support app or only health coaching [29]. Although both groups had improved HbA_{1c} levels, the coaching group showed accelerated improvements [29]. A handful of other health promotion interventions in general populations have compared text messaging alone against text messaging plus human counselors, but the samples in these interventions have been small and therefore more research is needed [30].

In summary, adherence to diabetes self-care remains a prevalent problem and sustainable real-world solutions for diverse patients are needed [31]. Automated text messaging interventions can be resource- and cost-effective and have improved adherence and HbA_{1c} among underserved groups up to 6 months [32-34]; however, few have been evaluated in long-term trials with diverse samples [35]. Furthermore, none to our knowledge have assessed sustainability of effects after text messaging ends. Finally, it remains unclear whether a human coach or educator in concert with automated text messaging would be more effective for improving diabetes outcomes than text messaging alone.

Objective

In response to these gaps in knowledge, we are conducting a 3-arm RCT to evaluate the effects of mobile phone–based diabetes self-care support interventions on self-care adherence and HbA_{1c} among adults with T2D who are diverse with respect to SES and race or ethnicity. The trial consists of 2 intervention arms and a control group. Intervention arms are (1) Rapid Encouragement/Education And Communications for Health (REACH) and (2) REACH + Family-focused Add-on for Motivating Self-care (FAMS). Both interventions were previously developed and tested for usability among racially/ethnically diverse and predominantly low-SES samples recruited from Federally Qualified Health Centers (FQHCs) [36,37]. REACH provides text messages tailored to address patient-specific barriers to medication adherence based on the Information-Motivation-Behavioral skills (IMB) model [38,39], whereas FAMS provides monthly phone coaching with related text message content focused on family and friend barriers to diet and exercise adherence [37].

The study is designed to evaluate the effects of REACH (either intervention arm) on HbA_{1c} relative to the control group, while assessing the additive effects of FAMS and effects of either intervention on adherence to self-care behaviors and diabetes self-efficacy. We will also explore the effects of each intervention arm on the psychosocial mechanisms targeted by each intervention and effect modification by race/ethnicity and SES.

Methods

Study Design

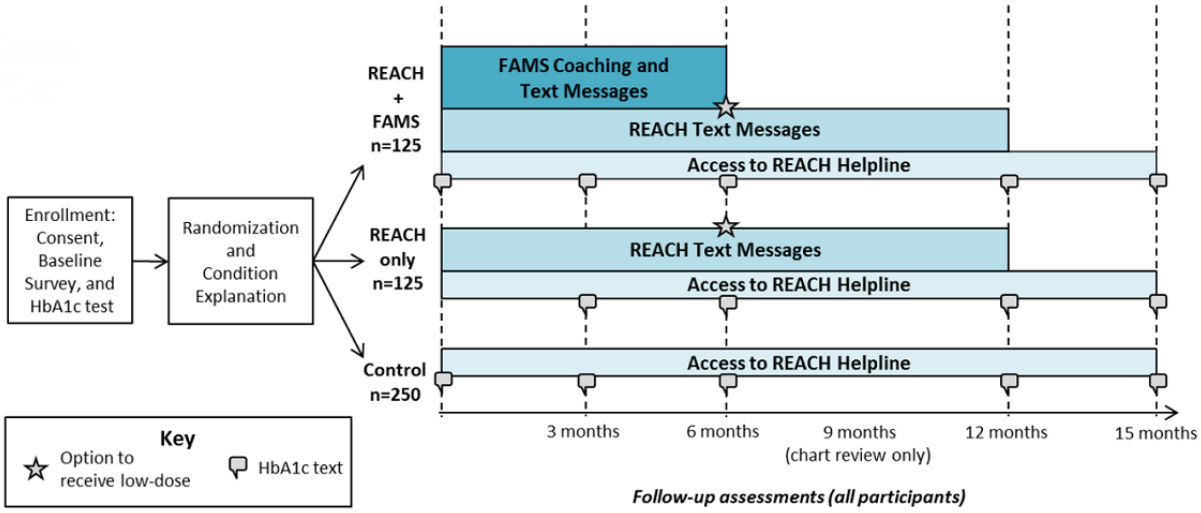
We are conducting a 15-month, 3-arm RCT with 2 treatment arms and 1 control arm. We are using an effectiveness-implementation hybrid design to evaluate the effectiveness of the interventions while planning for and collecting information about implementation potential (Type 1 approach) [40]. This paper focuses primarily on the protocol for evaluating effectiveness, but REACH was designed to be sustainable [36], and our community-based research methods lay the groundwork to explore barriers and facilitators to implementation in FQHCs (briefly described in the Discussion section). For the trial, interested and eligible patients with T2D were recruited from primary care clinics. We designed our recruitment approach to overrepresent racial/ethnic minorities and patients with low SES. Participants in each arm complete study measures at baseline and 3, 6, 12, and 15 months post baseline (Figure 1, top panel). Participants in either intervention arm receive intervention exposure for 12 months; sustained changes are assessed with a 15-month follow-up.

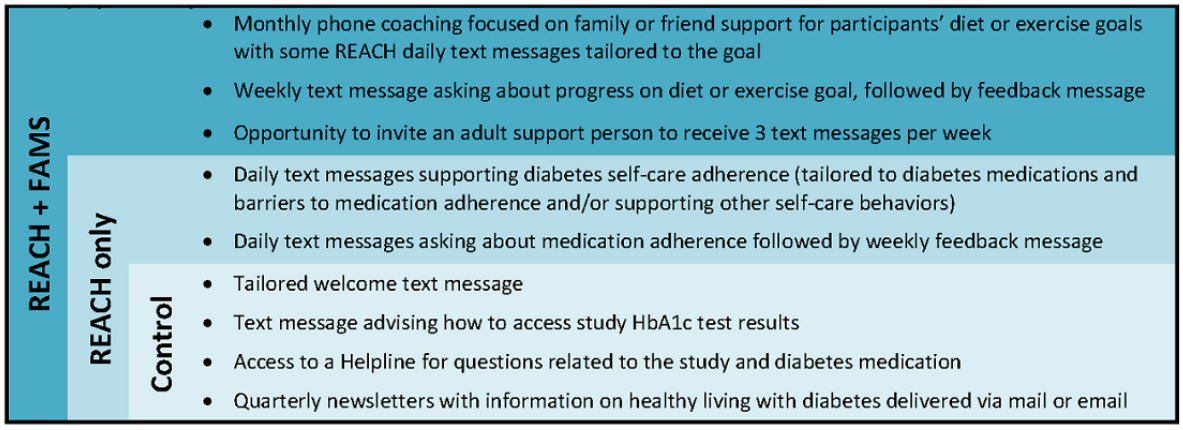
Recruitment and Eligibility

We recruited participants across clinic sites in and around Nashville, Tennessee, including 13 FQHC locations and 3 Vanderbilt University Medical Center primary care locations. Recruitment strategies included the use of flyers, interest cards, referrals from clinic staff, mailing opt-in or opt-out letters (depending on clinic preference) to patients identified through the electronic health record (EHR) with follow-up calls, and in-person contact with patients in clinic waiting rooms or at clinic and community events. We oversampled patients who are racial/ethnic minorities and those who have low SES in several ways. First, our goal was to recruit at least 200 participants from FQHCs which serve uninsured or underinsured patients.

Second, when recruiting from Vanderbilt clinics, we prioritized the recruitment of patients with public health insurance (eg, TennCare [Medicaid], Medicare) only and/or who were racial/ethnic minorities.

Figure 1. Top panel: Rapid Encouragement/Education And Communications for Health (REACH) randomized controlled trial design. Participants are randomized to REACH + Family-focused Add-on for Motivating Self-care (FAMS), REACH only, or the control condition. Bottom panel: Components received by each condition. Components are cumulative (eg, all participants receive control components). HbA_{1c}: hemoglobin A_{1c}.





Eligible participants were at least 18 years of age, had a diagnosis of T2D (both self-reported and confirmed either in the EHR or by a provider), were currently prescribed a daily diabetes medication (oral, insulin, and/or noninsulin injectables) and responsible for taking their diabetes medications (ie, without assistance from a caregiver), owned a cell phone with text messaging capability, received care at one of the participating clinics, and could speak and read in English. We excluded participants whose most recent HbA_{1c} value within 12 months was <6.8% to ensure room to lower HbA_{1c} and detect intervention effects (ie, avoid floor effects). In addition, because participants assigned to FAMS receive phone coaching, we excluded patients who had auditory limitations or an inability to orally communicate, as determined by trained research assistants (RAs). Patients who failed a brief cognitive screener [41] were excluded to help ensure accuracy of the measures and data integrity.

Finally, because all participants receive and are asked to interact using text messages, we excluded patients who were unable to receive, read or send text messages after demonstration by an RA (some participants with visual limitations were able to text and were therefore enrolled). We did not exclude participants based on comorbidities.

Data and Procedures

RAs met with interested patients in a private room at their respective clinics to verify eligibility, administer informed consent, and administer survey instruments. Most baseline surveys were administered aloud during the in-person meeting with the RA in a private room at the clinic. Less frequently, we consented patients over the phone and then mailed a copy of the consent and survey or emailed a link to sign the consent form and complete the survey via the Web (based on participant preference).

Participants have options on how to complete follow-up surveys, although we encourage in-person appointments in general, particularly for participants who may have trouble completing study materials independently due to limited health literacy or visual acuity difficulties. Survey completion can occur in one of 4 ways: (1) in-person with an RA at the participant's clinic, (2) independently using paper surveys, (3) independently using online surveys, or (4) by phone with an RA. For in-person appointments, we aim to schedule the study appointment on the same day as the patient's clinic appointment to make participation more convenient, and we try to align future clinic HbA_{1c} tests with follow-up study appointments.

Unless participants have had an HbA_{1c} test within the past 3 weeks or one is scheduled for the day of a study appointment, we either request that their provider order a lab-drawn HbA_{1c} test or ask participants to complete a mail-in HbA_{1c} test kit [42,43], depending on clinic preference. Mail-in kits contain all the necessary supplies to collect a sample of blood using a finger stick onto specialty paper (General Electric Health care) which is then mailed to the laboratory for dried blood spot analysis. Each kit is deidentified and linked to a unique barcode ID label. CoreMedica Laboratories (Lees Summit, Missouri), a specialty reference laboratory accredited by the College of American Pathologists, provides kits, analyzes the samples, and sends us the results.

RAs enter participants' responses to survey questions into Research Electronic Data Capture (REDCap; Nashville, TN), a secure, Web-based application developed at Vanderbilt and designed to support data capture for multisite studies [44]. RAs access patient participants' EHRs or clinics send us EHR data for enrolled participants, depending on clinic preference. EHR data are used to confirm and collect the type and quantity of prescribed diabetes medication and to collect results of clinic-administered HbA_{1c} tests. Participants' relevant survey responses, HbA_{1c} results, and EHR data are transferred from REDCap to a digital health platform called MEMOTEXT (Bethesda, MD), via an application programming interface. MEMOTEXT uses participant information to schedule text message delivery and to tailor and send text messages to participants. Survey procedures, HbA_{1c} test procedures, and EHR reviews are repeated at each assessment (3, 6, 12, and 15 months), and text message content tailoring is updated by MEMOTEXT to reflect most current data. Additionally, we conduct EHR reviews to collect participants' HbA_{1c} results at 9 months if a result is available.

Measures

The same study measures are administered to all participants, regardless of condition. The schedule of measures is shown in Table 1. In the section below we focus on those measures central to the analyses outlined in this paper.

Outcomes

The primary outcome is HbA_{1c}. Secondary outcomes include adherence to diabetes medication, self-care (diet, exercise, and SMBG), and diabetes self-efficacy. We assess diabetes medication adherence with 2 validated self-report measures: (1) the Adherence to Refills and Medications Scale for Diabetes (ARMS-D) [45] and (2) the Summary of Diabetes Self-Care Activities medications subscale (SDSCA-MS) [46]. We ask the SDSCA-MS questions for each prescribed medication, separately, and average responses across medications [45]. The SDSCA-MS is a commonly used and widely accepted measure of diabetes medication adherence [57] which asks about number of days adherent, whereas the ARMS-D is a more sensitive measure that asks about perceived frequency of nonadherence, and is a stronger predictor of HbA_{1c} [45]. Currently, there is not an ideal self-report measure of medication adherence. All available measures have limitations, so using multiple medication adherence measures is recommended [58,59].

Healthy diet is assessed with 2 subscales from the Personal Diabetes Questionnaire that assess Problem Eating Behavior and Use of Information for Diet Decision Making [47]. Exercise is assessed with the short form of the International Physical Activity Questionnaire [48,49], which provides information on the time spent walking, in vigorous and moderate intensity activities, and in sedentary activities. SMBG is assessed using the SDSCA blood glucose testing subscale [46]. Finally, self-efficacy is assessed with the Perceived Diabetes Self-Management Scale [50].

Table 1. Study measures across time points.

Construct	Description, example, scale	Baseline	Follow-ups (months after baseline)			
			3	6	12	15
Primary outcome						
Hemoglobin A_{1c}	Result from lab-drawn clinic test or mail-in test kit	X	X	X	X	X[a]
Secondary outcomes						
Medication adherence	Adherence to Refills and Medications Scale for Diabetes [45]; Summary of Diabetes Self-Care Activities medications subscale (SDSCA-MS) [46]	X	X	X	X	X
Diet adherence	Personal Diabetes Questionnaire subscales for Problem Eating Behavior and Use of Information for Diet Decision Making [47]	X	X	X	X	X
Exercise adherence	International Physical Activity Questionnaire–short form [48,49]	X	X	X	X	X
Self-monitoring of blood glucose (SMBG) adherence	SDSCA–SMBG subscale [46]	X	X	X	X	X
Diabetes self-efficacy	Perceived Diabetes Self-Management Scale [50]	X	X	X	X	
Mediators						
Barriers to diabetes medication adherence	Information, motivation, and behavioral skills-based barriers to medication adherence [36]	X	X	X	X	
Family behaviors	Frequency of family or friends' helpful and harmful behaviors over the past month	X	X	X	X	
Moderators						
Race and ethnicity	White, African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, and/or other race; Hispanic or Latino or not Hispanic or Latino	X				
Education	Years of school completed	X				
Income	Total household income in 1 year	X			X	
Insurance status	Uninsured, private, or public	X				
Other measures						
Other sociodemographics	Gender, age, marital status, living situation	X				
Diabetes characteristics	Insulin status, number of prescribed diabetes medications	X	X	X	X	X
Mobile phone use	Use of smartphones and health apps, frequency of text messaging, and frequency of not being able to text and/or call because of reaching monthly limits	X			X	
Depression	Patient Health Questionnaire–8 [51]	X	X	X	X	
Health literacy	Brief Health Literacy Screen [52]	X				
Numeracy	Subjective Numeracy Scale [53]	X				
Sociological stressors	Tool for Assessing Patients' Stressors [54]	X			X	
Trait self-control	Brief Self-Control Scale (8-item subset) [55]	X		X		
Diabetes duration	Length of time diagnosed with type 2 diabetes	X				
Emergency room (ER) visits and Hospitalizations	Number of times in ER and hospitalizations in the last year	X			X	
Smoking status	Behavioral Risk Factor Surveillance System items on tobacco use [56]	X	X	X	X	
Alcohol consumption	Frequency of having a drink containing alcohol	X	X	X	X	

[a]We will also review medical charts at 9 months to collect HbA_{1c} values for those participants who have this data available since there is no planned follow-up assessment at this time point.

Mediators and Moderators

We also evaluate hypothesized mediators targeted by each of the interventions and moderators of intervention effects. REACH seeks to improve medication adherence via reductions in personalized information, motivation, and behavioral skills barriers identified by study assessments. We measure participants' information, motivation, and behavioral skills-based barriers to adherence with an assessment developed for this trial, which maps barriers to diabetes medication adherence onto the IMB model constructs [36]. There are 31 barriers plus 5 insulin-specific barriers for participants who were prescribed insulin. To complete the measure, participants first indicate whether each barrier either "Sometimes" or "Never" applies to them. Next, for the barriers rated as "Sometimes," participants rate the degree to which the barrier applies to them from 1="a little" to 10="a lot." The purpose of this measure is (1) to identify REACH participants' barriers to diabetes medication adherence so text message content can be tailored to their 4 highest rated barriers and (2) to ascertain whether the REACH intervention reduced participants' barrier scores (relative to the control group) and whether changes in these barriers drove changes in diabetes medication adherence or HbA_{1c}.

FAMS targets diabetes-specific helpful and harmful behaviors from family and friends. To measure these behaviors, we use a measure developed for this trial which assesses the frequency with which participants' family or friends performed helpful and harmful behaviors over the past month. Example items are "How often do your family members… exercise with you or ask you to exercise with them?" (helpful item) or "…argue with you about your food choices or your health?" (harmful item), with response options on a scale from 1="never in the past month" to 5="twice or more each week." Helpful and harmful items are averaged separately to produce 2 scores ranging from 1 to 5 with higher scores indicating more helpful or harmful family involvement in the patients' diabetes self-care, respectively.

Finally, we plan to explore differential intervention effects based on participants' race/ethnicity and SES (ie, income, insurance type, and education). As described above, racial/ethnic minorities and persons with low SES who have T2D tend to have worse self-care adherence and HbA_{1c} [13,14,16,17]; therefore, we anticipate these participants will experience more benefit from the intervention compared with participants who are white or have high SES. Each of these variables will be assessed with self-report at baseline.

Randomization

During enrollment, RAs explain to participants that all study participants receive a mobile phone–based program with different types and frequencies of text messages and phone calls. RAs also tell participants that a member of the research team will call them in a few days to explain more about what to expect based on their assigned condition. After enrollment, participants are randomized to one of the 3 arms using optimal multivariate matching to ensure better balance in the primary outcome and important covariates across arms [60]. The variables we use to match participants include baseline HbA_{1c}, insulin status, race, age, duration of diabetes, gender, income, and education. We give diabetes duration (rank value to correct for skew) and HbA_{1c} greater weight [61]. Twice as many participants are assigned to the control condition (n=250) as those assigned to REACH only (n=125) or REACH + FAMS (n=125). To accommodate this 2:1:1 design, patients are matched and then randomized to control or REACH and those randomized to REACH are matched and randomized to REACH only or REACH + FAMS. This helps ensure covariate balance among all 3 arms. For those assigned to REACH + FAMS, the FAMS intervention components last for the first 6 months only. All participants in the intervention arms receive REACH only for the latter 6 months of the exposure period (Figure 1, top panel).

Within a week of enrollment, participants are randomized, and a member of the research team calls each participant to explain what to expect from the mobile phone program to which they are assigned and obtain any information needed specifically for their assigned condition (eg, preferred times to receive daily text messages if assigned to either intervention arm). If we are unable to reach participants for this condition explanation within 3 weeks, they are administratively withdrawn; we still include these participants' baseline data in our analyses but discontinue attempts to contact them. This run-in period ensures that the initiation of the study experience aligns with baseline data and identifies individuals who may be difficult to contact and therefore not good candidates for the 15-month trial. During the condition explanation we reiterate and assess participants' understanding of the intervention components available to them, based on their condition. We do not use the terms "intervention" or "control" to explain the assigned conditions. Each condition is described briefly below and in Figure 1, bottom panel; the intervention components are described in more detail in the respective development papers for REACH [36] and FAMS [37].

Control

Participants assigned to the control condition maintain care as usual (ie, medication treatment and physician monitoring) but also receive a welcome text message following enrollment, as well as a text message advising how to access their study HbA_{1c} test result following enrollment and each completed follow-up. Control participants also receive access to the REACH Helpline (for questions related to the study and diabetes medications) and receive quarterly newsletters with information on healthy living with diabetes. Providing support and resources to the control group was important for our partnerships with clinics and an ethical decision because of our goal to oversample patients who were at risk (eg, high HbA_{1c} and patients with low SES). We provided these same resources to participants in all arms.

REACH Only

Participants assigned to REACH only receive all the components that control participants receive, plus the REACH text messages. REACH messages include daily messages promoting self-care, including tailored messages to address user-specific barriers to medication adherence based on responses to the IMB barrier

assessment, nontailored text messages addressing other self-care behaviors, daily messages asking about the participant's medication adherence for the day, and weekly feedback messages on his or her adherence. After 6 months, participants have the option to receive fewer text messages for the remaining 6 months of the intervention (ie, the "low-dose" option). The ideal frequency or dose of text messages for improving outcomes in an intervention is unclear [62]; we included the low-dose option to sustain engagement among participants who may prefer fewer-than-daily text messages. In a recent meta-analysis, there was no difference in chronic disease medication adherence between interventions using daily text messages and those using less frequent messaging [20]. Other evidence suggests that decreasing the frequency of texts over time or allowing users to choose their desired frequency is more efficacious than applying predetermined fixed or varying frequencies [30]. REACH participants who choose the low-dose option receive 3 or 4 self-care promotion messages each week and 1 message asking about medication adherence each week followed by feedback on their adherence.

REACH + FAMS

Participants assigned to REACH + FAMS receive all the components delivered to the aforementioned conditions, plus additional intervention components for the first 6 months. FAMS components include monthly phone coaching with counselors or health coaches (established or in-training; ie, persons with experience using basic helping skills who have also been trained in the FAMS protocols). During coaching, participants set healthy diet and exercise goals, and work with coaches to improve their ability to manage family or friends' actions that might support or interfere with the goal. Text messages tailored to the goal set during coaching replace the nontailored diet and exercise messages in REACH. FAMS participants can adjust the goal or set a new goal during each coaching session and have the opportunity to invite a family member or friend to receive text messages as a support person at any point during the first 6 months. The support person text message content aims to help enrolled support persons to be thoughtful about providing support and to initiate conversations with the participant about his or her diabetes and self-care goals. After 6 months, the FAMS components end, participants are offered the low-dose option described above, and they continue to receive REACH text messages for the next 6 months.

Treatment Fidelity

We have implemented several fidelity checks to ensure that participants receive the interventions as intended. First, text messages are automated to help ensure users have the intended experience. Second, we monitor text messages to identify and correct errors and make contact with participants who stop responding to address any technical issues. MEMOTEXT securely collects and stores all text message data (eg, date and time text messages are sent and received, participants' text message responses). Our team performs weekly checks on these data to ensure the text messages are delivered and monitor participants' responses. As part of the REACH intervention, participants receive a daily adherence text message that asks them whether they have taken all of their diabetes medication that day. Participants are asked to reply either Yes or No. If they answer No, participants receive a follow-up text message asking them to please tell us why, with several response options (ie, "1=forgot, 2=sick, 3=clinic told me to, 4=ran out of meds, or type out a reason"). We monitor responses to these messages weekly, and if a participant does not respond to any adherence text messages for 14 consecutive days, a team member will call the participant to determine whether he or she is having any technical problems. To avoid coercing participants into responding to text messages, we only ask whether they have had any problems lately with receiving or responding to their text messages. The date of the call and the participant's response are documented, and we subsequently troubleshoot as needed. We do not make repeated calls if the participant remains nonresponsive but may contact a participant more than once if periods of consecutive nonresponse are separated by periods of responsiveness.

We also collect fidelity data on the FAMS coaching sessions. We track the number of FAMS phone coaching sessions completed by each participant and the content of each session. Fidelity data includes the goal set during coaching, the type of family or friend support or barrier discussed, the skill-building exercise employed, the verbal contract (eg, to implement a skill learnt during coaching, such as assertive communication, with a specific friend or family member), the participant's confidence rating of his or her ability to complete the verbal contract, and, for subsequent sessions, the outcome of the verbal contract from the previous session. Fidelity data will be presented with results to inform the degree to which the intervention was delivered as intended and to provide context for interpretation of study findings. Fidelity data will also serve as a process benchmark for future trials that may seek to reproduce the study findings or implementation studies that engage clinic staff in intervention delivery.

Statistical Analysis Plan

The study is designed to evaluate the effects of REACH (either intervention arm) on HbA_{1c} relative to the control group (primary analysis), while assessing the effects of FAMS. We will use generalized estimating equation models to estimate potentially time-varying intervention effects while adjusting for the baseline measure of the outcome and the type of HbA_{1c} test result (ie, lab-drawn at the clinic or by using the mail-in kit). The models use clustered data and allow nonlinear associations between baseline and follow-up outcome measures. A lag 1 autoregressive correlation structure will be used and alternative correlation structures tested to demonstrate the results are robust to model selection. We will use a longitudinal model to evaluate intervention effects. We will use an omnibus test for the intervention effect, then provide point-estimates with confidence intervals for each follow-up, and graphically depict our results.

Analysis will follow a conservative intention-to-treat principle, and participants with missing values will be included along with those with complete data. Multiple imputation will be used to impute missing covariate and outcome values. The analysis with multiple imputation assumes Missing-at-Random (ie, the model properly handles missing data by including covariates

associated with reasons for dropout). A sensitivity analysis for the impact of the imputation of missing outcome data will exclude the outcome from the imputation process and analyze only the observed outcomes.

Primary Analysis

We will test the effects of receiving REACH on HbA_{1c} (primary outcome) and medication adherence (secondary outcome) compared with the control condition. This model will not distinguish between the REACH only and REACH + FAMS arms. We hypothesize participants assigned to REACH will experience greater improvements in medication adherence and HbA_{1c} than participants assigned to the control condition.

Secondary Analysis

In addition, we will test the effects of both intervention arms (REACH only and, separately, REACH + FAMS) on diet, exercise, SMBG, and diabetes self-efficacy relative to the control group. Finally, we will assess whether participants assigned to REACH + FAMS experience greater improvements in HbA_{1c}, medication adherence, diet, exercise, SMBG, and self-efficacy compared with those assigned to REACH only.

Mediation and Moderation Analyses

We will conduct 2 separate mediation analyses, one for REACH (including participants in either REACH arm relative to the control arm) and one for FAMS (including participants in the REACH + FAMS arm relative to the control arm). REACH mediation analyses will examine whether REACH improves participants' IMB barriers to diabetes medication adherence and whether such improvements explain REACH's effect on adherence and/or HbA_{1c}. FAMS mediation analyses will examine whether FAMS improves participants' reported diabetes-specific helpful and harmful family and friend behaviors and whether such improvements explain REACH + FAMS effect on diet, exercise, and diabetes self-efficacy. We hypothesize that improvements in IMB barriers will drive improvements in medication adherence and HbA_{1c}, and improvements in family and friend behaviors will drive effects on diet, exercise, and diabetes self-efficacy. Specifically, we will use between-person mediation analyses with latent change scores for mediators and outcomes [63,64], and we will use bootstrapping to obtain CIs for indirect effects [65]. Lastly, we will explore whether race/ethnicity, education, and income modify the intervention effects by adding interaction terms to models evaluating intervention effects.

Sample Size and Power

Our target sample was 500 patient participants and we ultimately enrolled 512. With an anticipated dropout rate of 20%, we will have at least 400 participants for analysis of intervention effects up to 15 months. Power calculations were performed using Power and Sample Size (PS) software (Nashville, TN) at 80% power for a 2-sided text (alpha=.05). Based on HbA_{1c} data from a prior study with 314 adult patients with T2D from a FQHC in Nashville, TN, we estimate the residual error from a model of HbA_{1c} will have a standard deviation ≤2% [45]. Thus, this study will have 80% power to detect a true effect of 0.56% on HbA_{1c} by REACH at any follow-up time point if we have 400 participants for analysis.

Ethics and Informed Consent

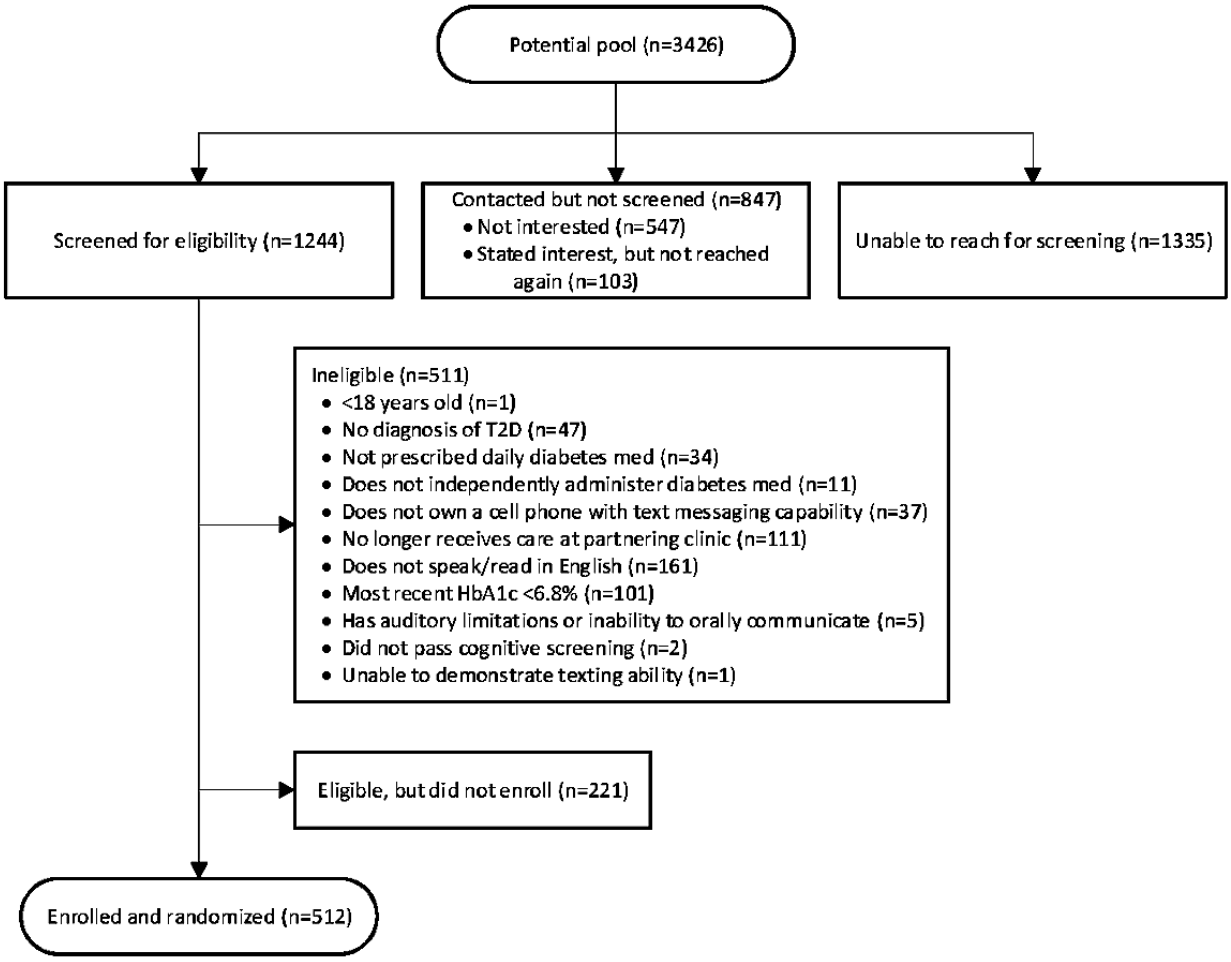
All procedures have been reviewed and approved by the Vanderbilt University Institutional Review Board (IRB) and this trial is registered on ClinicalTrials.gov (see NCT02409329 and NCT02481596). All data collected from participants at each assessment period are stored on REDCap's secure server. Any participant data sent to MEMOTEXT are deidentified and stored on their Health Insurance Portability and Accountability Act (HIPAA)-compliant secure server. In addition, all reporting of text message data by MEMOTEXT and all recorded REACH Helpline voicemails are stored on their HIPAA-compliant Web server, and only IRB-approved study staff can access these voicemail messages using a secure passcode. EHR data are shared with the study team according to the policies of each individual clinic.

We included specific language in the informed consent document outlining our processes for securing participants' data. We described that REACH Helpline voicemail messages, information shared via text message, and all study forms would be assigned a study number with no personal identifying information and be either password-protected on a secure server or in a locked filing cabinet at Vanderbilt. We explained that research team members would only access personal information for necessary study procedures, such as to issue payment or contact for follow-up appointments. Finally, we explained to participants that, if they share or lose their phone, the study text messages may disclose to others that they have diabetes, take diabetes medications, and/or received an HbA_{1c} test. All participants were provided with the REACH Helpline number and encouraged to call to ask questions about the study.

Results

Recruitment began in May 2016 and ended in December 2017. Figure 2 shows recruitment results. Of the 3426 patients identified as potentially eligible throughout study recruitment, we were able to contact 61.03% (2091/3426) by phone or in person and screen 36.31% (1244/3426) for eligibility. Of those screened, 41.08% (511/1244) were ineligible and 41.16% (512/1244) enrolled. Most common reasons for ineligibility were not speaking or reading in English (31.5%, 161/511, of those ineligible), no longer receiving care at a partnering clinic (21.7%, 111/511), and having a most recent HbA_{1c} <6.8% (19.8%, 101/511). We administratively withdrew 6 participants or 1.2% (6/512) of those enrolled. Enrolled participants (N=512) have an average age of 56.0 (SD 9.5) years, and 54.1% (277/512) are female.

Figure 2. Flowchart of potential patient participants through study recruitment. HbA_{1c}: hemoglobin A_{1c}.



Approximately half (47.3%, 242/512) are non-Hispanic white, 39.4% (202/512) are non-Hispanic African American, 6.0% (31/512) are Hispanic, and 7.2% (37/512) reported being of other race and/or ethnicity (including multiracial). In addition, 41.7% (210/503) reported educational attainment of a high school degree or less, 55.8% (286/512) have annual incomes less than US $35,000, and 48.6% (247/508) are underinsured (23.2%, 118/508, have no insurance; 25.4%, 129/508, have public insurance only). About half (48.8%, 250/512) are taking insulin and average HbA_{1c} at baseline is 8.6% (SD 1.8%, median 8.2%, IQR 7.2%-9.6%). Most (98.6%, 493/500) baseline HbA_{1c} tests were taken within 30 days of study enrollment, and all were taken within 70 days of enrollment. As of this publication, we have at least 87% completion among participants through each follow-up assessment. We plan to perform analyses on 6-month outcomes for FAMS in July 2018 and have 15-month data for REACH analyses in April 2019.

Discussion

Principal Considerations

This study will be one of the first RCTs to deliver a long-term, theory-based, text messaging intervention to promote self-care adherence among racially/ethnically and socioeconomically diverse adults with T2D. We designed the interventions to use basic mobile phone technology (text messaging and phone calls) and provide an experience that is individually tailored and interactive for adult patients with T2D. We developed both interventions with input from racially diverse patients with low SES [36,37] and designed our recruitment strategies for the RCT to oversample racial/ethnic minorities and patients with fewer resources. Moreover, our study will explore the feasibility of a family-focused intervention delivered via mobile phones, and allows exploratory analyses comparing the effects of text messaging alone versus text messaging plus phone coaching. We will also be the first to provide information on the feasibility and acceptability of inviting members of a patients' social support network to receive text messages about how to support the patient with his or her T2D, based on the 125 participants in our sample given the option to do so as part of FAMS.

Barriers to self-care adherence are personal, multidimensional, and change over time [66,67]. Findings from other studies suggest that helping patients overcome their unique barriers may improve adherence and HbA_{1c} [68]. For instance, in a 12-month RCT, intervention participants received phone calls from diabetes educators who provided tailored strategies for coping with self-care barriers [69]. HbA_{1c} decreased more among intervention participants than control participants, suggesting content addressing modifiable self-care barriers can be effective. However, study participants were predominantly

white and well-educated [69], limiting the generalizability of the results. Not only will our diverse patient sample provide more generalizable results, but including measures that assess patients' barriers to medication adherence and family and friend involvement in self-care will allow us to determine whether improvements in the psychosocial mechanisms targeted by the interventions explain improvements in outcomes.

Findings from the RCT will advance understanding of the health benefits of mobile phone–based interventions, with generalizability to racial/ethnic minorities and persons with low SES with chronic conditions such as diabetes [70,71]. The REACH intervention was designed to be incorporated into routine clinical care at FQHCs to support diabetes self-care adherence with minimal time investment from providers and staff. As a Type 1 effectiveness-implementation hybrid design, the primary focus of this study is to evaluate the intervention's effectiveness. Therefore, we had research staff execute protocols to ensure a structured test of effects. For the secondary goal of assessing facilitators and barriers to implementation, we will invite intervention participants who have finished the trial, as well as FQHC providers and administrators, to participate in interviews to collect qualitative and quantitative data on their perceptions of REACH and FAMS. These interviews will focus on strategies for uptake and sustainability in clinic settings. This information will be used to develop recommendations for implementing and evaluating mobile phone–delivered interventions, like REACH and FAMS, in FQHC settings.

Limitations

Limitations of this study include reliance on self-report measures of adherence. Compared with objective measures, self-report measures are subject to social desirability and recall bias. However, each measure of adherence has drawbacks. Self-report measures are inexpensive, brief, and unobtrusive, and we have selected validated measures with balancing strengths and weaknesses. Another challenge is participants changing their cell phone plans and numbers; however, the REACH Helpline (where participants can inform us of changes in their contact information), requesting secondary contact information (eg, a work number, a family member's or friend's number to use if we cannot reach them), calling participants after 14 consecutive days of nonresponse, and regular follow-ups help us maintain contact with participants. Our study is powered to examine the effects of receiving REACH on HbA_{1c}; therefore, analyses examining the effects of other outcomes (ie, self-care behaviors, self-efficacy) and comparing the effects of either intervention arm are potentially very informative but may be underpowered. Because the trial does not include a separate FAMS condition (ie, without REACH), we are not able to evaluate the effects of FAMS only. Finally, the interventions are currently only available in English, which was necessary to enhance feasibility of successfully completing this initial trial; however, translation to Spanish is a goal, should they prove effective.

Conclusions

We anticipate this study will help determine the effectiveness of a tailored text messaging intervention for supporting diabetes self-care adherence and reducing HbA_{1c} among racially/ethnically and socioeconomically diverse patients. Additionally, we aim to determine whether (1) tailoring IMB model-based content to user-specific medication adherence barriers is effective for improving medication adherence behavior and HbA_{1c}, thereby supporting the IMB model as an appropriate framework for interventions to promote medication adherence in diabetes and (2) basic mobile phone technology is a feasible and potentially effective medium for family-focused interventions and for engaging family members and friends in adults' self-care efforts. Beyond these primary aims, we will be able to examine data on users' responses to text messages throughout the trial, the choice to receive fewer text messages after 6 months, and participant characteristics associated with either. Findings will inform the design and length of future text message–delivered interventions in similar populations.

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Authors' Contributions

LAN contributed to the development of study protocols, led recruitment and retention efforts, and wrote the manuscript. All coauthors are coinvestigators or coordinators of the project and contributed to the development of study protocols and read and edited the manuscript. LSM is the principal investigator who led development of the research protocols, oversaw the execution of the research plan, and cowrote the manuscript.

Conflicts of Interest

KW is a member of the Advisory Board for EdLogics, Inc.

References

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract 2017 Jun;128:40-50. [doi: 10.1016/j.diabres.2017.03.024] [Medline: 28437734]
2. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. JAMA 2015 Sep 08;314(10):1021-1029. [doi: 10.1001/jama.2015.10029] [Medline: 26348752]
3. Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA 2016 Aug 09;316(6):602-610 [FREE Full text] [doi: 10.1001/jama.2016.10924] [Medline: 27532915]
4. Centers for Disease Control and Prevention. National diabetes statistics report, 2017 URL: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf [accessed 2017-03-02] [WebCite Cache ID 6v7PoSDch]
5. National Institute of Diabetes Digestive Kidney Diseases. Diabetes, heart disease, and stroke URL: https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/heart-disease-stroke [accessed 2017-03-02] [WebCite Cache ID 6v7PsD46W]
6. Centers for Disease Control and Prevention. National diabetes statistics report, 2014 URL: http://www.thefdha.org/pdf/diabetes.pdf [accessed 2017-03-01] [WebCite Cache ID 6v7QoOLBs]
7. Nam S, Chesla C, Stotts NA, Kroon L, Janson SL. Barriers to diabetes management: patient and provider factors. Diabetes Res Clin Pract 2011 Jul;93(1):1-9. [doi: 10.1016/j.diabres.2011.02.002] [Medline: 21382643]
8. Odegard PS, Gray SL. Barriers to medication adherence in poorly controlled diabetes mellitus. Diabetes Educ 2008;34(4):692-697. [doi: 10.1177/0145721708320558] [Medline: 18669811]
9. Mayberry LS, Osborn CY. Family support, medication adherence, and glycemic control among adults with type 2 diabetes. Diabetes Care 2012 Jun;35(6):1239-1245 [FREE Full text] [doi: 10.2337/dc11-2103] [Medline: 22538012]
10. Rosland A, Heisler M, Choi H, Silveira MJ, Piette JD. Family influences on self-management among functionally independent adults with diabetes or heart failure: do family members hinder as much as they help? Chronic Illn 2010 Mar;6(1):22-33 [FREE Full text] [doi: 10.1177/1742395309354608] [Medline: 20308348]
11. Betancourt JR, Duong JV, Bondaryk MR. Strategies to reduce diabetes disparities: an update. Curr Diab Rep 2012 Dec;12(6):762-768. [doi: 10.1007/s11892-012-0324-1] [Medline: 22976538]
12. Ngo-Metzger Q, Sorkin DH, Billimek J, Greenfield S, Kaplan SH. The effects of financial pressures on adherence and glucose control among racial/ethnically diverse patients with diabetes. J Gen Intern Med 2012 Apr;27(4):432-437 [FREE Full text] [doi: 10.1007/s11606-011-1910-7] [Medline: 22005941]
13. Lanting LC, Joung IMA, Mackenbach JP, Lamberts SWJ, Bootsma AH. Ethnic differences in mortality, end-stage complications, and quality of care among diabetic patients: a review. Diabetes Care 2005 Sep;28(9):2280-2288. [Medline: 16123507]
14. Juarez DT, Tan C, Davis JW, Mau MM. Using quantile regression to assess disparities in medication adherence. Am J Health Behav 2014 Jan;38(1):53-62 [FREE Full text] [doi: 10.5993/AJHB.38.1.6] [Medline: 24034680]
15. Osborn CY, de Groot M, Wagner JA. Racial and ethnic disparities in diabetes complications in the northeastern United States: the role of socioeconomic status. J Natl Med Assoc 2013;105(1):51-58 [FREE Full text] [Medline: 23862296]
16. Saydah S, Cowie C, Eberhardt MS, De RN, Narayan KMV. Race and ethnic differences in glycemic control among adults with diagnosed diabetes in the United States. Ethn Dis 2007;17(3):529-535. [Medline: 17985509]
17. Quandt SA, Bell RA, Snively BM, Smith SL, Stafford JM, Wetmore LK, et al. Ethnic disparities in glycemic control among rural older adults with type 2 diabetes. Ethn Dis 2005;15(4):656-663 [FREE Full text] [Medline: 16259490]
18. Arambepola C, Ricci-Cabello I, Manikavasagam P, Roberts N, French DP, Farmer A. The impact of automated brief messages promoting lifestyle changes delivered via mobile devices to people with type 2 diabetes: a systematic literature review and meta-analysis of controlled trials. J Med Internet Res 2016;18(4):e86 [FREE Full text] [doi: 10.2196/jmir.5425] [Medline: 27095386]
19. Saffari M, Ghanizadeh G, Koenig HG. Health education via mobile text messaging for glycemic control in adults with type 2 diabetes: a systematic review and meta-analysis. Prim Care Diabetes 2014 Dec;8(4):275-285. [doi: 10.1016/j.pcd.2014.03.004] [Medline: 24793589]
20. Thakkar J, Kurup R, Laba T, Santo K, Thiagalingam A, Rodgers A, et al. Mobile telephone text messaging for medication adherence in chronic disease: a meta-analysis. JAMA Intern Med 2016 Mar;176(3):340-349. [doi: 10.1001/jamainternmed.2015.7667] [Medline: 26831740]
21. Pew Research Center. Washington, DC: Pew Research Center; 2018 Feb 05. Mobile fact sheet URL: http://www.pewinternet.org/fact-sheet/mobile/ [accessed 2018-03-02] [WebCite Cache ID 6v7RR4F9a]
22. Wormald B. Pew Research Center. Washington, DC: Pew Research Center; 2015 Jun 10. Cell phone activities URL: http://www.pewinternet.org/chart/cell-phone-activities/ [accessed 2017-11-20] [WebCite Cache ID 6v7QutxWm]
23. Mayberry LS, Bergner EM, Chakkalakal RJ, Elasy TA, Osborn CY. Self-care disparities among adults with type 2 diabetes in the USA. Curr Diab Rep 2016 Nov;16(11):113 [FREE Full text] [doi: 10.1007/s11892-016-0796-5] [Medline: 27671320]
24. Peek ME. Can mHealth interventions reduce health disparities among vulnerable populations? Divers Equal Health Care 2017;14(2):44-45 [FREE Full text]

25. Heisler M, Piette JD. "I help you, and you help me": facilitated telephone peer support among patients with diabetes. Diabetes Educ 2005;31(6):869-879. [doi: 10.1177/0145721705283247] [Medline: 16288094]
26. Sacco WP, Malone JI, Morrison AD, Friedman A, Wells K. Effect of a brief, regular telephone intervention by paraprofessionals for type 2 diabetes. J Behav Med 2009 Aug;32(4):349-359. [doi: 10.1007/s10865-009-9209-4] [Medline: 19365719]
27. Wolever RQ, Dreusicke M, Fikkan J, Hawkins TV, Yeung S, Wakefield J, et al. Integrative health coaching for patients with type 2 diabetes: a randomized clinical trial. Diabetes Educ 2010;36(4):629-639. [doi: 10.1177/0145721710371523] [Medline: 20534872]
28. Heitkemper EM, Mamykina L, Travers J, Smaldone A. Do health information technology self-management interventions improve glycemic control in medically underserved adults with diabetes? A systematic review and meta-analysis. J Am Med Inform Assoc 2017 Sep 01;24(5):1024-1035. [doi: 10.1093/jamia/ocx025] [Medline: 28379397]
29. Wayne N, Perez DF, Kaplan DM, Ritvo P. Health coaching reduces HbA 1c in type 2 diabetic patients from a lower-socioeconomic status community: a randomized controlled trial. J Med Internet Res 2015;17(10):e224 [FREE Full text] [doi: 10.2196/jmir.4871] [Medline: 26441467]
30. Head KJ, Noar SM, Iannarino NT, Grant HN. Efficacy of text messaging-based interventions for health promotion: a meta-analysis. Soc Sci Med 2013 Nov;97:41-48. [doi: 10.1016/j.socscimed.2013.08.003] [Medline: 24161087]
31. Edelman SV, Polonsky WH. Type 2 diabetes in the real world: the elusive nature of glycemic control. Diabetes Care 2017 Nov;40(11):1425-1432. [doi: 10.2337/dc16-1974] [Medline: 28801473]
32. Fortmann AL, Gallo LC, Garcia MI, Taleb M, Euyoque JA, Clark T, et al. Dulce Digital: an mHealth SMS-based intervention improves glycemic control in hispanics with type 2 diabetes. Diabetes Care 2017 Oct;40(10):1349-1355. [doi: 10.2337/dc17-0230] [Medline: 28600309]
33. Nundy S, Dick JJ, Chou C, Nocon RS, Chin MH, Peek ME. Mobile phone diabetes project led to improved glycemic control and net savings for Chicago plan participants. Health Aff (Millwood) 2014 Feb;33(2):265-272 [FREE Full text] [doi: 10.1377/hlthaff.2013.0589] [Medline: 24493770]
34. Capozza K, Woolsey S, Georgsson M, Black J, Bello N, Lence C, et al. Going mobile with diabetes support: a randomized study of a text message-based personalized behavioral intervention for type 2 diabetes self-care. Diabetes Spectr 2015 May;28(2):83-91. [doi: 10.2337/diaspect.28.2.83] [Medline: 25987806]
35. Jang M, Johnson CM, D'Eramo-Melkus G, Vorderstrasse AA. Participation of racial and ethnic minorities in technology-based interventions to self-manage type 2 diabetes: a scoping review. J Transcult Nurs 2017 Jul 01:1043659617723074 Epub ahead of print. [doi: 10.1177/1043659617723074] [Medline: 28826353]
36. Nelson LA, Mayberry LS, Wallston K, Kripalani S, Bergner EM, Osborn CY. Development and usability of REACH: a tailored theory-based text messaging intervention for disadvantaged adults with type 2 diabetes. JMIR Hum Factors 2016 Sep 08;3(2):e23 [FREE Full text] [doi: 10.2196/humanfactors.6029] [Medline: 27609738]
37. Mayberry LS, Berg CA, Harper KJ, Osborn CY. The design, usability, and feasibility of a family-focused diabetes self-care support mHealth intervention for diverse, low-income adults with type 2 diabetes. J Diabetes Res 2016;2016:7586385 [FREE Full text] [doi: 10.1155/2016/7586385] [Medline: 27891524]
38. Fisher JD, Fisher WA, Amico KR, Harman JJ. An information-motivation-behavioral skills model of adherence to antiretroviral therapy. Health Psychol 2006 Jul;25(4):462-473. [doi: 10.1037/0278-6133.25.4.462] [Medline: 16846321]
39. Mayberry LS, Osborn CY. Empirical validation of the Information-Motivation-Behavioral Skills model of diabetes medication adherence: a framework for intervention. Diabetes Care 2014;37(5):1246-1253 [FREE Full text] [doi: 10.2337/dc13-1828] [Medline: 24598245]
40. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012 Mar;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]
41. Callahan CM, Unverzagt FW, Hui SL, Perkins AJ, Hendrie HC. Six-item screener to identify cognitive impairment among potential subjects for clinical research. Med Care 2002 Sep;40(9):771-781. [doi: 10.1097/01.MLR.0000024610.33213.C8] [Medline: 12218768]
42. Lorig K, Ritter PL, Moreland C, Laurent DD. Can a box of mailed materials achieve the triple aims of health care? The mailed chronic disease self-management tool kit study. Health Promot Pract 2015 Sep;16(5):765-774. [doi: 10.1177/1524839915571633] [Medline: 25690615]
43. Jones TG, Warber KD, Roberts BD. Analysis of hemoglobin A 1c from dried blood spot samples with the Tina-quantR II immunoturbidimetric method. J Diabetes Sci Technol 2010 Mar 01;4(2):244-249 [FREE Full text] [doi: 10.1177/193229681000400203] [Medline: 20307383]
44. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
45. Mayberry LS, Gonzalez JS, Wallston KA, Kripalani S, Osborn CY. The ARMS-D out performs the SDSCA, but both are reliable, valid, and predict glycemic control. Diabetes Res Clin Pract 2013 Nov;102(2):96-104 [FREE Full text] [doi: 10.1016/j.diabres.2013.09.010] [Medline: 24209600]

46. Toobert DJ, Hampson SE, Glasgow RE. The Summary of Diabetes Self-Care Activities measure: results from 7 studies and a revised scale. Diabetes Care 2000 Jul;23(7):943-950 [FREE Full text] [Medline: 10895844]
47. Stetson B, Schlundt D, Rothschild C, Floyd JE, Rogers W, Mokshagundam SP. Development and validation of the personal diabetes questionnaire (PDQ): a measure of diabetes self-care behaviors, perceptions and barriers. Diabetes Res Clin Pract 2011 Mar;91(3):321-332. [doi: 10.1016/j.diabres.2010.12.002] [Medline: 21215487]
48. Lee PH, Macfarlane DJ, Lam TH, Stewart SM. Validity of the International physical activity questionnaire short form (IPAQ-SF): a systematic review. Int J Behav Nutr Phys Act 2011;8:115 [FREE Full text] [doi: 10.1186/1479-5868-8-115] [Medline: 22018588]
49. Kim Y, Park I, Kang M. Convergent validity of the international physical activity questionnaire (IPAQ): meta-analysis. Public Health Nutr 2013 Mar;16(3):440-452. [doi: 10.1017/S1368980012002996] [Medline: 22874087]
50. Wallston KA, Rothman RL, Cherrington A. Psychometric properties of the perceived diabetes self-management scale (PDSMS). J Behav Med 2007 Oct;30(5):395-401. [doi: 10.1007/s10865-007-9110-y] [Medline: 17522972]
51. Kroenke K, Strine TW, Spitzer RL, Williams JBW, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009 Apr;114(1-3):163-173. [doi: 10.1016/j.jad.2008.06.026] [Medline: 18752852]
52. Wallston KA, Cawthon C, McNaughton CD, Rothman RL, Osborn CY, Kripalani S. Psychometric properties of the brief health literacy screen in clinical practice. J Gen Intern Med 2014 Jan;29(1):119-126 [FREE Full text] [doi: 10.1007/s11606-013-2568-0] [Medline: 23918160]
53. McNaughton CD, Cavanaugh KL, Kripalani S, Rothman RL, Wallston KA. Validation of a short, 3-item version of the subjective numeracy scale. Med Decis Making 2015 Nov;35(8):932-936 [FREE Full text] [doi: 10.1177/0272989X15581800] [Medline: 25878195]
54. Osborn CY, Mayberry LS, Wagner JA, Welch GW. Stressors may compromise medication adherence among adults with diabetes and low socioeconomic status. West J Nurs Res 2014 Oct;36(9):1091-1110 [FREE Full text] [doi: 10.1177/0193945914524639] [Medline: 24569697]
55. Tangney JP, Baumeister RF, Boone AL. High self-control predicts good adjustment, less pathology, better grades, and interpersonal success. J Pers 2004 Apr;72(2):271-324. [Medline: 15016066]
56. Centers for Disease Control Prevention. 2017. Behavioral risk factor surveillance system survey questionnaire URL: https://www.cdc.gov/brfss/questionnaires/pdf-ques/2017_BRFSS_Pub_Ques_508_tagged.pdf [accessed 2018-03-02] [WebCite Cache ID 6xcexSVGV]
57. Gonzalez JS, Schneider HE, Wexler DJ, Psaros C, Delahanty LM, Cagliero E, et al. Validity of medication adherence self-reports in adults with type 2 diabetes. Diabetes Care 2013 Apr;36(4):831-837 [FREE Full text] [doi: 10.2337/dc12-0410] [Medline: 23204245]
58. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther 1999 Jun;21(6):1074-90; discussion 1073. [doi: 10.1016/S0149-2918(99)80026-5] [Medline: 10440628]
59. Hansen RA, Kim MM, Song L, Tu W, Wu J, Murray MD. Comparison of methods to assess medication adherence and classify nonadherence. Ann Pharmacother 2009 Mar;43(3):413-422. [doi: 10.1345/aph.1L496] [Medline: 19261962]
60. Greevy R, Lu B, Silber JH, Rosenbaum P. Optimal multivariate matching before randomization. Biostatistics 2004 Apr;5(2):263-275. [doi: 10.1093/biostatistics/5.2.263] [Medline: 15054030]
61. Greevy RA, Grijalva CG, Roumie CL, Beck C, Hung AM, Murff HJ, et al. Reweighted Mahalanobis distance matching for cluster-randomized trials with missing data. Pharmacoepidemiol Drug Saf 2012 May;21 Suppl 2:148-154 [FREE Full text] [doi: 10.1002/pds.3260] [Medline: 22552990]
62. Nelson LA, Coston TD, Cherrington AL, Osborn CY. Patterns of user engagement with mobile- and web-delivered self-care interventions for adults with T2DM: a review of the literature. Curr Diab Rep 2016 Dec;16(7):66 [FREE Full text] [doi: 10.1007/s11892-016-0755-1] [Medline: 27255269]
63. MacKinnon DP. Introduction to statistical mediation analysis. New York, NY: Lawrence Erlbaum Associates; 2008.
64. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. Annu Rev Psychol 2007 Jan;58(1):593-614 [FREE Full text] [doi: 10.1146/annurev.psych.58.110405.085542] [Medline: 16968208]
65. Hayes A. Beyond Baron and Kenny: statistical mediation analysis in the new millennium. Commun Monogr 2009 Dec;76(4):408-420. [doi: 10.1080/03637750903310360]
66. Steiner JF. Rethinking adherence. Ann Intern Med 2012 Oct 16;157(8):580-585. [doi: 10.7326/0003-4819-157-8-201210160-00013] [Medline: 23070491]
67. Mayberry LS, Mulvaney SA, Johnson KB, Osborn CY. The MEssaging for Diabetes intervention reduced barriers to medication adherence among low-income, diverse adults with type 2. J Diabetes Sci Technol 2017 Jan;11(1):92-99 [FREE Full text] [doi: 10.1177/1932296816668374] [Medline: 27595710]
68. Piette JD, Farris KB, Newman S, An L, Sussman J, Singh S. The potential impact of intelligent systems for mobile health self-management support: Monte Carlo simulations of text message support for medication adherence. Ann Behav Med 2015 Feb;49(1):84-94 [FREE Full text] [doi: 10.1007/s12160-014-9634-7] [Medline: 25082177]
69. Munshi MN, Segal AR, Suhl E, Ryan C, Sternthal A, Giusti J, et al. Assessment of barriers to improve diabetes management in older adults: a randomized controlled study. Diabetes Care 2013 Mar;36(3):543-549 [FREE Full text] [doi: 10.2337/dc12-1303] [Medline: 23193208]

70. Krishna S, Boren SA. Diabetes self-management care via cell phone: a systematic review. J Diabetes Sci Technol 2008 May;2(3):509-517 [FREE Full text] [Medline: 19885219]
71. Misono AS, Cutrona SL, Choudhry NK, Fischer MA, Stedman MR, Liberman JN, et al. Healthcare information technology interventions to improve cardiovascular and diabetes medication adherence. Am J Manag Care 2010 Dec;16(12 Suppl HIT):SP82-SP92 [FREE Full text] [Medline: 21314228]

Abbreviations

ARMS-D: Adherence to Refills and Medications Scale for Diabetes
EHR: electronic health record
FAMS: Family-focused Add-on for Motivating Self-care
FQHC: Federally Qualified Health Center
HbA_{1c}: hemoglobin A_{1c}
HIPAA: Health Insurance Portability and Accountability Act
IMB: Information-Motivation-Behavioral Skills
IRB: institutional review board
RA: research assistant
RCT: randomized controlled trial
REACH: Rapid Encouragement/Education And Communications for Health
REDCap: Research Electronic Data Capture
SDSCA-MS: Summary of Diabetes Self-Care Activities medications subscale
SES: socioeconomic status
SMBG: Self-Monitoring of Blood Glucose
T2D: type 2 diabetes

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Protocol

DIABEO App Software and Telemedicine Versus Usual Follow-Up in the Treatment of Diabetic Patients: Protocol for the TELESAGE Randomized Controlled Trial

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Abstract

Background: Self-management of diabetes minimizes the risk of macrovascular and microvascular complications, but understanding and/or adherence to self-management recommendations is often suboptimal. DIABEO is a smartphone app (downloaded via the internet) used to calculate bolus insulin doses. A previous study (TELEDIAB 1) showed that the use of DIABEO was associated with a significant improvement in glycemic control in patients with poorly controlled type 1 diabetes mellitus, particularly when combined with teleconsultations with physicians.

Objective: Here, we present the protocol for a new study (Suivi A Grande Echelle d'une cohorte de diabétiques de type 1 et de type 2 sous schéma insulinique basal bolus par la TELEmédecine; abbreviated TELESAGE), conducted in a larger population of diabetic patients with poorly controlled basal-bolus insulin levels.

Methods: TELESAGE is a multicenter, double-randomized, open-label, three parallel–arms study, conducted in approximately 100 centers in France. The study will compare a control group (arm 1: usual follow-up) with two DIABEO telemedicine systems: (1) physician-assisted telemedicine (arm 2), and (2) nurse-assisted telemonitoring and teleconsultations by a diabetologist's task delegation (arm 3). Initial randomization will allocate the study arms in 12 French regions. A second randomization will assign patients in the groups allocated to each studied region. The primary objective of TELESAGE will be to investigate the effect of the DIABEO telemedicine system versus usual follow-up, with respect to improvements in the glycated hemoglobin levels of approximately 696 diabetic patients with poorly controlled basal-bolus insulin levels.

Results: The TELESAGE study is sponsored by Sanofi (Gentilly, France). A primary completion date is expected in June 2018, and publication of results is expected within 6 months of work completion.

Conclusions: The TELESAGE study is expected to confirm the previous results of the TELEDIAB 1 study using a larger sample of diabetic patients. It is also expected to evaluate a nurse-assisted telemonitoring system. We will assess the potential of the DIABEO telemedicine service in terms of its utility and explore whether it can become an integral part of diabetes care for patients.

Trial Registration: ClinicalTrials.gov NCT02287532; https://clinicaltrials.gov/ct2/show/NCT02287532 (Archived by WebCite at http://www.webcitation.org/6ykajhJKd)

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KEYWORDS

diabetes, diabetes mellitus, telemedicine, eHealth, mHealth, clinical protocols

Introduction

In its first global report on diabetes, the World Health Organization showed that the number of adults living with diabetes has almost quadrupled since 1980 to 422 million adults [1]. Diabetes complications can lead to blindness, heart attack, renal insufficiency, stroke and lower limb amputation. In 2012, diabetes caused 1.5 million deaths [1].

Self-management of diabetes is crucial to minimize the risk of macrovascular and microvascular complications [2,3]. This involves a daily planning of diet and physical activity, proper use of prescribed medication, and self-monitoring of capillary blood glucose levels. All this is done in order to adjust diet, physical activity and insulin treatment. However, adherence to self-management recommendations is often suboptimal, which is of importance for people whose diabetes is poorly controlled [4].

The Scottish registry linkage study [5] shows that only 13%–15% of patients with type 1 diabetes mellitus (T1DM) meet the glycated hemoglobin (HbA_{1c}) target level of less than 7.0% [5], whereas more than 20% have very poor glycemic control (HbA_{1c}>8.8%). The hazard ratios for death from cardiovascular causes increase from 2.9 in well controlled patients to 10.5 in the poorly controlled ones [6]. The reasons for the insufficient glycemic control among T1DM patients are numerous. T1DM is a complex, relatively infrequent disease that is managed by a diabetologist. The complex rules for calculating insulin doses can lead T1DM patients to inject inappropriate doses, especially during meals, leading to episodes of hypo- or hyperglycemia.

Patients with type 2 diabetes mellitus (T2DM) under intensive basal-bolus insulin regimens face similar problems [7]. An automatic system calculating bolus insulin doses on a daily basis is necessary to help both T1DM and T2DM patients undergoing an intensive insulin regimen. On the other hand, the extreme burden of daily routine (eg, glycemic control, carbohydrate counting, and determining an insulin dose that takes into account additional parameters such as irregular activities or unexpected physical activity) can be reduced through telemedical health care team support when needed. Telemedicine may also help intensively treated T1DM or T2DM patients, often those who are young and/or actively working, who find it difficult to comply with scheduled doctor visits to avoid progressive diabetes control degradation). It is essential for these patients to rapidly contact their caregiver, if necessary by telephone and email. Finally, alerts may help caregivers reach patients when needed.

The DIABEO system was created to overcome some of the above hurdles [8,9]. DIABEO is an app for insulin dosage calculation, available for download on smartphones. It calculates bolus insulin doses according to medical prescription and uses validated algorithms to take into account the carbohydrate intake, predrug glucose and anticipated physical activity reported by the patient. It provides glycemic targets and automatic algorithms for the adjustment of carbohydrate and basal insulin or basal pump rates when plasma postprandial or fasting glucose levels are off target. An internet connection ensures data transmission by means of automatic messages to medical staff (through a secure connection and website) to facilitate remote monitoring and teleconsultations.

In 2009, a pilot study demonstrated the feasibility, safety and accuracy of DIABEO [8]. Moreover, a six-month, open-label, randomized clinical trial conducted in 180 poorly controlled T1DM patients (TELEDIAB 1 study) showed that the DIABEO software combined with short teleconsultations (ie, five minutes

every two weeks) demonstrated a 0.91% improvement in HbA_{1c} over controls and a 0.67% reduction when the DIABEO software is used alone [9]. This benefit does not require more medical time and is obtained at a lower overall cost for the patient than usual care [9].

Following the TELEDIAB 1 study, the Haute Autorité de Santé, France (HAS) approved DIABEO as a medical device for use in T1DM patients (July 2016) [10]. DIABEO was approved for two years, and the HAS specified that the renewal will be conditioned on the results of the current study (*Suivi A Grande Echelle d'une cohorte de diabétiques de type 1 et de type 2 sous schéma insulinique basal bolus par la TELEmédecine*; abbreviated TELESAGE).

The purpose of TELESAGE is to investigate the metabolic efficacy of the DIABEO telemedicine service in a large population of patients with poorly controlled diabetes who are on a basal-bolus insulin regimen. Additionally, we will assess its economic impact in terms of cost reduction to the health insurance system. Here, we present the protocol of the TELESAGE study.

Methods

Objective

TELESAGE was designed to investigate the efficacy of the DIABEO telemedicine service in improving glycaemic control in a large population of diabetic patients sub-optimally controlled with insulin.

Study Design

TELESAGE is a randomized, open-label, three parallel-arms study that is to be conducted in approximately 100 public and private centers that employ diabetologists in France (Figure 1). The study protocol was designed by Centre d'Étude et de Recherche pour l'Intensification du Traitement du Diabète (CERITD; Evry, France). CERITD is a nonprofit clinical translational research center located in Corbeil Hospital (Corbeil-Essonnes, France). Selected centers have been already participating in the TELEDIAB 1 study [9]. Voluntis (Suresnes, France) provided the DIABEO software, Orange Telephone Company (Paris, France) provided the smartphone and telephone lines, and Sanofi (France) funded the study.

The study was designed to include a population of approximately 696 T1DM and T2DM patients poorly controlled with a basal-bolus insulin regimen (HbA_{1c}≥8%) in real-life conditions. The patient recruitment period was estimated to last approximately 36 months.

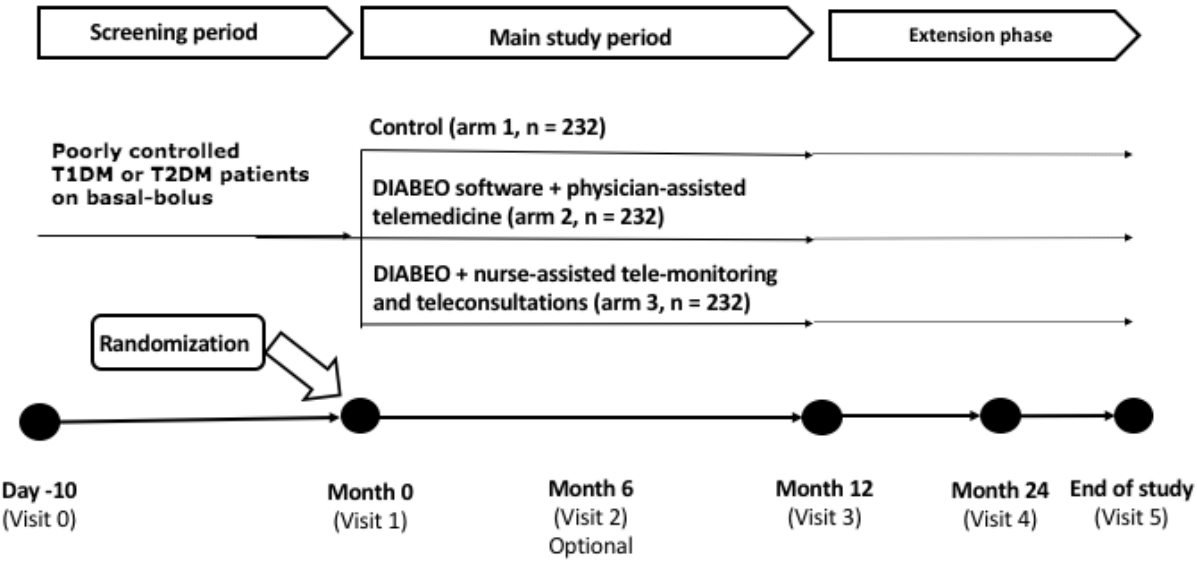
The trial compares a control group (arm 1: usual follow-up) with the previously investigated DIABEO telemedicine service (arm 2: software + physician-assisted telemedicine as in the TELEDIAB 1 study [9]) or a new DIABEO telemedicine service (arm 3: software + telemonitoring and teleconsultations delegated by the diabetologists to a nursing staff) (Figure 1). Participants are asked to carry out at least two self-monitoring plasma glucose (SMPG) every day during the study. Patients randomized to arms 2 and 3 receive a smartphone with the DIABEO software. The investigator-physician fixes glycemic targets and associated treatment, alarm values, and values for self-adaptations. Patient enters daily three types of variables in the app: (i) SMPG levels before and after meals (6 measurements) + 1 optional in the night; (ii) carbohydrate counts; and (iii) planned physical activity. Patient entry data is automatically uploaded by the smartphone to a secured website (available to investigators at any time). If fasting or postprandial SMPG do not meet target levels, the system can suggest adjustments for carbohydrate ratio, long-acting insulin analog dose, or pump basal rates.

Following a screening period of 10 days, the main study period will last 12 months, with an optional extension period of at least 12 additional months (Figure 1). If desired, patients from the control group can begin to use the software after 12 months.

Physician-Assisted Telemedicine (Arm 2)

Teleconsultations will be conducted with both patients and doctors in front of their computers or smartphone displaying data from the week before. These sessions focused on insulin dose adjustments and motivational support.

Figure 1. Study design. T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus.



Physician/Nurse Delegation Protocol (Arm 3)

Arm 3 of the study involves a nursing team supervised by a physician, based in Paris and its surrounding region. Figure 2 shows the road map of arm 3, which starts with the investigator-physician, who fixes glycemic targets and associated treatment, alarm values triggering a nurse action, and values for self-adaptations (step 1). A reference nurse performs patient initiations (step 2). The patient can now use the DIABEO app on their smartphone (step 3). The device performs a titration of the insulin dose (and eventually a proposal for dose adaptation) as a function of several factors, including blood glucose levels, physical activity and ingested carbohydrates. The data entered by the patient is sent to a secure platform every 2 hours (step 4). This platform is continuously visible to the referring nurse and the diabetologist. Automatic messages containing analytical data are generated every night (step 5). The referring nurse (who can call the patient and/or the diabetologist, if necessary) analyzes these messages during the morning of each working day. Finally, the diabetologist receives patient data and nursing reports (step 6).

DIABEO Software

The DIABEO software was described in the *Introduction* section (for details, see references [8,9]). Telemedicine is similar to that previously described [9], with the exception that patient teleconsultations in arm 3 are conducted by nurses instead of doctors.

Clinical Study Flow Diagram

The schedule of visits and measurements is given in Table 1. HbA_{1c} measures assessing glycemic control are performed at visits 1, 2 (optional), 3 and 4.

Ethical Conduct of the Study and Informed Consent

The study is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and in accordance with French privacy law (*Informatique et Libertés*) when processing personal data in the health care field (Act of 6 January 1978, amended by Law No 2004-801 of August 6, 2004).

This clinical trial began after the sponsor had obtained approval from the ethical committee (*Comité de Protection des Personnes* [CPP]; Committee for People Protection) of La Pitié-Salpetrière Hospital (Ile de France VI) and the authorization of the French *Agence Nationale de Sécurité du Médicament* (ANSM; National Agency for Drug Safety). The study was registered under ANSM# 2012-A00072-41. The sponsor communicates all serious and unexpected adverse events to the CPP and the ANSM.

Before inclusion, patients consented to participate in the trial. To that purpose, patients were informed about the nature, objective and possible consequences of the trial, and gave signed consent to participate and release medical-related data.

Patients

As calculated in the Statistical Analysis section, 696 subjects have been included in the study (the recommended number of subjects per center was 6-8 patients, the inclusion period lasted from April 24, 2013 to May 19, 2016). The trial is currently active, but not completed.

Figure 2. Road map of arm 3. Patient enters daily three types of variables in the DIABEO application (step 3): (i) Self-measured plasma glucose levels before and after meals (6 measurements) + 1 optional in the night; (ii) carbohydrate counts; and (iii) planned physical activity (see text for other technical details). HCP: health care practitioner.

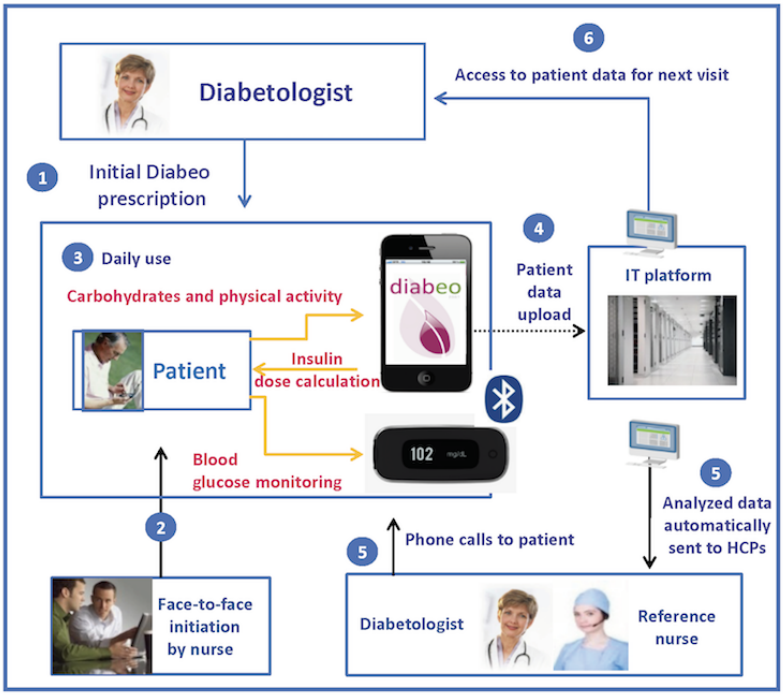


Table 1. Clinical study flow diagram; schedule of enrollment, interventions and assessments. EQ-5D: EuroQol five dimension scale; HbA_{1c}: glycated hemoglobin.

Conponents	Visit #1	Visit #2	Visit #3	Visit #4[a,b,c]	Visit #5[d] (Optional extension)
Evaluations	Day 0	Month 6	Month 12	Month 24	End of study
Informed consent	✓		✓[e]	✓[d]	
Inclusion / exclusion criteria	✓				
Medical history	✓				
Demographics	✓				
Concomitant treatments	✓	✓	✓	✓	✓
Clinical examination	✓	✓	✓	✓[a,f]	
Randomization	✓				
Weight	✓	✓	✓	✓	✓
Blood pressure	✓	✓	✓	✓[a,f]	
Last HbA_{1c} values	✓	✓	✓	✓	✓
Questionnaires (EQ-5D)	✓		✓	✓[a,f]	
DIABEO initiation	✓[a,b,f]		✓[c]		
Nursing appointment[a]	✓		✓[e]		
Fixing appointment for visit #3		✓			
Satisfaction questionnaire “DIABEO”			✓[a,f]	✓[a,f]	
Severe hypoglycemia		✓	✓	✓[a,f]	
Symptomatic hypoglycemia (≤15 days before)			✓		
Adverse events	To be reported all throughout the study				
Serious adverse events	To be declared to sponsor within 24 hours (next business day)				
Malfunction of the DIABEO software[f]	To be reported all throughout the study				
Care consumption	To be reported every month by all concerned patients				
Remittance of TELESAGE books	✓		✓[a,f]		

[a]Applicable to group 3 (software + nurses’ telemonitoring and teleconsultations).

[b]Initiation takes place within approximately 10 days after the inclusion visit.

[c]Applicable to patients of group 1 (control) continuing the study after 12 months and using the software.

[d]Applicable to patients wishing to use DIABEO during the extension phase and who have not yet signed a consent for that purpose.

[e]Applicable to patients of group 1 (control) continuing the study after 12 months and using the software + nurses’ telemonitoring and teleconsultations.

[f]Applicable to group 2 (software + physicians’ telemedicine).

Inclusion Criteria

Patients enrolled in the TELESAGE study should meet the following inclusion criteria: T1DM and T2DM patient performing self-monitoring of blood glucose (≥2 measured values per day), treated with insulin analogs according to a basal-bolus regimen for at least 1 year and using the same method of administration (pen or pump) for at least 3 months, possessing an Apple or Android smartphone compatible with DIABEO before starting the study, having two HbA_{1c} values ≥8%, one dating to more than 3 months ago and the other less than 1 month ago. Additionally, participants must have the capability to understand and follow the instructions of the study, and be able to provide written consent to participate and specify if they benefit from a social security scheme.

Exclusion Criteria

Key exclusion criteria included: age <18 years; subject having already used the DIABEO system in the 6 months preceding inclusion, or participating in a clinical trial within 6 months (except Meos, the TELEDIAB 3 study after a 6-month participation period), or treated with human insulin, or pregnant (or wishing to be pregnant during the study period), or subject requiring boluses >0.4 IU/gram (for subjects under functional

insulin therapy) or >99 IU per day (for subjects treated on a fixed diet plan), or subject living with staggered hours (eg, night work, meals shifted).

Randomization

Patient randomization is automatically done by using the electronic case report form software. A first randomization step allocates the study arms at the regional level: (i) six regions including patients in arms 1 and 2 (Aquitaine, Île-de-France, Lorraine, Nord-Pas-de-Calais, Rhône-Alpes, and Languedoc-Roussillon) and (ii) six other regions including patients in arms 1 and 3 (Alsace, Franche-Comté, Lower Normandy, Midi-Pyrénées, Pays de la Loire, and Provence-Alpes-Côte d'Azur). Then, within each region the patients are further randomized between the two groups (done at patients' inclusion, between arms 1 and 2 or between arms 1 and 3). The distribution by center was 1:2 (ie, 1 patient of arm 1 for 2 patients of arms 2 or 3).

Outcome Measures

The primary outcome measure of this study is to investigate the effect of a 12-month follow-up with the DIABEO system (software + physicians' telemedicine, or software + nursing telemonitoring, and teleconsultations by diabetologist's task delegation) versus usual follow-up in terms of improvement of glycemic control (HbA_{1c} levels) in T1DM or T2DM patients poorly controlled by a basal-bolus insulin regimen. HbA_{1c} high performance liquid chromatography assays are performed at qualified medical biology laboratories and then reported by participants to investigators. Secondary outcome measures are to compare groups for: HbA_{1c} levels, percent of responder patients (HbA_{1c} <7.5% or HbA_{1c} reduction ≥1%) and severe hypoglycemia at 6, 12 and 24 months, as well as for quality of life and satisfaction (of patients and physicians) at 12 and 24 months. Severe hypoglycemia was defined as requiring third-party assistance. Quality of life was assessed by a specific questionnaire, derived from the EuroQol five dimension scale (EQ-5D) questionnaire [11]. For participants of arms 2 and 3, satisfaction with the DIABEO telemedicine system is evaluated at each center, with a patient's self-assessed specific questionnaire.

Other secondary, medico-economic outcome measures, have been designed to compare groups at 12 and 24 months for resource consumption and health insurance costs (including overall costs of diabetes and complications, and costs per point of HbA_{1c} reduction and for severe hypoglycemia avoided). If the study demonstrates an overall statistically significant effect, subgroups analyses will be conducted to identify the patients' profiles with optimal costs consequences and cost-effectiveness ratios.

Statistical Analysis

Patient Population Size

The initial sample size to detect a ≥0.5% difference in HbA_{1c} from baseline to month 12 was estimated using a standard deviation of 1.2%, a rate of not evaluable patients of 15% and an intracluster correlation coefficient of .005 (a measure degree of homogeneity within the same region). This calculation predicted an initial sample size of 696 patients to achieve ≥90% power in detecting a difference in outcome.

Data Analysis

Efficacy outcomes are analyzed on an intention-to-treat basis. A confirmatory analysis adjusted by center and region will be carried out and a robustness analysis will be done on the population per protocol. Categorical data are expressed as frequencies and percentages, while quantitative data are expressed as means and standard deviations. The analysis of covariance (ANCOVA) is used to compare groups for the results on the primary end point. The ANCOVA, the chi-square test, and Fisher exact test are used for other comparisons.

Results

The TELESAGE study is sponsored by Sanofi (Gentilly, France). A primary completion date is expected in June 2018, and publication of results is expected within 6 months of work completion.

Discussion

Study Rationale

The DIABEO telemedicine system has previously showed superiority to usual follow-up in improving HbA_{1c} in patients with poorly controlled diabetes [9]. The current TELESAGE study is expected to confirm this result in a larger sample of diabetic patients and real-life conditions. Moreover, the TELESAGE study will validate the present physician/nurse delegation protocol.

The TELEDIAB 1 study showed that the DIABEO telemedicine system improves HbA_{1c} without requiring more medical time and providing far more services compared to usual care [9]. In this respect, the TELESAGE study will test the efficacy of a closer follow-up by the nursing staff as compared with the previous physician-assisted telemedicine system.

Usually, a T1DM or T2DM patient undergoing a basal-bolus insulin regimen sees their diabetologist every 3 to 6 months. At the hospital, the patient can also be monitored by a nurse for therapeutic education (whether or not the patient is hospitalized), which can help in difficult moments (eg, hospitalization following a serious adverse event or during a major treatment switch such as from injectable treatment to insulin pump treatment).

The DIABEO telemedicine service has several strengths. Patient data is daily analyzed by the DIABEO system to fight against glycemic instability and complications. In very serious cases, analysis of these data allows triggering nursing actions and/or physician actions. Nursing delegation also allows more availability to receive patients' calls and respond to daily issues. Continuity and continuity of care is thus organized from Monday to Saturday from 8am to 8pm.

If positive results are obtained, TELESAGE will clearly demonstrate that the DIABEO telemedicine service could be an integral part of the ambulatory care of an insulin-treated patient.

Limitations

Given the impossibility of double-blind assessment of open-label intervention versus usual follow-up, the effects of report bias cannot be eliminated.

Acknowledgments

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Authors' Contributions

SF, GC and GO helped to develop the DIABEO software. SF and GC designed and analyzed the research, with the help of HH, NJ, BD, GO, P Simon and YK. HH, LC, SF, PYB, P Serusclat, BC, AF, PF, BG, YR, NJ, AP, SB, P Schaepelynck and GC recruited patients. All authors read and approved the final manuscript.

Conflicts of Interest

NJ received personal compensation for board participation and speaking fees from Eli Lilly, Novo Nordisk, Sanofi Aventis and Roche. LC received personal compensation for board participation and speaking fees from Eli Lilly, Lifescan, Novo Nordisk, Roche Diagnostics, Medtronic and Sanofi Aventis. SF has received personal compensation for board participation and speaking fees from Novo Nordisk, Roche Diagnostics, Lifescan, Sanofi, Eli Lilly and received Research support from MSD. She is medical director and vice president of CERITD, which has developed the DIABEO system in collaboration with Voluntis, and is the main investigator of the TELESAGE study, sponsored by Sanofi-Diabetes (Gentilly, France). PYB has received personal compensation for board participation and speaking fees from Abbott, Eli Lilly, Lifescan, Novo Nordisk, Roche Diagnostics, Medtronic, Sanofi Aventis and Becton, Dickinson and Company. P Schaepelynck has received speaking fees from Sanofi, Abbott, Lilly and participation at boards of Novo-Nordisk and Sanofi. P Serusclat has received personal compensation for board participation and speaking fees from Johnson and Johnson, Astra-Zeneca, Eli Lilly, Medtronic, MSD, Novartis, Novo Nordisk and Sanofi Aventis. HH has received personal compensation for board participation and speaking fees from Abbott, Dexcom, Eli Lilly, Lifescan, Novo Nordisk, Roche Diagnostics, Medtronic, Sanofi Aventis and Becton, Dickinson and Company. BC and AF have no conflicts of interest to declare concerning this study. PF has received personal compensation for board participation and speaking fees from Abbott, Becton, Dickinson and Company, Eli Lilly, MSD, Novartis, Novo Nordisk and Sanofi. BG participated as advisory panel/board member of Sanofi, Eli Lilly, NovoNordisk, Novartis, GSK, MSD, Boehringer Ingelheim, AstraZeneca, Abbott, Medtronic and Roche Diagnostics. He also participated as clinical investigator for Sanofi, Eli Lilly, NovoNordisk, GSK, BMS, AstraZeneca, Medtronic, Abbott, Roche Diagnostics, MSD, Novartis, Janssen and Boehringer Ingelheim, and received research support from Medtronic, Vitalaire, Sanofi, Eli Lilly and Novo Nordisk. YR has received personal compensation for board participation and speaking fees from Novo Nordisk, Sanofi, Eli Lilly, Medtronic, Takeda, Abbott and Roche. AP received personal compensation for board participation and speaking fees from Abbott, Ascencia, Astra-Zeneca, Eli Lilly, Medtronic, MSD, Novartis, Novo Nordisk and Sanofi Aventis. SB has received honoraria from Sanofi, NovoNordisk, Lilly, Roche and Medtronic. YK is employee of Sanofi. GO is Chief Medical Officer at Voluntis (Suresnes, France). BD is employed by Cemka-Eval, a consulting team specializing in health economics, epidemiology, and outcomes research. He also received personal compensation for board participation and speaking fees from MSD, Novo-Nordisk, Sanofi, Lilly and Pfizer. P Simon received personal compensation for board participation and speaking fees from Sanofi Aventis. GC is employed by CERITD and received personal compensation for board participation, research funding or speaking fees from Astra-Zeneca, Boehringer, Eli Lilly, Johnson & Johnson, MSD, Novo-Nordisk, Sanofi-Aventis and Voluntis. The TELESAGE study is sponsored by Sanofi (Gentilly, France).

References

1. World Health Organization. Global report on diabetes. WHO Press 2016 [FREE Full text]
2. Haas L, Maryniuk M, Beck J, Cox CE, Duker P, Edwards L, 2012 Standards Revision Task Force. National standards for diabetes self-management education and support. Diabetes Care 2013 Jan;36 Suppl 1:S100-S108 [FREE Full text] [doi: 10.2337/dc13-S100] [Medline: 23264420]
3. Abubakari A, Cousins R, Thomas C, Sharma D, Naderali E. Sociodemographic and Clinical Predictors of Self-Management among People with Poorly Controlled Type 1 and Type 2 Diabetes: The Role of Illness Perceptions and Self-Efficacy. J Diabetes Res 2016:A. [doi: 10.1155/2016/6708164]
4. Nam S, Chesla C, Stotts N, Kroon L, Janson S. Barriers to diabetes management: patient and provider factors. Diabetes Res Clin Pract 2011;93(1):1-9. [doi: 10.1016/j.diabres.2011.1002.1002]
5. Livingstone SJ, Looker HC, Hothersall EJ, Wild SH, Lindsay RS, Chalmers J. Risk of cardiovascular disease and total mortality in adults with type 1 diabetescottish registry linkage study. PLoS Med 2012;9(10):e1001321. [doi: 10.1371/journal.pmed.1001321]
6. Lind M, Svensson AM, Kosiborod M, Gudbjornsdottir S, Pivodic A, Wedel H. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med 2014;371(21):1972-1982. [doi: 10.1056/NEJMoa1408214]

7. Crowley M, Holleman R, Klamerus M, Bosworth H, Edelman D, Heisler M. Factors associated with persistent poorly controlled diabetes mellitus: clues to improving management in patients with resistant poor control. Chronic Illn 2014;10(4):291-302. [doi: 10.1177/1742395314523653]
8. Franc S, Dardari D, Boucherie B, Riveline JP, Biedzinski M, Petit C. Real-life application and validation of flexible intensive insulin-therapy algorithms in type 1 diabetes patients. Diabetes Metab 2009;35(6):463-468. [doi: 10.1016/j.diabet.2009.05.006]
9. Charpentier G, Benhamou PY, Dardari D, Clergeot A, Franc S, Schaepelynck-Belicar P. The Diabeo software enabling individualized insulin dose adjustments combined with telemedicine support improves HbA 1c in poorly controlled type 1 diabetic patients: a 6-month, randomized, open-label, parallel-group, multicenter trial (TeleDiab 1 Study). Diabetes Care 2011;34(3):a-6. [doi: 10.2337/dc10-1259]
10. Haute Autorité de Santé. Solution DIABEO. www.has-sante.fr 2016;Available at:A [FREE Full text]
11. Gusi N, Olivares PRR. R. The EQ-5D Health-Related Quality of Life Questionnaire. In: Preedy VR. In: Watson RR (eds) Handbook of Disease Burdens and Quality of Life Measures. New York, NY: Springer,; 2010:87-99.

Abbreviations

ANCOVA: analysis of covariance
ANSM: Agence Nationale de Sécurité du Médicament (National Agency for Drug Safety)
BMS: Bristol-Myers Squibb
CERITD: Centre d'Étude et de Recherche pour l'Intensification du Traitement du Diabète
CPP: Comité de Protection des Personnes (Committee for People Protection)
EQ-5D: EuroQol five dimension scale
GSK: GlaxoSmithKline
HAS: Haute Autorité de Santé (France)
HbA_{1c}: hemoglobin A_{1c}
MSD: Merck Sharp and Dohme
SMPG: self-monitoring plasma glucose
T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus
TELESAGE: Suivi à Grande Échelle d'une cohorte de diabétiques de type 1 et de type 2 sous schéma insulinique basal bolus par la TELEmédecine

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Protocol

Universal Versus Conditional Third Day Follow-Up Visit for Children With Nonsevere Unclassified Fever at the Community Level in Ethiopia: Protocol for a Cluster Randomized Noninferiority Trial

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Abstract

Background: Under the World Health Organization's integrated community case management strategy, febrile children seen by community health workers (on day 1) without a diagnosable illness and without danger signs are advised to return on day 3, regardless of symptom resolution. This advice might be unnecessary and place additional time and cost burdens on caregivers and community health workers. However, the safety of not following up with respect to children with unclassified fever is unknown.

Objective: The objective of this study is to establish the safety of conditional follow-up of nonsevere unclassified fever, that is, nonsevere illness with fever, no malaria, pneumonia, diarrhea, or danger signs, compared with universal follow-up on day 3, through a 2-arm cluster randomized controlled noninferiority trial.

Methods: The study is being conducted in 3 districts in southwest Ethiopia. A total of 25 health facilities are randomized to one of the 2 intervention arms; all 144 health posts and 284 community health workers are included. All enrolled children are followed-up after 1 week (on day 8) for re-assessment. If still sick on day 8, additional follow-up takes place after 2 weeks (day 15) and 1 month (day 29). To demonstrate that there is no significant increase in the percentage of children deteriorating clinically, the sample size needed for a noninferiority margin of 4%, a power of 80%, an alpha of 5%, and a design effect of 3 is 4284 children with unclassified fever. Main outcome is treatment failure on day 8, defined as death, hospitalization, one or more danger signs, or persistent fever.

Results: The project was funded in 2015 and enrollment was completed 2016. Data analysis is currently under way, and the first results are expected to be submitted for publication in 2018.

Conclusions: This study addresses the question as to whether there is any benefit in recommending universal follow-up among children seen for nonsevere unclassified fever, or whether parents can be counseled to return in the event of persistent fever, using

a cluster randomized controlled trial design embedded in a national program. Outcomes will be relevant for policy makers and are important for the evaluation of current and future World Health Organization guidelines for the management of children with fever.

Trial Registration: ClinicalTrials.gov NCT02926625; https://clinicaltrials.gov/ct2/show/NCT02926625 (Archived by WebCite at http://www.webcitation.org/6xrQWn50t)

(JMIR Res Protoc 2018;7(4):e99) doi:10.2196/resprot.9780

KEYWORDS

community health workers; Ethiopia; malaria; fever; child

Introduction

Burden of Disease in Children in Sub-Saharan Africa

Even though substantial progress has been made in reducing child mortality around the world, many countries did not achieve the Millennium Development Goal 4 [1]. For countries to reach the Sustainable Development Goals by 2030 [2], it is crucial that child health interventions focus on management of infectious diseases in children. Globally, mortality in children under 5 years stands at 43 per 1000 live births; it is estimated that 5.6 million children under 5 years die each year [3,4]. A large proportion of deaths are caused by infectious diseases such as pneumonia (15.5%), diarrhea (8.9%), and malaria (5.2%)—diseases with symptoms that overlap, making differential diagnosis difficult [5]. In response, many countries in sub-Saharan Africa have introduced integrated community case management (iCCM), where community health workers (CHWs) are trained to assess, classify, and treat uncomplicated cases of pneumonia, diarrhea, and malaria in children U5, and refer children with danger signs and malnutrition for facility-based care [6]. Although the mortality impact of iCCM has been difficult to demonstrate [7], there is clear evidence that it can increase the treatment rate among sick children [8].

Control Strategies for Childhood Illnesses

In Ethiopia, the under-five mortality rate stands at 58 per 1000 live births; it is estimated that 187,000 children under 5 years died in the year 2016 [4,9]. As part of Ethiopia's Health Extension Program, the Government has deployed over 42,000 female CHWs, or Health Extension Workers (HEWs) [10,11], to provide preventive, promotive, and curative health services at the community level; since 2010, iCCM has been scaled up in most regions of the country. There are typically 2 HEWs assigned to a health post in a sub-district with a population of 3000-5000. The HEWs are supervised by health centers that oversee approximately 5 health posts each. Medicines and supplies are distributed to the health posts by the Federal Ministry of Health, Regional Health Bureaus, and woreda (district) health offices, as well as by implementing partners. On the basis of surveys conducted in 2012, 90% of HEWs had all the essential iCCM drugs and supplies [12], and HEWs provided correct case management for 64% of children [13].

As per the World Health Organization's iCCM guidelines [14], children diagnosed by a CHW with an illness are given treatment (on day 1) and counseled to return on day 3 to assess treatment compliance and illness resolution. Children with fever but without a diagnosable illness and without danger signs (ie, nonsevere unclassified fever) for whom treatment should be withheld are also told to return to the CHW on day 3, even if the child has recovered. This *universal* follow-up visit is either done through a return visit to the health post or through a home visit by the CHW.

Unclassified Fever in Children

However, febrile illness is common in childhood, and is often due to viruses or other self-resolving illnesses [15,16]. In a large proportion of cases, fever resolves rapidly, almost always within 96 hours [17]. A number of studies have suggested that it is safe to withhold medical treatment for children with unclassified fever [18]. In Ethiopia, HEWs are instructed to follow the integrated management of neonatal and childhood illness (IMNCI) manual, which recommends that children seen by HEWs should only return for a re-assessment if the illness persists or deteriorates, that is, a *conditional* follow-up visit to the health post. However, HEWs and their supervisors report that a range of practices are applied for children with unclassified fever, including both conditional (as recommended) and universal follow-up advice, immediate referral to health centers, or treatment with antimalarial tablets, despite a negative malaria Rapid Diagnostic Test (mRDT).

There is limited evidence on which of the 2 follow-up recommendations (conditional as in IMNCI or universal as in iCCM) is safer for the child, and it is unclear whether caregivers of children actually come back promptly to the health post for their conditional follow-up visit if the child is not improving, or if they come back at all if the child in a universal follow-up situation has improved. Bacterial infections can develop quickly, and delaying care-seeking is a major risk factor for death in both pneumonia and malaria [19,20]; hence, children with untreated persistent fever may be at risk if caregivers do not comply with the conditional follow-up advice. A universal follow-up visit 2 days after an initial assessment for all children may promote detection of those at risk of developing severe illness. However, it could also potentially lead to delayed care-seeking for children whose health rapidly deteriorates at home if caregivers instead wait for their booked follow-up visit. In addition, the visit may add extra burden to families and HEWs and might be unnecessary if fever has resolved. On the caregiver side, opportunity costs and other barriers often hinder care-seeking for sick children, even when community-based providers are near and free of charge [21]. It is therefore unclear whether caregivers and HEWs would comply better with the conditional follow-up advice compared with the universal follow-up advice and whether the universal follow-up visit is even necessary.

This paper presents a protocol for a 2-arm cluster randomized controlled noninferiority trial conducted to assess whether conditional follow-up is noninferior to universal follow-up for nonsevere febrile illness in children U5, in whom malaria, pneumonia, diarrhea, or danger signs are absent.

Methods

Study Aim and Objectives

The study aims to assess the safety, in terms of the proportion of children whose health clinically deteriorates, of a follow-up visit conditional on nonresolution of symptoms for mRDT-negative children with no fast breathing, pneumonia, diarrhea, or danger signs, managed at the community level, compared with a universal visit for all these children on day 3.

Primary Objectives

The primary objective of the study was to assess the treatment failure after 1 week (on day 8), defined as the proportion of children with nonsevere unclassified fever who subsequently declined clinically (death, hospitalization, one or more danger signs, or persistent fever) subsequent to (1) conditional versus (2) universal follow-up of children under 5 years who present to HEWs with unclassified, nonsevere fever in 3 woredas (districts) in the Southern Nations, Nationalities and People's Region (SNNPR) in southwest Ethiopia.

Secondary Objectives

The secondary objectives of this study were as follows:

1. To describe the clinical presentation and outcome of illness in those children whose symptoms do not resolve or where danger signs develop at day 8, to measure the rate of treatment failure at day 15 and 29 in both study arms for children who did not recover by day 8, and to determine the percentage of children who return for scheduled visits on day 3 (universal arm) or spontaneous visits before day 8 (universal and conditional arms).
2. To determine the percentage of secondary treatment (antimicrobial medicines prescribed during visits to any providers after initial presentation to HEWs) in both study arms on day 8.
3. To assess acceptability of the conditional or universal follow-up recommendations and no treatment with an antimicrobial to caretakers and HEWs, and determine why caretakers chose to return or not return to the HEW.

Study Design

This is a 2-arm cluster randomized controlled trial (cRCT) carried out in 3 woredas in SNNPR in Ethiopia. Clusters defined by the health center (the lowest administrative unit where HEW services are coordinated) are randomized into either the *conditional* or *universal* follow-up arm. All children seeking care from the HEW health posts in these clusters are potential recipients of the interventions, in addition to having access to routine care available from private and public health services. Caregivers of children who meet the inclusion criteria (fever without malaria, pneumonia, diarrhea, or other symptoms requiring referral) are counseled to follow 1 of the 2 pathways, based on which intervention cluster the HEW belongs to. There are 25 clusters; 13 clusters in the universal follow-up arm and 12 in the conditional follow-up arm.

Study Site

This research study will be conducted in 3 woredas , namely, Boloso Sore, Damot Gale, and Halaba in the Wolayita zone of SNNPR in southwest Ethiopia (see Figure 1). The iCCM program is functioning in all districts of SNNPR through support to the Regional Health Bureau from Save the Children International and the Integrated Family Health Program. It will therefore be an ideal environment to implement this research, as iCCM services are stable and the program is implemented by the Regional Health Bureau, which will provide technical oversight to this project.

According to the latest malaria indicator surveys, the rate of prompt care-seeking for fever is currently low, with only 46.3% of children under 5 years with fever taken for early treatment [22]. However, care-seeking at health post level shows an upward trend, presumably as a result of the increased awareness of the availability and proximity of child health services [12]. In addition, Malaria Consortium, with funding from the James Percy Foundation, has recently started implementing the Integrated Community-based Interventions for Malaria Services project in SNNPR. Activities include case detection by the volunteer Health Development Army who will work to ensure that all children with fever receive prompt diagnosis and treatment, and that children with danger signs get referred. As part of this grant, refresher training will also be provided to HEWs to negotiate optimal practices using behavior change communication tools and facilitation skills in community conversation. It is anticipated that these changes will lead to an increased use of HEWs in the study area.

The 3 woredas will be selected based on: (1) strength of iCCM program (ie, consistency in HEW supervision and supply), (2) HEW use rate among caregivers (≥50 children assessed for fever each month over a 12-month period), and (3) concurrent community mobilization activities under other grants (to ensure that demand was kept high during the study period). There are 25 health centers and 144 health posts with 284 HEWs in the 3 selected woredas.

The Interventions

Children aged 2-59 months with fever (≥37.5 degrees Celsius) or a history of fever, a negative mRDT, no other symptoms of pneumonia or diarrhea, and no danger signs will be eligible to participate in the study. Figure 2 outlines the areas that consenting caregivers will be counseled on how to detect danger signs and seek care immediately from a health center if danger signs develop or the illness worsens; fever reduction strategies, such as tepid sponging and paracetamol; and that a study visit to assess clinical outcomes will take place after 1 week. Caregivers in the conditional arm will also be advised to return at any point to the HEW at the health post for re-assessment if symptoms persist or deteriorate (as per the Ethiopian IMNCI Guidelines), whereas caregivers in the conditional arm will be advised to return on day 3 to the HEW for a follow-up assessment, even if the child has recovered (as is common practice).

Figure 1. Map of Ethiopia with the Southern Nations, Nationalities and People's Region (SNNPR) and the three study woredas.

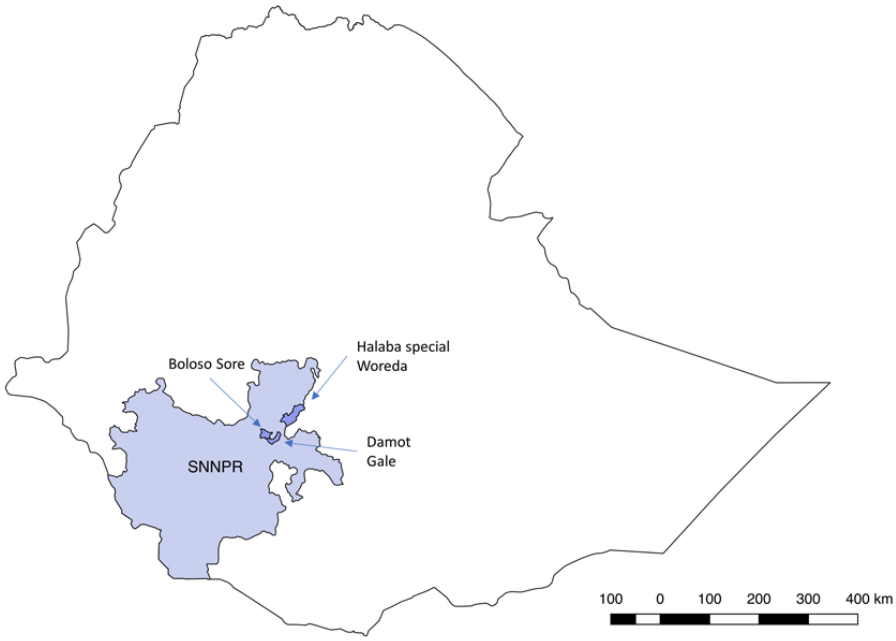
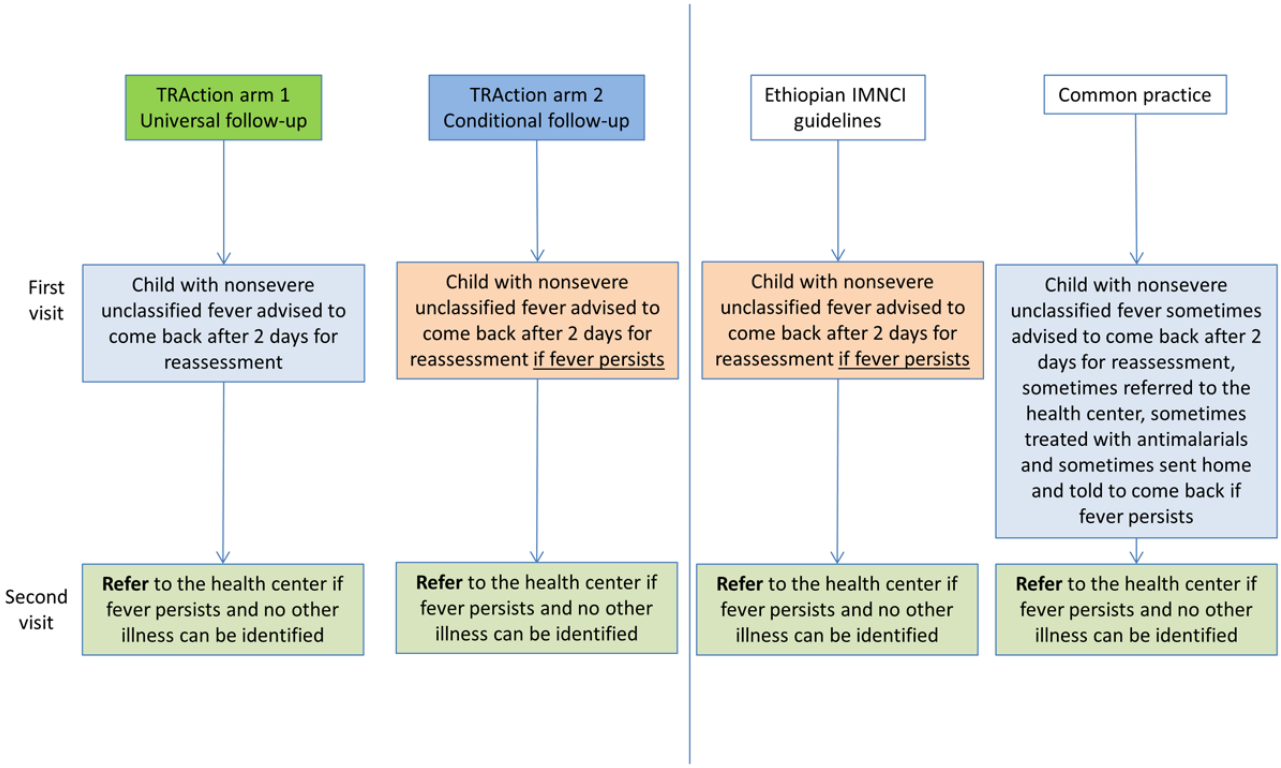


Figure 2. Description of the 2 interventions arms, the current guidelines, and observed common practice. IMNCI: integrated management of neonatal and childhood illness.



At the day 3 re-assessment visit in the universal follow-up arm and at any spontaneous visit in both arms, the child will have a full re-assessment of their condition and the HEW will fill out a child assessment form. Caregivers will be asked whether the child remains febrile or whether the illness has resolved. If the child still has unclassified fever and a negative mRDT on re-assessment, the child will be referred to the nearest health center, as recommended in the national IMNCI guidelines. If the illness has resolved, the child will be sent home.

A clinically trained independent evaluator (IE) who is blinded to the study arm will visit all enrolled children at their home after 1 week to assess their clinical outcome. If caregivers report that the child is no longer ill and no fever is recorded, the child will be considered cured and no more follow-up will be done. If the caregiver reports that the child still has symptoms or if fever or other illness symptoms are detected during the assessment, the IE will follow the IMNCI algorithm and refer/treat the child accordingly. The IE will then follow-up

again via a home visit after 2 weeks (day 15) and, if the child is still ill, on day 29.

At the day 8 visit, the IE will use a questionnaire to ask about individual and household characteristics, care-seeking and other treatments for the current illness episode, and reasons for returning/not returning to the HEW for follow-up care.

Qualitative Component

Caregivers' recognition and responses to childhood fevers and HEWs' views and experiences of their position in the health care system during previous and, in particular, the current recommendations in the respective intervention arms will be explored using semistructured interviews at a time point when the interventions are fully adopted by the HEWs (determined based on a stable enrollment rate). A subset of mothers and HEWs in both arms will be selected for inclusion in these interviews to help put the findings into context.

Randomization

Cluster randomization will be at the health center level, corresponding to the lowest administrative unit where HEW services are coordinated; there will be 25 clusters in the 3 study woredas, with an average of 5 health posts and 7.5 HEWs per cluster. All clusters will be eligible for randomization. Restricted randomization will be performed to minimize the difference between intervention and control arms on key indicators, including average under-five population size, cluster distance to nearest zonal referral hospital, and number of unclassified fevers in children under 5 years seen by HEWs [23]. A validity matrix will be produced to confirm that no pairs are more or less likely to appear together than they would by chance. Sorting of clusters and random selection of schemes will be carried out in STATA 13 (STATA Corp, College Station, TX, USA).

Sample Size

The primary outcome on which sample size is based is the percentage of children with persistent fever, illness, or decline (hospital, danger signs develop, or death) at day 8. It is assumed that about 5% of children in both groups will still be ill at day 8 (based on rates of ~3% and 8% in previous studies [16,24]) and that this percentage will be approximately equivalent between groups. To calculate sample size, the outcome rate (ill at day 8) in the universal follow-up group is set to 5%, and it is assumed that the (true) corresponding outcome percentage in the conditional follow-up group will be no more than 6%. For the purpose of concluding that the conditional follow-up is noninferior to the universal follow-up approach, the upper bound of a one-sided 95% CI around the absolute difference in outcome rate (conditional minus universal) must not exceed 4% (noninferiority margin), assuming a power of 80% and an alpha of 5%. A design effect of 3 is used to account for clustering at HEW and health facility levels, generating a total sample size of 4284 children, with 2142 in each arm. To compensate for 10% loss to follow-up at day 8 and an additional 5% loss between day 8 and day 15, a total of 4900 children will be enrolled. Enrollment will occur over a period of 1 year to account for seasonality of various causes of febrile illness, starting in December 2015 and is expected to be completed around December 2016.

Outcomes

All enrolled children will have a study visit in their home with an IE after 1 week to assess their clinical outcome. Children who have not recovered on day 8 will be re-assessed after 2 weeks, and those whose illness persists on day 15 will be re-assessed on day 29. In addition, all enrolled children will be followed-up via a phone call for vital status on day 28. Management of illness at any follow-up visit (ie, return to HEW on any day; return to HEW for universal day 3 visit; or day 8, 15, and 29 assessment) will follow established national IMNCI guidelines.

The primary outcome is treatment failure on day 8, defined as the proportion of children with unclassified fever who subsequently declined clinically (death, hospitalization, one or more danger signs or persistent fever).

Secondary outcomes include:

- Clinical presentation in those with unresolved illness at day 8 in each arm
- Treatment failure on day 15 and 29, defined as the proportion of children with unclassified fever who subsequently declined clinically (death, hospitalization, one or more danger signs or persistent fever)
- Percentage of children who present to the HEW for the follow-up visit on day 3 in the universal follow-up arm
- Percentage of children who spontaneously represent to HEW for persistence or worsening of symptoms in the conditional follow-up arm, and the timing of these visits
- Percentage of children receiving secondary treatment (antimicrobial medicines prescribed during visits to any providers after initial presentation to HEW) in each arm between enrollment and day 8
- Caregiver and HEW acceptability of universal and conditional follow-up recommendations

Data Collection

HEWs will collect data using an Open Data Kit (ODK) [25] data collection form on mobile phones. Data will include date of enrollment, child identifiers, and clinical indicators (fever/axillary temperature, cough, respiratory rate, diarrhea, and danger signs). The enrollment data will be synchronized with a server which is accessed by a data manager who will download enrollments on a daily basis and schedule follow-up visits for 6 IEs using an online Google calendar.

The IEs will be equipped with tablets programmed with 3 ODK data collection forms; one for the day 8 visit, one for any extra visits (on day 15 or 29), and one vital status form for day 29. The data that will be collected during the household follow-up visits on day 8, 15, and 29 will include clinical data for the children following the IMNCI algorithm (eg, fever/axillary temperature, cough, respiratory rate, diarrhea, mid-upper arm circumference (MUAC) measure, and danger signs), any secondary treatment (antimicrobial medicines prescribed during visits to any providers after initial presentation to HEWs), hospitalization, care-seeking history, and costs, as well as caregiver and household characteristics. For children who cannot be found at home at the time of the home visit, 2 more attempts will be made over the 2 following days. After this, the child

will be registered as a loss-to-follow-up for the primary outcome.

Moreover, 3 research assistants will enter data collected by HEWs for children who come back to the HEW spontaneously (universal and conditional arm) or on day 3 (universal arm) into an ODK sick child assessment form every 2 weeks.

A rigorous monitoring system will be implemented by the study team and will be part of the continuous quality assurance. The data manager will review forms submitted to the server daily and check for duplicates, completeness, and accuracy before storing them in the project database. Discrepancies, overdue follow-up visits, and other issues will be resolved by phone calls to the IEs and during weekly supervision meetings with field research staff. Biweekly field supervision visits to all HEWs will be carried out, and district HEW supervisors will be trained to monitor HEW trial activities during routine weekly group supervisions. A minimum of 10% of all enrolled cases and 50% of children with treatment failure will have a quality control re-assessment by a research assistant. The final dataset will be exported to STATA 13.

Semistructured interviews with HEWs and caregivers of children enrolled in the study will be conducted when a stable enrollment rate has been established in the study (assumed to be after 3 months). HEW interviews focus on what decentralization of health care mean to HEWs, how changes in follow-up recommendations are perceived, how they describe their roles in the communities, and how health system changes affect this role and their work situation. Caregiver interviews will aim to improve the understanding of caregiver perceptions of childhood illnesses, their perceived causes, and treatment options in the 3 woredas. Interview guides will capture how caregivers (assume primarily mothers) of sick children experience illness episodes and treatment seeking inside and outside the household. Focus will be on how caregivers describe the illness episode from the beginning to the recovery, current health status, actions that are taken or not taken when a young child gets fever, who is involved in the care of the child, and what their perceptions and experiences are with the recommended follow-up action they have been exposed to when visiting the HEW. Half of the HEWs and mothers to be interviewed will be from the study arm using the universal follow-up advice and the other half will follow the conditional follow-up recommendation. HEWs will be purposively selected, based on who has enrolled the highest number of children for the cRCT. Mothers of children enrolled in the study in the 2 weeks preceding the start of the qualitative data collection will be included using simple random sampling. A minimum of 1 week should have passed since the day 8 visit was completed to avoid study fatigue.

Interview guides will be separately prepared for the HEW and caregiver interview and translated into Amharic. In addition, 2 male, Amharic-speaking interviewers will conduct the HEW interviews and 1 additional male Amharic interviewer will be recruited for the caregiver interviews.

Data Analyses

The analysis of the primary outcome, treatment failure on day 8, will be done following a per-protocol approach. The baseline characteristics of the children and caregivers in both arms will be summarized using descriptive statistics. The difference between the percentage of the main study outcomes (persistent fever, persistent illness, or clinical deterioration [mortality, hospitalization, or danger signs], and these outcomes combined) of the 2 follow-up arms will be calculated. If the upper bound of the 95% CI of the difference in this percentage is less than 4%, the null hypothesis will be rejected; the conclusion will be that the conditional follow-up approach is not inferior to the standard approach. If there are imbalances in baseline characteristics across the 2 intervention arms, adjusted analyses of the difference in percentages will be conducted using multivariate logistic regression models.

The primary outcome will be compared between groups using generalized linear models with a binomial distribution and identity link using a robust variance estimator, treating cluster as a random effect. We will apply a conventional statistical noninferiority test using a CI approach using the exact binomial CI for the difference in overall treatment failure between intervention arms. The main analysis will be done using the per-protocol population (only including children for whom the primary outcome was collected on day 8±1 and whose caregiver reported receiving follow-up advice from the HEW that was aligned with the study arm), as is appropriate for noninferiority and equivalence studies, together with sensitivity analysis in the per-protocol and intention-to-treat populations [26]. Other descriptive statistics, such as cost of care seeking and compliance with the intervention protocol, will be compared between study arms using *t test* and chi-square statistics, respectively.

Qualitative interview transcripts from HEWs and caregivers will be coded and merged into sub-categories, categories, and themes using Nvivo (NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 11, 2015). HEW interviews will be analyzed first and its results reviewed after caregiver interviews are read. For the purpose of this study, caregiver interviews will be analyzed and compared with main themes identified in the HEW interviews.

Interim data analysis reports are produced on a quarterly basis to document cluster-specific cumulative enrollment rates, adherence to follow-up recommendations, and characteristics of the children and households enrolled. Deviance from the study protocol, or in expected enrollment rates, is acted on by providing refresher training and supervision to HEWs and research staff.

Ethics Approval and Consent to Participate

The trial protocol was approved by the SNNPR State Health Bureau on September 23, 2015 (ref P026-19/4511). In addition, approval was obtained from the district authorities and local leaders in the woredas where the study is being conducted. Co-investigators from Centers for Disease Control and Prevention participated under a nonengaged determination from their Human Research Protection Office.

Each caregiver whose child is eligible for enrollment is provided with a sheet containing information about the study in Amharic. Caregivers are given time to read the information sheet, and the

HEW verbally summarizes key points and answers any questions. Agreement to participate is indicated by signature or thumb print. The individual's right to refuse consent or to stop the interview at any time after consent has been given is preserved.

The project has a 3-person Data Monitoring Committee (DMC) with external members having expertise in child health, epidemiology, iCCM, and randomized controlled trials. The DMC is responsible for safeguarding the interests of study participants, assessing the safety of the intervention during the trial, and for monitoring the overall conduct of the study. The DMC provides recommendations about stopping or continuing the study and other aspects of trial implementation, using interim data analysis reports on cluster-specific enrollment rates, adherence to follow-up recommendations, and on characteristics of the children and households enrolled.

The DMC is advisory to the study Steering Committee, which comprises the lead study investigators, who are jointly responsible for the design, conduct, and analysis of the trial. The Steering Committee is responsible for promptly reviewing the DMC recommendations, to decide whether to continue or terminate the study, and to determine whether amendments to the protocol or changes in study conduct are required.

Results

The project was funded in 2015, and enrollment was completed in 2016. Data analysis is currently under way, and the first results are expected to be submitted for publication in 2018.

Discussion

Febrile illnesses are among the leading causes of deaths in children U5. There is limited evidence on the safest and most efficient approach to manage unclassified fevers at the community level, and current practice is not always in line with the recommended guidelines. This cluster randomized controlled noninferiority trial aims to address this question by comparing universal follow-up recommendations, which are currently recommended for community management of sick children by WHO, with conditional follow-up recommendations, which are currently the guidelines provided to HEWs in Ethiopia, for children with nonsevere, unclassified fever.

The main strength of this study is the embedding of a robust randomized controlled trial into a national program context. An additional strength was the multidisciplinary research team, which had strong involvement of local researchers and Ministry of Health staff, and which was advised by a data monitoring committee comprising global child health epidemiologists. This constellation enables the application of robust methods for both quantitative and qualitative evaluation, as well as high-quality implementation, while creating evidence with greater potential for direct policy influence.

A potential limitation of this study is the generalizability of the findings, given that caregivers' knowledge of the upcoming study visit could affect their care-seeking behavior. However, although the caregivers in both arms are informed that a research team member will come to their household in the next 4 weeks, they are not told which day they will expect the visit by the study team. Another possible limitation is that the qualitative interviews will all be done by men, whereas all the interviewees (HEWs and caregivers) are women. Although we attempted to recruit female qualitative research assistants, it was not possible to find women with the experience required, including fluency in the 3 local languages spoken in the region. To compensate for this, we will address this issue during interviews, as well as on pilot testing of the interview guides, to ensure that any gender-related issues will be prevented. This study, along with a sister study in Democratic Republic of Congo [27], is the only study designed to look at this critical policy issue. It therefore has high potential to contribute to the knowledge base by assessing and evaluating recommended practices for treating febrile children whose illness cannot be diagnosed at the community level using iCCM guidelines. Research outcomes from this study are relevant for both local and international policy makers, as they will provide an evaluation of current guidelines as well as information for the development of future World Health Organization guidelines.

This study is designed to directly influence policy and practice, especially for government-led implementation of iCCM in Ethiopia and other sub-Saharan African countries. Implementation has been carried out in close consultation with policy makers. During the early stages of the project, a communications and research uptake strategy was developed, which aims to increase the likelihood of the results being used to influence policy and practice by engaging with stakeholders throughout the research process. A sensitization workshop was conducted at the beginning of the project to ensure that stakeholders are involved in the technical aspects of the project from the beginning. HEWs were involved in the consultations throughout the study, and their opinions and experiences with the 2 follow-up recommendations, which were collected during the qualitative interviews, were discussed in depth in several of the dissemination events. An in-country technical advisor has agreed to support the team on this project by bridging the research results to planning and policy functions in the Federal Ministry of Health. Further anticipated communication outputs include a stakeholder report, a policy brief, a peer-reviewed publication of results, national- and regional-level dissemination meetings, and presentation in regional and international conferences. Results of this research will be shared with national decision makers, program implementers, HEWs, researchers, and other stakeholders to promote learning and inform potential modification of iCCM and the Integrated Management of Childhood Illness Guidelines.

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Authors' Contributions

JG, LS, and LB conceived the study; KK, TA, MP, JG, LS, and LB designed the study protocol; KK, AA, AH, and DG designed and implemented the interventions and accompanying materials; AH and AA managed the data; KK, TA, and MP will conduct the data analysis. KK coordinated the study and drafted the first version of the paper. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. GBD 2015 Child Mortality Collaborators. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016 Oct 08;388(10053):1725-1774 [FREE Full text] [doi: 10.1016/S0140-6736(16)31575-6] [Medline: 27733285]
2. United Nations. Sustainable development knowledge platform URL: https://sustainabledevelopment.un.org/sdgs [WebCite Cache ID 6wrUpKDgE]
3. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). 2017. Levels & Trends in Child Mortality: Report 2017, Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation URL: https://www.unicef.org/publications/files/Child_Mortality_Report_2017.pdf [WebCite Cache ID 6yFjqTXGt]
4. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet 2016 Dec 17;388(10063):3027-3035 [FREE Full text] [doi: 10.1016/S0140-6736(16)31593-8] [Medline: 27839855]
5. Källander K, Nsungwa-Sabiiti J, Peterson S. Symptom overlap for malaria and pneumonia--policy implications for home management strategies. Acta Trop 2004 Apr;90(2):211-214. [doi: 10.1016/j.actatropica.2003.11.013] [Medline: 15177148]
6. Young M, Wolfheim C, Marsh DR, Hammamy D. World health organization/United Nations children's fund joint statement on integrated community case management: an equity-focused strategy to improve access to essential treatment services for children. Am J Trop Med Hyg 2012 Nov;87(5 Suppl):6-10 [FREE Full text] [doi: 10.4269/ajtmh.2012.12-0221] [Medline: 23136272]
7. Amouzou A, Morris S, Moulton LH, Mukanga D. Assessing the impact of integrated community case management (iCCM) programs on child mortality: review of early results and lessons learned in sub-Saharan Africa. J Glob Health 2014 Dec;4(2):020411 [FREE Full text] [doi: 10.7189/jogh.04.020411] [Medline: 25520801]
8. Oliphant NP, Muñiz M, Guenther T, Diaz T, Laínez YB, Counihan H, et al. Multi-country analysis of routine data from integrated community case management (iCCM) programs in sub-Saharan Africa. J Glob Health 2014 Dec;4(2):020408 [FREE Full text] [doi: 10.7189/jogh.04.020408] [Medline: 25520798]
9. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). New York, USA & Geneva, Switzerland: United Nations Children's Fund, World Health Organization, The World Bank, United Nations, Department of Economic and Social Affairs, Population Division & United Nations Economic Commission for Latin America and the Caribbean, Population Division; 2015. Levels and trends in child mortality 2015 URL: http://www.who.int/maternal_child_adolescent/documents/levels_trends_child_mortality_2015/en/ [WebCite Cache ID 6yH6NoQIU]
10. Workie N, Ramana G. The World Bank. 2013. The health extension program in Ethiopia URL: https://openknowledge.worldbank.org/bitstream/handle/10986/13280/74963.pdf;sequence=1 [accessed 2018-03-29] [WebCite Cache ID 6yH6brmR8]
11. Ethiopia Ministry of Health (FDRE MoH). Addis Ababa, Ethiopia: FDRE MoH; 2007. Health Extension Program Profile URL: http://www.moh.gov.et/documents/20181/21665/Health+Extension+Program+in+Ethiopia.pdf/0c486437-71bf-485b-b614-7e720dc924b6 [WebCite Cache ID 6yTbLrBCw]
12. Ethiopian Federal Ministry of Health, iCCM Implementation Partners. 2013. 4.6 million children URL: https://www.unicef.org/ethiopia/iCCM_update_April_2014.pdf [WebCite Cache ID 6wrThkXIl]
13. Miller NP, Amouzou A, Tafesse M, Hazel E, Legesse H, Degefie T, et al. Integrated community case management of childhood illness in Ethiopia: implementation strength and quality of care. Am J Trop Med Hyg 2014 Aug;91(2):424-434 [FREE Full text] [doi: 10.4269/ajtmh.13-0751] [Medline: 24799369]

14. World Health Organization. Geneva, Switzerland: World Health Organization; 2009. Integrated management of childhood illness: caring for newborns and children in the community URL: http://apps.who.int/iris/bitstream/10665/44398/1/9789241548045_Manual_eng.pdf
15. Crump JA, Morrissey AB, Nicholson WL, Massung RF, Stoddard RA, Galloway RL, et al. Etiology of severe non-malaria febrile illness in Northern Tanzania: a prospective cohort study. PLoS Negl Trop Dis 2013;7(7):e2324 [FREE Full text] [doi: 10.1371/journal.pntd.0002324] [Medline: 23875053]
16. D'Acremont V, Kilowoko M, Kyungu E, Philipina S, Sangu W, Kahama-Maro J, et al. Beyond malaria--causes of fever in outpatient Tanzanian children. N Engl J Med 2014 Feb 27;370(9):809-817. [doi: 10.1056/NEJMoa1214482] [Medline: 24571753]
17. Dagan R, Sofer S, Phillip M, Shachak E. Ambulatory care of febrile infants younger than 2 months of age classified as being at low risk for having serious bacterial infections. J Pediatr 1988 Mar;112(3):355-360. [Medline: 3346773]
18. McMorrow M, Ahmed S, Lyaruu P, Maganga M, Lyimo T, Abdulla S. Randomized, controlled trial of treatment of febrile children with a negative malaria rapid diagnostic test with Artemether-Lumefantrine vs. no antimalarial in Bagamoyo district, Tanzania. Am J Trop Med Hyg 2012;87(5):252-253. [doi: 10.4269/ajtmh.2012.87.226]
19. Saravu K, Rishikesh K, Kamath A. Determinants of mortality, intensive care requirement and prolonged hospitalization in malaria - a tertiary care hospital based cohort study from South-Western India. Malar J 2014 Sep 19;13:370 [FREE Full text] [doi: 10.1186/1475-2875-13-370] [Medline: 25233836]
20. Källander K, Hildenwall H, Waiswa P, Galiwango E, Peterson S, Pariyo G. Delayed care seeking for fatal pneumonia in children aged under five years in Uganda: a case-series study. Bull World Health Organ 2008 May;86(5):332-338 [FREE Full text] [Medline: 18545734]
21. Rutebemberwa E, Kallander K, Tomson G, Peterson S, Pariyo G. Determinants of delay in care-seeking for febrile children in eastern Uganda. Trop Med Int Health 2009 Apr;14(4):472-479 [FREE Full text] [doi: 10.1111/j.1365-3156.2009.02237.x] [Medline: 19222823]
22. The Ethiopian Health and Nutrition Research Institute & partners. 2012. Ethiopia national malaria indicator survey 2011 URL: https://www.unicef.org/ethiopia/ET_MIS_2011_Report.pdf [WebCite Cache ID 6yH7e9UlM]
23. Moulton LH. Covariate-based constrained randomization of group-randomized trials. Clin Trials 2004;1(3):297-305. [doi: 10.1191/1740774504cn024oa] [Medline: 16279255]
24. Hamer DH, Brooks ET, Semrau K, Pilingana P, MacLeod WB, Siazeele K, et al. Quality and safety of integrated community case management of malaria using rapid diagnostic tests and pneumonia by community health workers. Pathog Glob Health 2012 Mar;106(1):32-39 [FREE Full text] [doi: 10.1179/1364859411Y.0000000042] [Medline: 22595272]
25. Open Data Kit. Open Data Kit - Magnifying human resources through technology URL: https://opendatakit.org/ [WebCite Cache ID 6wrSJTDMj]
26. White IR, Carpenter J, Horton NJ. Including all individuals is not enough: lessons for intention-to-treat analysis. Clinical trials 2012;9(4):396-407. [doi: 10.1177/1740774512450098] [Medline: 22752633]
27. van Boetzelaer E, Ho L, Gutman J, Steinhardt L, Wittcoff A, Barbera Y. Universal versus conditional three-day follow up visit for children with uncomplicated fever at the community level: design of a cluster-randomized, community-based, non-inferiority trial in Tanganyika, Democratic Republic of Congo. BMC Pediatr 2017;17(1):36. [doi: 10.1186/s12887-017-0792-1] [Medline: 28122542]

Abbreviations

CHW: community health workers
DMC: Data Monitoring Committee
HEW: health extension workers
iCCM: integrated community case management
IE: independent evaluator
IMNCI: integrated management of neonatal and childhood illness
mRDT: malaria Rapid Diagnostic Test
ODK: Open Data Kit
SNNPR: Southern Nations, Nationalities and People's Region

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Protocol

An Exercise Intervention to Unravel the Mechanisms Underlying Insulin Resistance in a Cohort of Black South African Women: Protocol for a Randomized Controlled Trial and Baseline Characteristics of Participants

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Abstract

Background: The pathogenesis of type 2 diabetes (T2D) in black African women is complex and differs from that in their white counterparts. However, earlier studies have been cross-sectional and provide little insight into the causal pathways. Exercise training is consistently used as a model to examine the mechanisms underlying insulin resistance and risk for T2D.

Objective: The objective of the study was to examine the mechanisms underlying the changes in insulin sensitivity and secretion in response to a 12-week exercise intervention in obese black South African (SA) women.

Methods: A total of 45 obese (body mass index, BMI: 30-40 kg/m^2) black SA women were randomized into a control (n=22) or experimental (exercise; n=23) group. The exercise group completed 12 weeks of supervised combined aerobic and resistance training (40-60 min, 4 days/week), while the control group maintained their typical physical activity patterns, and both groups were requested not to change their dietary patterns. Before and following the 12-week intervention period, insulin sensitivity and secretion (frequently sampled intravenous glucose tolerance test) and its primary and secondary determinants were measured. Dietary intake, sleep quality and quantity, physical activity, and sedentary behaviors were measured every 4 weeks.

Results: The final sample included 20 exercise and 15 control participants. Baseline sociodemographics, cardiorespiratory fitness, anthropometry, cardiometabolic risk factors, physical activity, and diet did not differ between the groups (P>.05).

Conclusions: The study describes a research protocol for an exercise intervention to understand the mechanisms underlying insulin sensitivity and secretion in obese black SA women and aims to identify causal pathways underlying the high prevalence of insulin resistance and risk for T2D in black SA women, targeting specific areas for therapeutic intervention.

Trial Registration: Pan African Clinical Trial Registry PACTR201711002789113; http://www.pactr.org/ATMWeb/appmanager/atm/atmregistry?_nfpb=true&_pageLabel=portals_app_atmregistry_portal_page_13 (Archived by WebCite at http://www.webcitation.org/6xLEFqKr0)

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KEYWORDS

diabetes mellitus, type 2; insulin resistance; body fat distribution; adipose tissue; skeletal muscle; gastrointestinal microbiome; exercise; fatty liver; inflammation; energy metabolism; cardiorespiratory fitness; lipids; metabolomics; fatty acids; diet records; mitochondria; ectopic fat

Introduction

Background

Type 2 diabetes (T2D) is a significant contributor to morbidity and mortality worldwide [1]. Globally, sub-Saharan Africa has the highest projected rate of increase in T2D over the next 25 years, increasing by 2.5-fold from 14.2 million in 2015 to 34.2 million by 2040 [1]. T2D and its associated morbidity and mortality rates are more prevalent in populations of black African origin than white populations [2-4]. Within South Africa (SA), the prevalence of T2D has increased significantly over the past 20 years, particularly in black African urban-dwelling populations [5]. Higher prevalence rates in SA are found in women (14.7%) compared with men (11.3%) [5]. This high T2D rate is compounded by the high prevalence of obesity and insulin resistance in black women [6-8]. Insulin resistance in black populations is associated with hyperinsulinemia, as a result of greater insulin secretion and reduced hepatic insulin clearance [7-9]. However, with increasing age, insulin secretion in relation to insulin sensitivity decreases in black women and is associated with impaired glucose tolerance and T2D [10].

The pathogenesis of insulin resistance in black women is complex and differs from that in their white counterparts [11]. Despite greater insulin resistance, black women have less visceral adipose tissue (VAT) but more peripheral (gluteal-femoral) subcutaneous adipose tissue (SAT) deposition [12-14]. This paradox may be explained, in part, by differences in adipose tissue biology [11]. Compared with white women, SAT of black women is hypertrophic, has a reduced adipogenic capacity [15], a higher inflammatory profile [16], less vascularization, and increased fibrosis [17]. These findings are suggestive of pathological adipose tissue expansion, which is typically associated with ectopic fat deposition and insulin resistance [18]. However, we found that obese black women accumulated less hepatic fat than their white counterparts [19], which corresponds with their lower VAT levels [12], but had similar intra- and intermyocellular lipid content of the soleus muscle [19]. Furthermore, the association between ectopic fat and insulin sensitivity was more robust in black as compared with white women [19]. These distinct obesity-related phenotypic differences may differentially impact the risk for insulin resistance and T2D in black and white women. However, these studies were cross-sectional and provide little insights into the causal pathways involved.

Exercise training, via its effects on multiple organs and systems, reduces insulin resistance and the risk of T2D (for reviews [20-22]). Recent studies have suggested an important crosstalk between skeletal muscle, liver, adipose tissue and the pancreas [23-25], which is altered in response to exercise training [23]. The effects of exercise training on insulin sensitivity are primarily through insulin action in skeletal muscle [26], which involves many mechanisms, including changes in the insulin signaling, inflammation, reactive oxygen species (ROS), metabolic flexibility, mitochondrial biogenesis, and ectopic fat accumulation. Within adipose tissue, exercise training decreases the obesity-induced dysregulated expression of adipokines, adipocyte size, ROS and inflammation, and increases vasculature [27]. In addition, the importance of the gastrointestinal microbiome for diabetes risk has recently been recognized [28] and is responsive to exercise [29,30]. Indeed, advances in omics technologies have improved our understanding of systems biology in diseased states and can be used to identify novel pathways underlying insulin resistance and T2D risk.

Although, we can identify biological and physiological correlates of insulin resistance in black women, these may merely reflect adaptations to environmental and lifestyle factors. There are marked ethnic differences in socioeconomic status, dietary intake, and physical activity between black and white SA women [12]. In terms of physical activity, black women accumulate activity through walking for transport (typically performed at a low intensity), while participation in leisure activities that are generally performed at moderate-to-high intensities is uncommon [12,31]. Accordingly, black women have very low cardiorespiratory fitness levels, which associates with their high levels of obesity and insulin resistance [32].

Overall, exercise training improves cardiorespiratory fitness and reduces cardiometabolic risk factors associated with the development of T2D. Accordingly, exercise training is consistently used as a model to examine putative mechanisms underlying insulin resistance and risk for T2D. To our knowledge, there are no studies that have examined the effect of exercise training on insulin resistance in obese black SA women who are at high risk for T2D. Therefore, the primary

purpose of this research study is to gain a better understanding of the causal mechanisms underlying insulin resistance and risk for T2D in black SA women, using exercise as an intervention.

Aims and Objectives

The aim of the study was to identify mechanisms underlying the changes in insulin sensitivity and secretion in response to a 12-week aerobic exercise intervention in obese black SA women.

The objectives of the study were as follows:

1. to measure changes in insulin sensitivity and secretion (primary outcomes) in response to the 12-week intervention compared with the nonexercise control group
2. to measure changes in potential primary and secondary determinants (secondary outcomes) of insulin sensitivity and secretion
3. to examine the associations between changes in insulin sensitivity and secretion and changes in the primary and secondary determinants

Primary determinants were as follows:

- cardiorespiratory fitness
- body composition and body fat distribution
- blood pressure
- lipid profile, including high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol subclasses and HDL functionality
- ectopic fat deposition (skeletal muscle, liver, and pancreas)
- skeletal muscle expression of genes and proteins involved in insulin signaling, oxidative capacity, and mitochondrial biogenesis
- skeletal muscle and serum metabolomics and lipidomic profile
- gluteal and abdominal subcutaneous adipose tissue expression of genes and proteins involved in inflammation, insulin signaling, oxidative stress, vascularization, adipogenesis, and lipid metabolism
- circulating inflammatory cytokine, myokine, and adipokine concentrations
- skeletal muscle and adipose tissue mitochondrial respiration and hydrogen peroxide production;
- gastrointestinal microbiota

Secondary determinants were as follows:

- energy expenditure and substrate metabolism at rest and during exercise
- habitual physical activity and sedentary behavior patterns
- dietary intake, red blood cell, and adipose tissue fatty acid composition
- sleep quantity and quality
- psychological well-being
- perceptions of body image, healthy behaviors, and the exercise intervention

Methods

Study Design

In this randomized controlled research study, 45 obese sedentary black SA women were block (2-4 participants) randomized (Microsoft Office, Excel, 2013) into control or experimental (exercise) groups (Figure 1). Block randomization was performed by the project manager after participants completed preintervention testing to ensure that investigators performing the testing were blinded to group allocation. The exercise group completed 12 weeks of supervised combined aerobic and resistance training (40-60 min, 4 days/week) but maintained their usual dietary behaviors. The control group were instructed to continue their habitual physical activity and dietary behaviors and to refrain from initiating any exercise programs. Before and following the 12-week intervention period (exercise or control), insulin sensitivity and secretion (primary outcome), as well as the proposed determinants of insulin sensitivity and secretion (secondary outcomes) were measured. In addition, dietary intake, sleep quality and quantity, physical activity, and sedentary behavior were monitored for a minimum of 4 days every 4 weeks.

This study was approved by the Human Research Ethics Committee at the University of Cape Town (HREC REF:054/2015). The study was performed in accordance with the principles of the Declaration of Helsinki (1964, amended last in Fortaleza Brazil, 2013), ICH Good Clinical Practice (GCP), and the laws of SA. Participants provided written informed consent before participation in the screening and the research study. Participant recruitment and testing procedures occurred over an 18-month period, between July 2015 and December 2016. Sample and data analysis began in January 2017 and are currently ongoing.

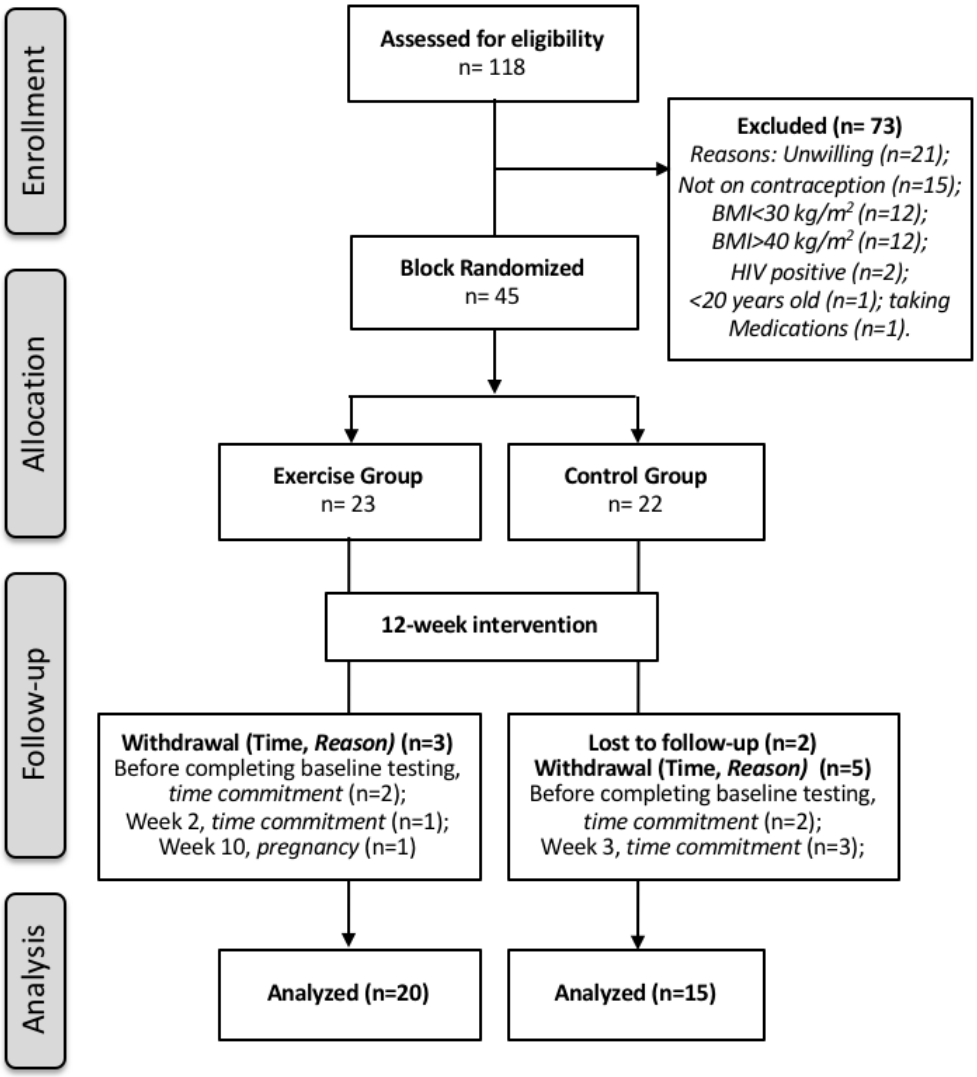
Participants

Participants were recruited via advertisements in local papers and the distribution of flyers at local churches, universities and community groups in Cape Town, SA. Participants were included if they met the following inclusion criteria: (1) black SA women (based on the Xhosa ancestry of both parents) between the ages of 20 and 35 years; (2) obese (body mass index (BMI) 30-40 kg/m^2); (3) weight stable (weight not changed more than 5 kg or no change in clothes size over the past 6 months); (4) sedentary (not participating in exercise training (>1 session of >20 min per week) within the last 12 months); (5) on injectable contraceptive (depot medroxyprogesterone acetate, 400 mg) for a minimum of 2 months; (6) no known metabolic or inflammatory diseases; (7) no hypertension (≥140/90 mmHg), diabetes (random plasma glucose concentration of >11.1 mmoL/L, and/or hemoglobin A_{1c} (HbA_{1c}) result >6.5% A_{1c}), HIV, or anemia (hemoglobin (Hb) <12 g/dL); (8) not taking any medications; (9) nonsmokers; (10) not currently pregnant or lactating; (11) no orthopedic or medical problems that may prevent exercise participation; and (12) no surgical procedures within the last 6 months.

Screening

Before participation in the trial, volunteers completed screening procedures. Weight and height were measured to calculate BMI. Blood pressure was measured 3 times at 1-min intervals using an automated blood pressure monitor (Omron 711, Omron Health Care, Hamburg, Germany). A venous blood sample was drawn for the determination of glucose, Hb and $HbA1_c$. HIV screening was performed and participants were excluded based on a confirmed positive test or if they refused to complete the test.

Figure 1. Consort diagram outlining participant enrollment, allocation, follow-up, and analysis. BMI: body mass index.



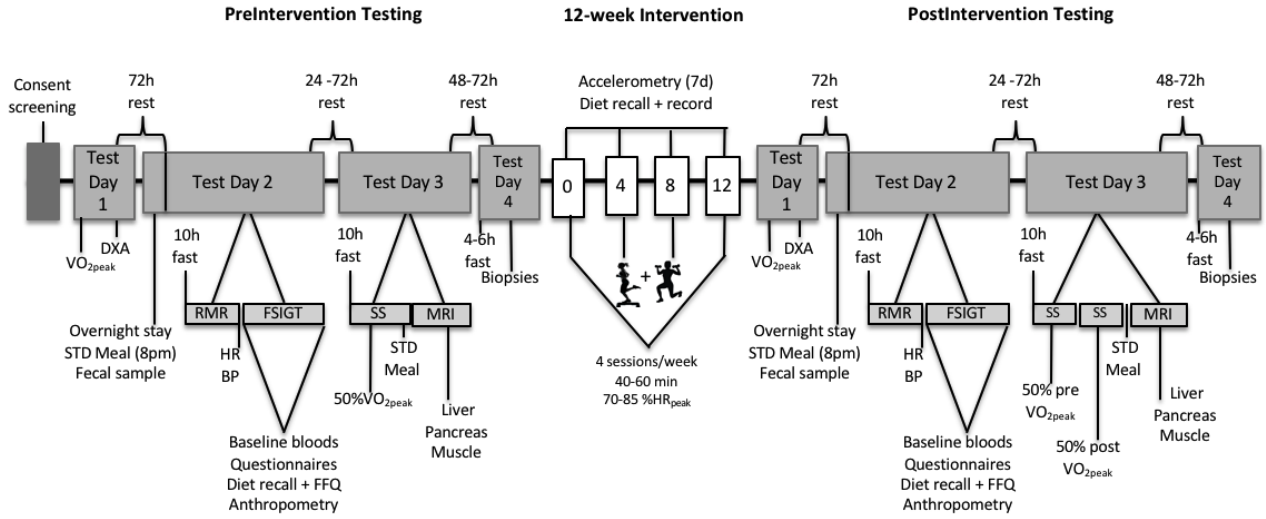
Participants received pre- and posttest counseling from a trained counselor, and a referral was made to appropriate HIV clinics for those participants who were found to be HIV-positive. Participants completed the physical activity readiness questionnaire (PARQ) [33] and were excluded if they answered "yes" to any of the questions. In addition, the participants completed a questionnaire about their exercise training, contraceptive use, ancestry, smoking status and history, medication use, and clinical conditions.

Overview of Testing Procedures

The study design and stepwise stages of the protocol are described in Figure 2. Before and following the 12-week intervention, participants completed 4 data collection sessions. At the first session, participants completed a cardiorespiratory fitness test of peak oxygen consumption (VO_{2peak}), and body composition was measured by dual energy x-ray absorptiometry (DXA). At least 72 hours later, the participants spent a night at the laboratory where they were given a standardized evening meal at 8 PM and then required to fast overnight (10 hours). During the evening or early morning, participants were requested to provide a fecal sample. At 6 AM, the participants completed measures of resting metabolic rate (RMR) and substrate metabolism, and resting heart rate and blood pressure were measured. At 7 AM, fasting blood samples were collected and participants underwent a frequently sampled intravenous glucose tolerance test (FSIGT). During the FSIGT, the field worker administered the questionnaires, and the participants completed a 24-hour dietary recall and food frequency questionnaire with a Health Professions Council of South Africa registered

dietician. The participants were then requested to complete a 3-day food diary. On a separate day, after a 10- to 12-hour overnight fast, participants completed steady-state exercise testing at 50% VO_{2peak}. Thereafter, participants were provided a standardized meal and underwent a magnetic resonance imaging (MRI) scan. On the fourth day of data collection, and after 4 to 6 hours of fasting and 48 hours of rest, participants underwent skeletal muscle and abdominal and gluteal SAT biopsies. Accelerometers (ActiGraph and ActivPAL) were attached to the participants and worn for 7 days.

Figure 2. Schematic overview of testing timelines and procedures. VO2peak: peak oxygen consumption; STD: standard; DXA: dual-energy absorptiometry x-ray; RMR: resting metabolic rate, FSIGT: frequently sampled intravenous tolerance test; HR: heart rate; BP: blood pressure; FFQ: food frequency questionnaire; MRI: magnetic resonance imagery; SS: steady state treadmill test; %HRpeak: percent of peak HR.



Every 4 weeks following the start of the intervention, dietary intake (3-day dietary recall), physical activity and sleep quality and quantity (ActiGraph), and sedentary behavior (ActivPAL) were monitored. Following completion of the intervention, a subsample of women were invited to participate in focus group discussions and key informant interviews. Due to the large time commitments and travel requirements, participants were reimbursed at an hourly rate based on recommendations from the Health Sciences Human Research Ethics Committee of the University of Cape Town.

12-Week Exercise/Control Intervention

The exercise intervention consisted of 12-weeks of supervised aerobic and resistance training at a moderate-vigorous intensity for 40 to 60 min, 4 days per week by a trained facilitator. The exercise intervention was structured based on the results of a focus group study undertaken in the same community [34]. Exercises included cardiovascular exercises in the form of aerobic dance, running, skipping, and stepping that were performed at a moderate-vigorous intensity (75%-80% peak heart rate, HR_{peak}). Resistance exercises included the participants using their own body weight and progressed to the use of equipment (eg bands and free weights). These exercises included squats, lunges, bicep curls, push-ups and shoulder press with a prescribed intensity of 60% to 70% HR_{peak}. Attendance was recorded at each training session, and a heart rate monitor (Polar A300, Kempele, Finland) was worn by participants to ensure the prescribed exercise intensity was maintained throughout the 12-week period. Similarly, the respective resistance exercises were altered to ensure progression and to maintain the required intensity throughout the 12-week intervention. Training dose for the exercise group is calculated as the total number of sessions attended multiplied by the average percent of HR_{peak} attained over the 12-week period.

The control group was instructed to maintain their normal daily physical activity patterns, and not start any exercise training, which was verified through monthly monitoring using accelerometry. Following posttesting, the control participants were given the opportunity to participate in the 12-week exercise program, for which they were also reimbursed for their time and travel costs.

Pre- and Postintervention Testing

Sociodemographic and Basic Health Information

The participants completed a demographic questionnaire that included measures of socioeconomic status (on the basis of factors such as asset index, education, housing and housing density, employment, and income) [35], family history of disease, personal health, reproductive history, supplement use, body image [36], alcohol use, and household food security [37]. In addition, measures of psychological well-being, including the Pittsburgh Sleep Quality Index [38], Beck Depression Inventory [39], the Kessler 10 [40], and the General Self-Efficacy [41] Questionnaires, were administered.

Body Composition Assessment

Basic anthropometry, including weight and height, in lightweight clothing without shoes, as well as waist circumference at the level of umbilicus, and hip circumference at the largest protrusion of the buttocks, were measured to the nearest 0.1 cm. Whole body composition, including fat mass and fat-free soft tissue mass (FFSTM), were measured by DXA (Discovery-W, software version 12.7.3.7; Hologic, Bedford, MA) according to standard procedures, with a coefficient of variation of 0.7%

for FFSTM and 1.67% for fat mass. Subtotal (excluding the head) fat and FFSTM were used for all analyses. Regional body fat distribution, including arm, leg, trunk, gynoid, and android fat mass, was characterized as previously described [42] and abdominal VAT and SAT areas estimated [43].

Cardiorespiratory Fitness

To determine cardiorespiratory fitness, VO_{2peak} was measured using a treadmill-based (C, Quasar LE500CE, HP Cosmos, Nussdorf-Traunstein, Germany) graded exercise test. Participants were familiarized to the equipment before beginning the test, and heart rate was monitored throughout for the determination of HR_{peak} (Polar A300, Kempele, Finland). The initial 6 min of the test was designed based on a modified Bruce protocol to obtain three stages of steady state metabolism (see steady state protocol below) and the subsequent minutes were designed to obtain VO_{2peak} using a ramp protocol, adapted from Takagi et al [44]. Participants began at 3 km/hour at a 2% gradient for 2 min. The gradient increased by 2% for a further two 2-min segments. The following stages increased by 2% gradient every minute until 16%. Following this there was an alternate increase in speed (0.5 km/hour) and gradient (1%) until volitional exhaustion. This walking cardiorespiratory fitness test was designed for participants who were sedentary and are not familiar with gym-based equipment.

Pulmonary gas exchange was measured by determining O_2 and CO_2 concentrations and ventilation to calculate VO_2 consumption using a metabolic gas analysis system (CPET, Cosmed, Rome Italy). Before each test, the gas meter was calibrated with a Hans Rudolph 3-liter syringe (Vacumed, Ventura, CA) and analyzers calibrated using standard gas mixtures of oxygen (26% O_2 with the balance nitrogen) and carbon dioxide (4% CO_2, 16% O_2, and the balance nitrogen) (BOC Special Gas, Afrox Cape Town, South Africa). Ethanol burns for equipment calibration were conducted every 4 weeks (mean variance<2%).

Energy Expenditure and Substrate Metabolism During Submaximal Steady-State Exercise

Following an overnight fast (10-12 hours) respiratory exchange (Cosmed Quark CPET, Rome, Italy) was measured during 15 min of steady-state treadmill walking at 50% VO_{2peak}, a level shown to be consistent with maximal fat oxidation [45,46]. Measures of energy expenditure and substrate metabolism were averaged over the last 10 min of the test. This test (50% pre-intervention VO_{2peak}) was repeated at posttesting, which reflects the same absolute intensity. Participants then rested for 10 min and completed a second steady-state exercise test, at 50% of the postintervention VO_{2peak}, which reflects the same relative exercise intensity.

Resting Metabolic Rate, Substrate Metabolism, and Blood Pressure

Participants slept overnight at the laboratory and were given a standardized evening meal at 8 PM (Energy: 2,456 kJ, 21 g protein (14% energy), 49 g carbohydrate (33% energy), and 32 g fat (48% energy). At 6 AM (following a 10-hour overnight fast), the participants rested in the supine position, in a quiet room (21°C -24°C), and were instructed to remain awake, still, and quiet. Basal respiratory exchange was measured for 40 min, using the ventilated hood technique (CPET, Cosmed, Rome Italy). The first 10 min were excluded to ensure measures of steady state respiratory gas exchange and the average of the last 30 min was used to determine resting measures. Weir [47] and Frayn [48] equations were used to calculate RMR and total rates of fat and carbohydrate oxidation, respectively. During the respective 40 min, the lowest recorded heart rate was recorded and reported as the resting heart rate.

Fasting Blood Samples and Frequently Sampled Intravenous Glucose Tolerance Test (FSIGT)

Following the RMR measures, fasting blood samples were drawn, and an FSIGT was performed. A cannula was inserted into a vein of each arm. One arm was used for intravenous glucose and insulin infusions, and the other arm was heated and used for blood sampling. Fasting blood samples were drawn for the determination of adipokines, myokines, inflammatory markers and cytokines, lipid profiles and HDL- and LDL-cholesterol subtypes and HDL functionality, and red blood cell fatty acid composition, metabolomic and lipidomic analysis.

For the FSIGT, further 2 baseline samples were collected at −5 and −1 min before a bolus of glucose (50% dextrose; 11.4 g/m^2 body surface area) was infused intravenously over 60 seconds beginning at time 0. At 20 min, human insulin (0.02 U/kg; NovoRapid, Novo Nordisk) was infused over 5 min at a constant rate (HK400 Hawkmed Syringe Pump, Shenzhen Hawk Medical Instrument Co., Shenzhen, China). Samples for determination of plasma glucose and serum insulin and c-peptide concentrations were drawn at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 220, and 240 min.

Fasting blood samples were collected into EDTA, lithium heparin, fluoride oxalate, and SST tubes. Samples in SST tubes clotted for 30 min at room temperature, while the remaining samples were placed on ice before centrifugation. Samples were centrifuged at 3000 rpm for 10 min at 4°C. Plasma for glucose analysis was stored at −20°C, while the remaining serum and plasma was stored at −80°C. Red blood cells collected from EDTA tubes were washed by 2 cycles of sequential centrifugation at 1000 rpm and a final cycle of centrifugation at 3000 rpm for 10 min. Between cycles, saline (0.9% NaCl in distilled water) was used for resuspension and washing. Red blood cells were then stored at −80°C until the analysis.

Glucose and insulin concentrations from the FSIGT will be used to calculate the insulin sensitivity index (S_I) using Bergman's minimal model of glucose kinetics [49]. Glucose and c-peptide data will also be used in a two-compartment minimal model of C-peptide secretion and kinetics to calculate insulin secretion rate (ISR) using WinSAAM (version 3.3.0). ISR will then be used in a one-compartment insulin minimal model to determine insulin hepatic extraction index [50].

Fecal Sample Collection

Participants provided fecal samples for the analysis of gastrointestinal microbial composition using the Easy Sampler stool collection kit (EasySampler, GP medical devices, Denmark), as per the manufacturer's instructions. The samples were immediately stored at −80°C, until subsequent analysis.

Ectopic Lipid Content

After the steady-state exercise test, the participants consumed a standardized meal (Energy: 2553 kJ; protein: 20.9 g; carbohydrates: 83.0 g; fat: 22.2 g). Hepatic, pancreatic, and skeletal muscle (tibialis anterior and soleus) lipid content were then measured on a 3-Tesla Skyra wholebody human MRI scanner (Siemens, Erlangen). Sequence protocols for fat assessments included MRI using two-point Dixon fat-water separation (Dixon-VIBE) and T1-VIBE with and without fat saturation, and finally, MRS with PRESS technique.

Postprocessing of MRI data for Dixon and T1-VIBE was performed in MATLAB R2009a (MathWorks Inc, Natick, MA, USA). The MRS voxel locations were coregistered to T1-VIBE images (with and without fat suppression) and Dixon images (fat and water images) to compute the fat fraction. The signal fat-fraction was calculated as the signal without fat suppression minus signal with fat suppression divided by signal without fat suppression for the T1-VIBE method [51]. The signal fat fraction obtained by the Dixon method was calculated by combining images obtained from the water and fat phases, as the fat fraction divided by the fat plus water fractions [52]. MRS data were quantified using LCModel (version 6.3-1J) **.** The MRS method was used to decompose the lipid signals into several components, each one representing different parts of the lipid metabolite molecules. The lipid signals were reported relative to the water signal.

Skeletal Muscle and Adipose Tissue Biopsies

After a 4- to 6- hour fast and at least 48 hours after exercise, fat and muscle samples were collected. Fat samples were obtained from the gluteal and abdominal SAT depots using a mini-liposuction technique [16]. After local anesthesia with Lignocaine hydrochloride (2%, Intramed, Port Elizabeth, South Africa), a small incision was made into the region of interest and 200 mL of normal saline with 20 mL 2% Lignocaine (Intramed) was infused using an infiltration cannula (Lamis 14 ga x 15 cm, Byron Medical Inc., Tucson, AZ, USA). An aspiration cannula (Coleman, 12 ga x 15 cm, Byron Medical Inc.) attached to a 10-mL syringe was used to aspirate fat. Using this procedure, abdominal samples were obtained from directly above the umbilicus, and gluteal samples were obtained from the right upper outer quadrant. Approximately 2 cm^3 to 3 cm^3 of fat was extracted from each site and washed 3 times with normal saline or until no blood was visible. A subsample of the adipose tissue was placed in ice-cold BIOPS for immediate analysis of mitochondrial respiration. The remaining adipose samples were placed into vials and frozen immediately in liquid nitrogen (N_2) and stored at −80°C for the analysis of gene and protein expression, and fatty acid composition. After local anesthesia (2%, Intramed), a skeletal muscle biopsy was taken from the *M vastus lateralis* muscle using a 5-mm Bergstrom needle according to the needle biopsy technique of Bergstrom [53]. A subsample was placed in ice-cold BIOPS, for immediate analysis of mitochondrial respiration. The remaining samples were immediately frozen in liquid N_2 and stored at −80°C for subsequent analysis of gene and protein expression, as well as metabolomics and lipidomics.

Monthly Monitoring

Physical Activity, Sedentary Behavior, and Sleep

Physical activity and sleep quality and quantity were measured using accelerometry (ActiGraph GTX3+, ActiGraph LLC, Pensacola, Florida), and sedentary behavior was measured using activPAL (activPAL3c, PAL Technologies Ltd, Glasgow, UK) at preintervention, week 4, week 8, and postintervention. The ActiGraph was initialized to record data in 60-second epochs and was set to measure motion in all 3 axes, with the inclinometer function activated. The ActiGraph was worn on the right hip with a lightweight belt, and participants were instructed to wear it for 24 hours a day over a 7-day period, except when swimming, bathing, and showering. Participants were instructed to complete a sleep diary to capture awake and sleep times. Physical activity and sleep data were captured and analyzed using the ActiLife Software Version 6 (ActiLife software; Pensacola, FL, USA). A minimum of 4 days of wear time, with 600 min per day of wake time was required for data analysis. The 4 days of wear needed to be inclusive of 3 weekdays and 1 weekend day. For the exercise group, at least one of the weekdays needed to be an "exercise day." Nonwear time was defined as 60 continuous minutes of no counts (zeros) [54]. Vector magnitude cut-points were used for analysis [55,56]. The vector magnitude represents the summed value of all 3 axes measured from the ActiGraph, calculated as the square root of the total sum of each axis, squared ($X^2+Y^2+Z^2$), then square rooted [57]. Counts/minute between 200 and 2689 represents light intensity physical activity, 2690 to 6166 represents moderate intensity physical activity, 6167 to 9642 represents hard intensity physical activity, and >9643 counts per minute represents very hard intensity physical activity. Data were analyzed for any physical activity occurring in 1-min and 10-min bouts/intervals. Within each 10-min bout, 1- or 2-min of "dropped" counts were allowed, thereby excluding bouts of activity where a drop-in count is greater than 2 min (within the 10-min period) occurred. Sleep data were analyzed for sleep latency, total sleep time, wake after sleep onset, and sleep efficiency. Participants completed a sleep diary that was used to mark wake and sleep hours, which was further verified based on movement measured by the activPAL.

The activPAL was attached to the midanterior right thigh using a waterproof sleeve and dressing and worn concurrently with the ActiGraph, without removal of the device, even during bathing or swimming. All data were downloaded using the activPAL software (PAL Technologies, version 7.2.32, Glasgow, UK), and event files were used to create second-level files to show time spent in sitting (or lying), standing, stepping, sit-to-stand transition, and stand-to-sit transition.

Dietary Intake

At the same time points as the physical activity data collection, dietary intake was estimated using a 24-hour recall and a 3-day dietary record, including 2 weekdays and 1 weekend day. In addition, a food frequency questionnaire was administered before and following the intervention. Nutrient intake and food group analysis were calculated using the South African Food Composition Database System (SAFOOD, the South African Food Composition Database, South African Medical Research Council, Cape Town, South Africa).

Perceptions of the Exercise Intervention

Focus group discussions (FGDs) and in-depth interviews were used to explore the perceptions participants had of the exercise intervention. A multiple-category qualitative research design was applied in this study [58]. This type of design includes conducting focus groups with different types of participants either sequentially or simultaneously [58]. This approach ensures a comparison from one group to another within a category and/or from one category to another category [58].

The focus group interview schedule included questions such as "What are some of the things that influenced your attendance to the exercise sessions?", whereas the in-depth interviews included 1 main open ended question aimed at obtaining the participants' experience of the exercise sessions (Multimedia Appendix 1). The latter were conducted after the FGD and participants who were the most vocal during the group discussions were purposively selected for the in-depth interviews.

Four FGDs were conducted (3-5 participants per group), including exercise participants, and control participants who had chosen to participate in the exercise sessions upon completion of the 12-week intervention. The group discussions were moderated by a trained facilitator, fluent in isiXhosa, which is the language predominantly spoken by the participants. The audio recording of the FGDs was translated and transcribed by a trained professional. Immediately after completion of the FGDs, the researcher and moderator identified participants to be invited to participate in the in-depth interviews. A total of 5 in-depth interviews were conducted . Thematic analysis was used to determine the salient themes that emerged during the FGDs using Atlas.ti Qualitative Data Analysis Software (Scientific Software Development GmbH, Berlin, Germany) [59].

Biochemical Analysis

Glucose, Insulin, C-Peptide, and Lipid Profile

Plasma glucose and serum lipids concentrations were determined using a colorimetric assay (Randox, Gauteng, South Africa) and serum insulin, C-peptide were measured using immunochemiluminometric assays (IMMULITE 1000 immunoassay system, Siemens Healthcare, Midrand, South Africa).

Serum Inflammatory and Oxidative Stress Markers

Inflammatory cytokines, including interleukin (IL)6, IL1R, IL8, IL10, monocyte chemotactic protein (MCP)1, IL15, interferon (IFN) gamma, and tumor necrosis factor (TNF) alpha, were measured using Milliplex MAP MAG Human Cytokine kit (Merck, Johannesburg, South Africa) and xMAP technology (Luminex, Austin, Texas) according to the manufacturer's instruction. Serum concentrations of leptin and high molecular weight (HMW) adiponectin (EMD Millipore Corporation, St Charles, Missouri, USA) were analyzed using commercially available ELISA kits according to the manufacturer's protocols. High-sensitive C-reactive protein (CRP) was measured by an immunochemiluminometric assay (IMMULITE 1000 immunoassay system, Siemens Healthcare, Midrand, South Africa). Lipid peroxidation was assessed by measuring the concentration of thiobarbituric acid reactive substance (TBARS); antioxidant capacity was assessed by measuring oxygen radical capacity absorbance (ORAC), as well as catalase and superoxide dismutase (SOD) activities as described previously [60].

Red Blood Cell and Adipose Tissue Fatty Acid Composition

Total lipids of red blood cell aliquots (RBC; 300 µL) and adipose tissue portions (100 mg) were extracted (2:1; v:v; chloroform:methanol containing 0.01% butylated hydroxytoluene) by using a modification of the Folch et al method [61,62]. Red blood cell total phospholipid fatty-acid (FA) and adipose tissue total FA percentage composition were determined by gas-liquid chromatography as previously described [62]. Pairwise analysis of gluteal and abdominal samples was performed including the pre- and postsamples of a participant in the same batch on the same day. Product to precursor FA ratios were used as a proxy to reflect delta-6- and delta-5-desturase enzyme activity [63].

Comprehensive Metabolite Profiling of the Serum and Muscle Metabolome

For the metabolite analyses, a combined platform of liquid (LC-QTOF-MS) and gas (GCTOF-MS lipids) chromatography coupled to mass spectrometry, in both positive and negative ionization modes will be used. This approach will enable a comprehensive coverage of serum and muscle metabolites with different chemical properties. All sample preparation and analyses will be performed according to a run order design to circumvent methodological biases that may interfere with results interpretation [64]. For example, samples from the same individual are prepared and analyzed in close connection while keeping the internal sample order randomized. Analytical batches will be balanced in terms of treatment group and quality control (QC) samples (ie, pooled from all samples) will be analyzed continuously.

Serum samples will be prepared according to A et al [65], using a 90/10, v/v methanol:water extraction including internal standards for metabolomics; and a 70/30, v/v chloroform:methanol extraction for lipidomics [66].

On an average, we will detect 2000 to 3000 peaks or more, and annotation/identifications will be done via the use of publically available library, in combination with *in house* library at the Swedish Metabolomics Centre (SMC). For targeted analyses and validation of findings, we will use triple quadrupole mass spectrometry techniques, such as LC-QqQ-MSMS or GC-QqQ-MSMS together with LC-TQMSMS and

GC-TQMSMS in MRM-mode. Absolute quantification of specific compounds will be achieved by using calibration curves calculated from stable isotope labeled internal standards.

Serum HDL- and LDL-Cholesterol Subclasses and HDL Functionality

HDL was isolated from aliquots of serum using density shift ultracentrifugation as described previously [67,68]. HDL anti-inflammatory function was measured by assessing expression levels of vascular cell adhesion molecule (VCAM) human umbilical vein endothelial cells (HUVEC) treated with participant HDL and stimulated with murine TNF-α, as described previously [67]. HDL antioxidant function was quantified by measuring serum paraoxonase-1 (PON1) activity as described previously [67]. HDL-induced reverse cholesterol efflux was quantified using a modified method [69]. Briefly, RAW264.7 cells (Gill Dealtry, Nelson Mandela Metropolitan University), were labeled with [^{3}H] cholesterol in a medium containing acyl-CoA cholesterol acyltransferase (ACAT) inhibitor. Isolated participant HDL was then added and cholesterol efflux was carried out for 4 hours. Reverse cholesterol efflux capacity was calculated as label present in the cell media relative to the untreated control. HDL anti-thrombotic function was quantified by measuring serum platelet activating factor acetylhydrolase (PAF-AH) activity using the PAF Acetylhydrolase Assay Kit (Cayman Chemical, 760901). Serum HDL and LDL subclass were determined using the Lipoprint HDL and LDL systems (Quantimetrix, Redondo Beach, CA) as described previously [67,70].

Skeletal Muscle and Adipose Tissue Gene and Protein Expression

RNA was extracted from adipose tissue and skeletal muscle samples using RNeasy Mini lipid kit (Qiagen Ltd, Germantown, MD, USA) and mirVana miRNA Isolation kit (Invitrogen, Life technologies, Carlsbad, CA, USA), respectively. Skeletal muscle RNA was DNAse treated using DNA-free Kit (Invitrogen, Life technologies, Carlsbad, CA, USA). RNA was reverse transcribed to cDNA using the High-Capacity cDNA Reverse Transcription Kit with RNase inhibitors (Applied Biosystems Foster City, CA, USA).

For the adipose tissue, RT-PCR will be performed in triplicate using Applied Biosystems QuantStudioTM 3 Real-Time PCR system with predesigned Taqman assays from Applied Biosystems (Warrington, UK) (see Multimedia Appendix 2). The genes of interest will be measured and presented as the ratio of abundance of the gene of interest: mean of abundance of the relevant housekeeping genes (LRP10 and RPLPO). Protein expression, and phosphorylation status, for genes of interest will be analyzed using ELISA and/or Western Blot analyses.

For skeletal muscle, a gene array was conducted using Human Affymetrix Cartridge Clariom S Platform (Affymetrix, Santa Clara, CA, USA) and analyzed with Affymetrix Expression Console using the SST-RMA method. Unlogged signals were compared using a 2-tailed paired Student *t*-test. The q-values (false discovery rates) were calculated by the R/Bio-conductor function and set at q<.05. Target and novel pathways will be investigated using the gene array data, and genes of interest and associated proteins will be further validated using RT-PCR and western blots analyses, respectively.

Skeletal Muscle and Adipose Tissue Mitochondrial Respiratory Function

Measures of mitochondrial respiration were performed in respiration medium (MiR05) at 37°C using high-resolution Oxygraph-2k (Oroboros, Innsbruck, Austria) [71]. All measures were completed in duplicate and carried out in a hyperoxygenated (250-450 nmoL/mL) environment. Skeletal muscle and adipose tissue (abdominal and gluteal subcutaneous adipose tissue) samples were prepared and analyzed according to the methods described [71,72]. Briefly, immediately after tissue collection, samples were stored in ice-cold BIOPS [71] for a maximum of 4 hours before analyses. Skeletal muscle fibers (1-3 mg w/w) and adipose tissue (50-60 mg w/w) were permeabilized in saponin (5 mg/mL BIOPS) for 30 min and 20 min, respectively. Tissue was immediately washed in MiR05 for 2 x 10 min. The multiple substrate-uncoupler-inhibitor titration protocol applied to all tissue is as follows [73,74]:

1. Medium chain fatty acid oxidation through leak respiration in the absence of adenylates with the addition of malate (2 mM) and octanoly-carnitine (0.2 mM)
2. Maximal flow of electrons through electron transferring flavoprotein and fatty-acid oxidation (ADP 5 mM)
3. Submaximal state 3 respiration capacity specific to complex I (pyruvate 5 mM; glutamate 10 mM)
4. Maximal state 3 respiration, oxidative phosphorylation capacity (Succinate, 10 mM)
5. State 4o respiration, oligomycin-induced leak respiration through inhibition of ATP synthase (Oligomycin 2.5 µM)
6. Electron transports system capacity with the titration of CCCP (0.5 µM titration steps)
7. Inhibition of complex I with the addition of rotenone (0.5 µM)
8. The inhibition of complex III with the addition of antimycin A (2.5 µM)

Complex III inhibition was used for the determination and correction of residual oxygen consumption (nonmitochondrial oxygen consumption in the chamber). Ascorbate (2 mM) and TMPD (0.5 mM) were added to assess cytochrome c oxidase (COX), complex IV activity. TMPD and ascorbate are redox substrates that donate electrons directly to COX, and activity was measured by pmol of O_2 a minute per mg of wet weight.

Hydrogen peroxide (H_2O_2) flux was measured simultaneously with respirometry in the O2k-Fluorometer (O2k-Fluo LED2-Module Fluorescence-Sensor Green) using the H_2O_2 sensitive probe Amplex UltraRed. Then 10 µM Amplex UltraRed and 1 U/mL horseradish peroxidase (HRP) was added to the chamber. The reaction between Amplex UltraRed and H_2O_2 catalyzed by HRP is fluorescent, similar to resorufin. Calibrations were performed throughout the respirometry experiment to account for degradation of fluorescent over time, with 2 steps of H_2O_2 added at 0.1 µM per step. Mass-specific H_2O_2 were calculated relative to oxygen flux (H_2O_2/O_2 flux). The H_2O_2/O_2 flux ratio is frequently applied to evaluate the

relative importance of H_2O_2 production at different respiratory states [75].

Fecal Bacterial Community Analysis

Bacterial DNA will be extracted using the ZymoBIOMICS DNA Miniprep kit (Zymo Research Corp., Irvine, USA) according to the manufacturer's instructions. Bacterial composition will be described by sequencing the V4 hypervariable region of the 16S ribosomal RNA gene. Sequencing libraries will be prepared as per the Illumina MiSeq system instructions (Illumina, San Diego, CA). The pooled library will then be sequenced on the Illumina Miseq sequencing platform (Illumina, San Diego, CA). Raw sequences obtained from the Illumina Miseq will be subjected to a quality check using the FastQC software [76]. Preliminary analysis of the raw data will involve removing primers, barcodes, contaminants, and low-quality bacterial sequences. The 16S pair-end reads will be assembled by joining forward and reverse of demultiplexed sequence reads. The output file will then be processed for quality filtering. Chimeric sequences will be filtered by UCHIME algorithm in USEARCH platform. We will use QIIME [77] to cluster sequences into operational taxonomic units (OTUs) based on a sequence similarity threshold of 97%. The SILVA database will be used to assign taxonomic identities to the OTUs. Moreover, we will use the PICRUSt (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States) and BugBase softwares to predict the metabolic function [78,79]. Raw data in fastq format will be made available in a public sequence database.

Statistics

Sample Size Determination

Sample size determination was based on our primary outcome using the study of Nordby et al [80], with a significance level of $P<.05$ and power of 80%. On the basis of the change in normalized glucose clearance (measured using a euglycemic hyperinsulinemic clamp) from pre- to postintervention (12-week aerobic training) compared with the nontrained control group (8.2 [SD 5.9] vs −1.8 [SD 6.2] mL/kg/min FFM/nmoL/L insulin, respectively), 6 participants per group would be required to detect a significant difference between groups. These numbers correspond to those of Ortega et al [81] who compared glucose tolerance tests to detect the insulin sensitizing effects of a bout of continuous exercise and reported that 6 participants would be required to detect a change in insulin sensitivity when using a FSIGT. In order to account for the secondary outcomes, using changes in skeletal muscle glucose transporter (GLUT)4 in response to a 12-week training program as the proxy (0.65 [SD 0.69] vs 0.01 [SD 0.69] AU for training vs control group), 18 women would be required to detect a difference between groups [81]. On the basis of these calculations, and a dropout rate of 10% (2/20), 20 participants per group were selected.

Proposed Statistics

Results will be presented as means (SD), or medians and interquartile ranges for non-normally distributed data. Data will be normalized by log transformation if required. Repeated measures ANOVA will be used to compare differences in the change of outcome variables between the control and exercise groups in response to the exercise/control intervention. Pearson and/or Spearman correlations will be used to examine associations between changes in primary and secondary outcome variables. Data will be analyzed using StataSE (version 14, StatCorp, Texas, USA) and IBM SPSS Statistics 24 (Version 24.0, Armonk, NY, USA).

Comprehensive metabolite profiling data will be evaluated via a combination of multivariate analysis methods and univariate statistics, that is, Principal Component Analysis (PCA), Orthogonal Partial Least Squares (OPLS), and its extensions [64]. In addition, we will perform an extensive validation to determine the model significances, using both internal, ANOVA on the cross-validated model patterns, and external validation, independent sample prediction. Model scores (subject level) will be used to visualize and interpret the differences in metabolic response between predefined patient groups or subgroups, or of individual patients responding differently to the interventions. Model loadings (variable level) combined with univariate *P* values will be used as the base for mechanistic interpretation and to highlight significant metabolites or metabolite patterns.

For bacterial community analysis, basic statistical tests will be performed using QIIME [77] and R software will be used for advanced statistical analysis. Beta-diversity will be evaluated by calculation of weighted and unweighted Unifrac distances. The Shannon and Simpson diversity indices will be employed to study alpha-diversity. The relationship between the composition of the fecal bacteria and exposure variables will be determined using weighted generalized ridge regression methods [82] and the lasso [83]. We will use Dirichlet multinomial models or ecological approaches such as multi-species occupancy models to evaluate interactions and shift in fecal bacterial communities over time [84,85].

Results

Participant Enrollment, Allocation, Follow-Up, and Analyses

Information on participant enrollment, allocation, follow-up, and analysis is shown in Figure 2. Standards of reporting were based on the CONSORT 2010 checklist for randomized control trials. A total of 45 participants were enrolled in the study and randomized into exercise (n=23) and control (n=22) groups. Of these, 10 participants did not complete the intervention (dropout; n=3 exercise, n=7 control) resulting in a final sample of 20 exercise and 15 control participants.

Participant Baseline Characteristics

The sociodemographic characteristics of the participants at baseline are presented in Table 1. The average age of the whole group (n=45) was 24 (SD 4) years. Sociodemographic characteristics were not different between participants of the exercise, control, and dropout groups. The majority (67%, 30/45) of participants had completed at least grade 12 education, and 27% (12/45) of participants were currently enrolled students, while 51% (23/45) were employed. A quarter of the participants earned less than R2500/month (US $210/month at exchange rate of R11.9/US $, 13 February 2018), whereas 42% (19/45)

earned between R2500-R5000/month (US $210-420/month), and the remaining participants (31%, 14/45) earned greater than R5000/month (US $420/month). Most of the participants were not married (89%, 40/45) and 42% (23/45) had at least 1 child. Apart from hypertension (42%, 19/45) and diabetes (13.6%, 6/45), the known family history of disease was relatively low.

Table 1. Baseline sociodemographic characteristics.

Variables	Control (n=15)	Exercise (n=20)	Dropout (n=10)	*P* value
Age in years, mean (SD)	24 (4)	23 (3)	26 (4)	.24
Informal housing, n (%)	6 (40)	4 (20)	6 (60)	.09
Housing density (persons/room), median (interquartile range)	1.3 (1.0-1.6)	1.0 (0.8-1.5)	1.0 (1.0-2.7)	.38
Asset index (% of 14 commodities), n (%)	53 (15)	54 (20)	47 (23)	.62
Education, n (%)				.87
< Grade 12	6 (43)	5 (25)	3 (30)	
Grade 12	5 (36)	9 (45)	4 (40)	
Tertiary	3 (21)	6 (30)	3 (30)	
Employment, n (%)				.63
Employed	9 (60)	10 (50)	4 (40)	
Student	5 (33)	9 (45)	4 (40)	
Unemployed	1 (7)	1 (5)	2 (20)	
Income, n (%)				.09
R0-2499/month	6 (40)	2 (10)	4 (40)	
R2500-R4999/month	7 (47)	8 (40)	4 (40)	
>R5000/month	2 (13)	10 (50)	2 (20)	
Marital status, married, n (%)	1 (7)	3 (15)	1 (10)	.73
Parity, n (%)				.33
None	7 (48)	15 (75)	4 (40)	
1 child	4 (27)	2 (10)	3 (30)	
2-3 children	4 (27)	3 (15)	3 (30)	
Known family history of disease, n (%)				
Hypertension	7 (47)	9 (45)	3 (30)	.38
Heart disease	0 (0)	3 (16)	1 (10)	.63
Stroke	1 (7)	1 (5)	1 (10)	.67
Diabetes	2 (13)	2 (11)	2 (20)	.74
Obesity	0 (0)	1 (5)	0 (0)	.66

The baseline cardiorespiratory fitness, physical activity, and dietary intake did not differ between groups (Table 2). For the whole group, despite cardiorespiratory fitness being low (<25 mL/kg/min), the participants accumulated an average of 9338 steps per day. However, most of the day was spent in sedentary behavior (54%). The majority of dietary energy intake (8390 [6577.0-9540.0] kJ/day) was derived from carbohydrate (56.3%, 7.0%), followed by fat (29.4%, 7.0%) and then protein (14.0%, 2.6%). Dietary sugar intake was high (64.7 [51.5-108.6] g/day), and fiber intake below recommendations for adequate intake (17.0 [14.3-23.2] g/day vs recommendations of 25 g/day).

The baseline anthropometry and cardiometabolic risk factors of the participants are presented in Table 3. Body composition did not differ between groups. For the whole group, the mean BMI, waist and waist to hip ratio were 33.9 (SD 2.8) kg/m^2, 103.8 (SD 8.0) cm and 0.90 (SD 0.07), respectively. Cardiometabolic risk factors did not differ by group. The participants were all normotensive (systolic: 110.1 [SD 10.7] mm Hg; diastolic: 73.1 [SD 9.0] mmHg) and had normal glucose tolerance based on HbA_{1c} (5.2 [SD 0.3] A_{1c}%).

Table 2. Baseline cardiorespiratory fitness, physical activity and dietary intake.

Variable	Control	Exercise	Dropout	*P* value
Cardiorespiratory fitness, mean (SD)				
n	15	20	9	
VO_{2peak}[a] (mL/min)	2099 (281)	2077 (211)	1989 (296)	.55
VO_{2peak} (mL/kg/min)	23.9 (3.0)	24.9 (2.4)	23.4 (4.5)	.43
Physical activity (ActivPAL), mean (SD)				
n	15	19	7	
Steps (No. Day)	10013 (2650)	9349 (2334)	7858 (2756)	.19
Stepping (% day)	14 (4)	12 (3)	11 (3)	.19
Standing (% day)	34 (9)	34 (8)	32 (8)	.83
Sedentary (% day)	52 (10)	54 (9)	58 (9)	.48
Dietary intake, median (interquartile range) or mean (SD)				
n	15	20	10	
Energy intake (kJ/day)	8138 (6493-9434)	8966 (7119-11,775)	8921 (7875-9396)	.45
Fat (%EI[b])	30.9 (5.6)	30.3 (6.2)	27.1 (7.1)	.32
Protein (%EI)	14.3 (1.9)	13.1 (5)	14.2 (3.6)	.37
Carbohydrate (%EI)	54.1 (.7)	55.3 (5.8)	57.9 (8.4)	.38
Sugar (g/day)	64.7 (35.3-108.0)	62.5 (54.3-92.1)	75.8 (53.9-130.8)	.57
Fiber (g/day)	16.2 (11.9-23.2)	18.9 (15.1-24.4)	17.0 (10.4-23.7)	.51

[a]VO_{2peak}: peak oxygen consumption.

[b]%EI: percentage of total energy intake.

Table 3. Baseline anthropometry and cardio-metabolic risk factors.

Variable	Control	Exercise	Dropout	*P* value
Anthropometry, mean (SD)				
n	15	20	10	
Height (m)	1.62 (.06)	1.57 (.06)	1.60 (.06)	.05
Weight (kg)	87.8 (10.9)	84.1 (8.7)	87.5 (12.0)	.52
BMI[a] (kg/m^2)	33.4 (2.7)	34.1 (2.8)	34.1 (3.3)	.72
Waist (cm)	103.4 (8.1)	103.6 (7.4)	106.8 (11.9)	.75
WHR[b]	0.88 (0.05)	0.91 (0.07)	0.90 (0.08)	.45
Cardio-metabolic risk factors, mean (SD)				
n	15	20	4	
Systolic BP[c] (mmHg)	111.7 (11.3)	109.0 (11.1)	109.5 (8.0)	.76
Diastolic BP (mmHg)	75.0 (9.7)	72.2 (9.4)	70.8 (1.5)	.57
HbA_{1c}[d]	5.2 (0.4)	5.2 (0.3)	5.2 (0.1)	.90

[a]BMI: body mass index.

[b]WHR: waist to hip ratio.

[c]BP: blood pressure.

[d]HbA_{1c}: hemoglobin A_{1c}.

Discussion

This is the first study, to our knowledge, that has used an exercise intervention to understand the mechanisms underlying the high risk for T2D in a black African population. The study uses state-of-the-art technology to characterize the determinants of insulin sensitivity and secretion. Using exercise as a model ensures a holistic approach that focuses on the complex interaction of biological systems, within the context of associated environmental and lifestyle factors. Novel biological aspects of the protocol in this cohort include (1) measurement of pancreatic fat content by MRS; (2) an array approach in the skeletal muscle to identify novel pathways and genes involved in the regulation of insulin sensitivity, in combination with metabolomic and lipidomic analyses; and (3) characterization of the gastrointestinal microbiome. Although the aim of the study was to understand the primary and secondary determinants of insulin sensitivity, the study results, as well as the findings of the focus group discussions and key informant interviews can be used to inform the suitability of this intervention for large-scale roll out in similar communities.

The participants were a homogenous cohort of young women of Xhosa ancestry who mostly resided in an informal urban settlement and were of a low socioeconomic status. Notably, 38% (17/45) of the participants were meeting physical activity guidelines by accumulating more than 10,000 steps/day [86]. As shown in our previous research [31], these steps are usually accumulated through walking for transport that is typically conducted at a low intensity [32], which is subsequently reflected in the participants low cardiorespiratory fitness levels (VO_{2peak}) and a rating of "poor," according to the American College of Sports Medicine [33]. Accordingly, exercise training at a moderate to high intensity offers an ideal intervention within this population to ensure improvements in cardiorespiratory fitness and associated cardiometabolic outcomes, specifically insulin sensitivity. It is anticipated that the exercise training will improve insulin sensitivity and reduce the risk for T2D within this high-risk population.

Although 118 women were screened, only 45 women were willing and eligible to be enrolled in the study. A requirement for screening was to consent for HIV testing, which deterred many potential participants from screening and is likely related to the high rates (20%) of HIV in women in the City of Cape Town [87]. The main reasons for ineligibility after screening included (1) not meeting the BMI criteria, (2) not using injectable contraception, and (3) time limitations and/or the invasiveness of procedures involved in the study. The injectable contraception was chosen as part of the selection criteria to ensure a more homogenous participant profile. The injectable contraception is freely available to all women in the community clinics and is thus the contraception of choice for the majority of women. Of the 45 women recruited, 35 completed the 12-week intervention, with the greatest dropout being in the control group (7 out of the 10 participants; Figure 1). This may be explained by the control groups' disappointment on not being assigned to the exercise group, resulting in a lack of commitment and loss of interest in the study. This occurred despite the assurance that the control group could participate in the 12-week exercise intervention following the 12-week control period, for which they would be reimbursed for their time, inconvenience, and travel. Interestingly, only 9 of the 15 control participants initiated the exercise training, of which 6 attended more than 30 of the 48 training sessions, and 3 participants attended less than 3 sessions. In contrast, there was a low dropout rate in the exercise group (3 out of the 10 participants). It is anticipated that the outcomes from the focus group and informant interviews will provide insight regarding the reasons for the discrepancies in the dropout rates between the groups.

There are several strengths to this exercise intervention that involve, among others, monitoring and collaboration. First, every exercise session was facilitated by a trained exercise physiologist, who ensured that the prescribed exercise intensity was attained by using heart rate monitoring and ratings of perceived exertion. Moreover, changes in lifestyle factors, including dietary intake (red blood cell and adipose tissue fatty acid composition), sleep, physical activity, and sedentary behavior (accelerometry) were objectively monitored every 4 weeks over the 12-week intervention. Finally, the collaborative nature of the study ensures the incorporation of diverse skills and expertise from both local (South African) and international (Sweden and USA) collaborators. This allows for a systems biology approach to understand the mechanisms underlying the high risk for T2D in an African population. However, the sample size is limited due to the costs associated with the extensive testing and time and commitment requirements from the participants. Nevertheless, the study is powered for the main outcome measures, and partial least squares regression will be used due to its capacity to deal with very small sample sizes and many parameters [64]. Furthermore, the data from the secondary outcomes may also be used as pilot data to inform future studies.

In conclusion, we have described a research protocol for an exercise intervention to understand the mechanisms underlying insulin sensitivity and secretion in obese black SA women. The knowledge gained from this study will be used to inform future interventions and treatments to combat insulin resistance and T2D in this high-risk population.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Focus group discussion open-ended guide questions.

[PDF File (Adobe PDF File), 26KB - resprot_v7i4e75_app1.pdf]

Multimedia Appendix 2

Adipose tissue genes of interest.

[PDF File (Adobe PDF File), 27KB - resprot_v7i4e75_app2.pdf]

References

1. IDF Diabetes Atlas Group. Update of mortality attributable to diabetes for the IDF Diabetes Atlas: Estimates for the year 2013. Diabetes Res Clin Pract 2015 Sep;109(3):461-465. [doi: 10.1016/j.diabres.2015.05.037] [Medline: 26119773]
2. Duke CMP, Plowden TC, Armstrong AY. Disparate cardiovascular and diabetic outcomes in young adult black women: studies from across the globe. Curr Cardiovasc Risk Rep 2012 Mar 2;6(3):251-258. [doi: 10.1007/s12170-012-0229-1]
3. Golden SH, Brown A, Cauley JA, Chin MH, Gary-Webb TL, Kim C, et al. Health disparities in endocrine disorders: biological, clinical, and nonclinical factors—an Endocrine Society scientific statement. J Clin Endocrinol Metab 2012 Sep;97(9):E1579-E1639. [doi: 10.1210/jc.2012-2043]
4. World Health Organisation. WHO. Geneva: World Health Organisation; 2011. WHO Global status report on noncommunicable diseases URL: http://www.who.int/nmh/publications/ncd_report2010/en/ [accessed 2018-02-14] [WebCite Cache ID 6xEC16qyK]
5. Peer N, Steyn K, Lombard C, Lambert E, Vythilingum B, Levitt N. Rising diabetes prevalence among urban-dwelling black South Africans. PLoS One 2012;7:e43336. [doi: 10.1371/journal.pone.0043336.t004] [Medline: 22962583]
6. Haffner S, D'Agostino R, Saad M, Rewers M, Mykkänen L, Selby J, et al. Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites. The Insulin Resistance Atherosclerosis Study. Diabetes 1996 Jun;45(6):742-748. [Medline: 8635647]
7. Rasouli N, Spencer HJ, Rashidi AA, Elbein SC. Impact of family history of diabetes and ethnicity on β-cell function in obese, glucose-tolerant individuals. J Clin Endocrinol Metab 2007 Dec;92(12):4656-4663. [doi: 10.1210/jc.2007-0919]
8. Goedecke JH, Dave JA, Faulenbach MV, Utzschneider KM, Lambert EV, West S, et al. Insulin response in relation to insulin sensitivity: an appropriate beta-cell response in black South African women. Diabetes Care 2009 Feb 05;32(5):860-865. [doi: 10.2337/dc08-2048]
9. Osei K, Schuster D. Ethnic differences in secretion, sensitivity, and hepatic extraction of insulin in black and white Americans. Diabet Med 1994 Oct;11(8):755-762. [Medline: 7851069]
10. Goedecke JH, George C, Veras K, Peer N, Lombard C, Victor H, et al. Sex differences in insulin sensitivity and insulin response with increasing age in black South African men and women. Diabetes Res Clin Pract 2016 Dec;122:207-214. [doi: 10.1016/j.diabres.2016.11.005] [Medline: 27889690]
11. Goedecke JH, Mtintsilana A, Dlamini SN, Kengne AP. Type 2 diabetes mellitus in African women. Diabetes Res Clin Pract 2017 Jan;123:87-96. [doi: 10.1016/j.diabres.2016.11.017] [Medline: 28006698]
12. Goedecke JH, Levitt NS, Lambert EV, Utzschneider KM, Faulenbach MV, Dave JA, et al. Differential effects of abdominal adipose tissue distribution on insulin sensitivity in black and white South African women. Obesity (Silver Spring) 2009 Aug;17(8):1506-1512 [FREE Full text] [doi: 10.1038/oby.2009.73] [Medline: 19300428]
13. Rush EC, Goedecke JH, Jennings C, Micklesfield L, Dugas L, Lambert EV, et al. BMI, fat and muscle differences in urban women of five ethnicities from two countries. Int J Obes (Lond) 2007 Aug;31(8):1232-1239. [doi: 10.1038/sj.ijo.0803576] [Medline: 17342075]
14. Lovejoy J, de la Bretonne JA, Klemperer M, Tulley R. Abdominal fat distribution and metabolic risk factors: effects of race. Metabolism 1996 Sep;45(9):1119-1124. [Medline: 8781299]
15. Goedecke JH, Evans J, Keswell D, Stimson RH, Livingstone DE, Hayes P, et al. Reduced gluteal expression of adipogenic and lipogenic genes in Black South African women is associated with obesity-related insulin resistance. J Clin Endocrinol Metab 2011 Dec;96(12):E2029-E2033 [FREE Full text] [doi: 10.1210/jc.2011-1576] [Medline: 21956425]
16. Evans J, Goedecke JH, Söderström I, Burén J, Alvehus M, Blomquist C, et al. Depot- and ethnic-specific differences in the relationship between adipose tissue inflammation and insulin sensitivity. Clin Endocrinol (Oxf) 2011 Jan;74(1):51-59. [doi: 10.1111/j.1365-2265.2010.03883.x] [Medline: 20874774]
17. Kotzé-Hörstmann LM, Keswell D, Adams K, Dlamini T, Goedecke JH. Hypoxia and extra-cellular matrix gene expression in adipose tissue associates with reduced insulin sensitivity in black South African women. Endocrine 2017 Jan;55(1):144-152. [doi: 10.1007/s12020-016-1089-0] [Medline: 27628582]

18. Bays HE, González-Campoy JM, Bray GA, Kitabchi AE, Bergman DA, Schorr AB, et al. Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. Expert Rev Cardiovasc Ther 2008 Mar;6(3):343-368. [doi: 10.1586/14779072.6.3.343] [Medline: 18327995]
19. Goedecke JH, Keswell D, Weinreich C, Fan J, Hauksson J, Victor H, et al. Ethnic differences in hepatic and systemic insulin sensitivity and their associated determinants in obese black and white South African women. Diabetologia 2015 Nov;58(11):2647-2652 [FREE Full text] [doi: 10.1007/s00125-015-3720-7] [Medline: 26232099]
20. Hawley JA. Exercise as a therapeutic intervention for the prevention and treatment of insulin resistance. Diabetes Metab Res Rev 2004 Aug;20(5):383-393. [doi: 10.1002/dmrr.505] [Medline: 15343584]
21. Hawley JA, Lessard SJ. Exercise training-induced improvements in insulin action. Acta Physiol (Oxf) 2008 Jan;192(1):127-135. [doi: 10.1111/j.1748-1716.2007.01783.x] [Medline: 18171435]
22. Bird S, Hawley J. Exercise and type 2 diabetes: new prescription for an old problem. Maturitas 2012 Aug;72(4):311-316. [doi: 10.1016/j.maturitas.2012.05.015] [Medline: 22748760]
23. Muoio D, Newgard C. Obesity-related derangements in metabolic regulation. Annu Rev Biochem 2006;75:367-401. [doi: 10.1146/annurev.biochem.75.103004.142512] [Medline: 16756496]
24. Mizgier ML, Casas M, Contreras-Ferrat A, Llanos P, Galgani JE. Potential role of skeletal muscle glucose metabolism on the regulation of insulin secretion. Obes Rev 2014 Jul;15(7):587-597. [doi: 10.1111/obr.12166] [Medline: 24618283]
25. Eckardt K, Görgens SW, Raschke S, Eckel J. Myokines in insulin resistance and type 2 diabetes. Diabetologia 2014 Jun;57(6):1087-1099. [doi: 10.1007/s00125-014-3224-x] [Medline: 24676645]
26. Dela F, Stallknecht B. Effect of physical training on insulin secretion and action in skeletal muscle and adipose tissue of first-degree relatives of type 2 diabetic patients. Am J Physiol Endocrinol Metab 2010 Jul;299(1):E80-E91 [FREE Full text] [doi: 10.1152/ajpendo.00765.2009] [Medline: 20407006]
27. Sakurai T, Ogasawara J, Kizaki T, Sato K, Ishibashi Y, Takahashi M, et al. The effects of exercise training on obesity-induced dysregulated expression of adipokines in white adipose tissue. Int J Endocrinol 2013;2013:801743 [FREE Full text] [doi: 10.1155/2013/801743] [Medline: 24369466]
28. Bäckhed F, Fraser CM, Ringel Y, Sanders ME, Sartor RB, Sherman PM, et al. Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications. Cell Host Microbe 2012 Nov 15;12(5):611-622 [FREE Full text] [doi: 10.1016/j.chom.2012.10.012] [Medline: 23159051]
29. Petriz BA, Castro AP, Almeida JA, Gomes CP, Fernandes GR, Kruger RH, et al. Exercise induction of gut microbiota modifications in obese, non-obese and hypertensive rats. BMC Genomics 2014 Jun 21;15:511 [FREE Full text] [doi: 10.1186/1471-2164-15-511] [Medline: 24952588]
30. Matsumoto M, Inoue R, Tsukahara T, Ushida K, Chiji H, Matsubara N, et al. Voluntary running exercise alters microbiota composition and increases n-butyrate concentration in the rat cecum. Biosci Biotechnol Biochem 2008 Feb;72(2):572-576 [FREE Full text] [doi: 10.1271/bbb.70474] [Medline: 18256465]
31. Dickie K, Micklesfield LK, Chantler S, Lambert EV, Goedecke JH. Meeting physical activity guidelines is associated with reduced risk for cardiovascular disease in black South African women; a 5.5-year follow-up study. BMC Public Health 2014 May 23;14:498 [FREE Full text] [doi: 10.1186/1471-2458-14-498] [Medline: 24886324]
32. Dickie K, Micklesfield LK, Chantler S, Lambert EV, Goedecke JH. Cardiorespiratory fitness and light-intensity physical activity are independently associated with reduced cardiovascular disease risk in urban black South African women: a cross-sectional study. Metab Syndr Relat Disord 2016 Feb;14(1):23-32. [doi: 10.1089/met.2015.0064]
33. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 9th Edition. Baltimore: Lippincott Williams & Wilkins; 2014.
34. Draper CE, Davidowitz KJ, Goedecke JH. Perceptions relating to body size, weight loss and weight-loss interventions in black South African women: a qualitative study. Public Health Nutr 2015 May 26;19(03):548-556. [doi: 10.1017/S1368980015001688]
35. Department of Health, Medical Research Council, OrcMacro. dhsprogram. Pretoria: Department of Health; 2007. South African Demographic and Health Survey 2003 URL: https://dhsprogram.com/pubs/pdf/FR206/FR206.pdf [accessed 2018-02-19] [WebCite Cache ID 6xLFkrQQd]
36. Mciza Z, Goedecke JH, Steyn NP, Charlton K, Puoane T, Meltzer S, et al. Development and validation of instruments measuring body image and body weight dissatisfaction in South African mothers and their daughters. Public Health Nutr 2007 Jan 2;8(05):509-519. [doi: 10.1079/PHN2005814] [Medline: 16153332]
37. Coates J, Swindale A, Bilinsky P. FAO. Washington: Academy for Educational Development; 2007. Household Food Insecurity Access Scale (HFIAS) for Measurement of Household Food Access: Indicator Guide (v. 3) URL: http://www.fao.org/fileadmin/user_upload/eufao-fsi4dm/doc-training/hfias.pdf [accessed 2018-02-19] [WebCite Cache ID 6xLFuB2OY]
38. Buysse D, Reynolds C, Monk T, Berman S, Kupfer D. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989 May;28(2):193-213. [Medline: 2748771]
39. Beck A, Beamesderfer A. Assessment of depression: The depression inventory. In: Pichot P, Olivier-Martin R, editors. Psychological measurements in psychopharmacology. Basel: Karger; 1974.
40. Andrews G, Slade T. Interpreting scores on the Kessler Psychological Distress Scale (K10). Aust N Z J Public Health 2001 Dec;25(6):494-497. [Medline: 11824981]

41. Schwarzer R, Jerusalem M. Generalized self-efficacy scale. In: Measures in health psychology: A user's portfolio Causal and control beliefs. Windsor: NFER-NELSON; 1995:35-37.
42. Goedecke JH, Micklesfield LK, Levitt NS, Lambert EV, West S, Maartens G, et al. Effect of different antiretroviral drug regimens on body fat distribution of HIV-infected South African women. AIDS Res Hum Retroviruses 2013 Mar;29(3):557-563. [doi: 10.1089/aid.2012.0252] [Medline: 23330599]
43. Micklesfield LK, Goedecke JH, Punyanitya M, Wilson KE, Kelly TL. Dual-energy X-ray performs as well as clinical computed tomography for the measurement of visceral fat. Obesity (Silver Spring) 2012 May;20(5):1109-1114 [FREE Full text] [doi: 10.1038/oby.2011.367] [Medline: 22240726]
44. Takagi S, Sakamoto S, Midorikawa T, Konishi M, Katsumura T. Determination of the exercise intensity that elicits maximal fat oxidation in short-time testing. J Sports Sci 2014;32(2):175-182. [doi: 10.1080/02640414.2013.815360] [Medline: 24015928]
45. Venables MC, Achten J, Jeukendrup AE. Determinants of fat oxidation during exercise in healthy men and women: a cross-sectional study. J Appl Physiol (1985) 2005 Jan;98(1):160-167 [FREE Full text] [doi: 10.1152/japplphysiol.00662.2003] [Medline: 15333616]
46. Steffan H, Elliott W, Miller W, Fernhall B. Substrate utilization during submaximal exercise in obese and normal-weight women. Eur J Appl Physiol Occup Physiol 1999 Aug;80(3):233-239. [Medline: 10453926]
47. Weir J. New methods for calculating metabolic rate with special reference to protein metabolism. 1949. Nutrition 1990;6(3):213-221. [Medline: 2136000]
48. Frayn K. Calculation of substrate oxidation rates in vivo from gaseous exchange. J Appl Physiol Respir Environ Exerc Physiol 1983 Aug;55(2):628-634. [doi: 10.1152/jappl.1983.55.2.628] [Medline: 6618956]
49. Bergman R, Ider Y, Bowden C, Cobelli C. Quantitative estimation of insulin sensitivity. Am J Physiol 1979 Jun;236(6):E667-E677. [doi: 10.1152/ajpendo.1979.236.6.E667] [Medline: 443421]
50. Campioni M, Toffolo G, Basu R, Rizza RA, Cobelli C. Minimal model assessment of hepatic insulin extraction during an oral test from standard insulin kinetic parameters. Am J Physiol Endocrinol Metab 2009 Oct;297(4):E941-E948 [FREE Full text] [doi: 10.1152/ajpendo.90842.2008] [Medline: 19671837]
51. Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. J Magn Reson Imaging 2011 Oct;34(4) [FREE Full text] [doi: 10.1002/jmri.22775] [Medline: 22025886]
52. Dong Z, Luo Y, Zhang Z, Cai H, Li Y, Chan T. MR quantification of total liver fat in patients with impaired glucose tolerance and healthy subjects. PLoS One 2014;9:e111283. [doi: 10.1371/journal.pone.0111283.t001]
53. Bergstrom J. Percutaneous needle biopsy of skeletal muscle in physiological and clinical research. Scand J Clin Lab Invest 1975 Nov;35(7):609-616. [Medline: 1108172]
54. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. Med Sci Sports Exerc 2011 Feb;43(2):357-364 [FREE Full text] [doi: 10.1249/MSS.0b013e3181ed61a3] [Medline: 20581716]
55. Sasaki JE, John D, Freedson PS. Validation and comparison of ActiGraph activity monitors. J Sci Med Sport 2011 Sep;14(5):411-416. [doi: 10.1016/j.jsams.2011.04.003] [Medline: 21616714]
56. Keadle SK, Shiroma EJ, Freedson PS, Lee IM. Impact of accelerometer data processing decisions on the sample size, wear time and physical activity level of a large cohort study. BMC Public Health 2014 Nov 24;14:1210 [FREE Full text] [doi: 10.1186/1471-2458-14-1210] [Medline: 25421941]
57. Santos-Lozano A, Torres-Luque G, Marín P, Ruiz J, Lucia A, Garatachea N. Intermonitor variability of GT3X accelerometer. Int J Sports Med 2012 Jul 12;33(12):994-999. [doi: 10.1055/s-0032-1312580]
58. Krueger R, Casey M. Focus Groups. A practical guide for applied research. 5th Edition. Singapore: Sage publications; 2014.
59. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
60. Maarman G, Blackhurst D, Thienemann F, Blauwet L, Butrous G, Davies N, et al. Melatonin as a preventive and curative therapy against pulmonary hypertension. J Pineal Res 2015 Aug 11;59(3):343-353. [doi: 10.1111/jpi.12263]
61. Folch J, Lees M, Sloane SG. A simple method for the isolation and purification of total lipids from animal tissues. J Biol Chem 1957;226(1):497-509. [Medline: 13428781]
62. Hon G, Hassan M, van Rensburg SJ, Abel S, Marais DW, van Jaarsveld P, et al. Immune cell membrane fatty acids and inflammatory marker, C-reactive protein, in patients with multiple sclerosis. Br J Nutr 2009 May 19;102(09):1334. [doi: 10.1017/S0007114509382185]
63. Warensjö E, Rosell M, Hellenius M, Vessby B, De Faire U, Risérus U. Associations between estimated fatty acid desaturase activities in serum lipids and adipose tissue in humans: links to obesity and insulin resistance. Lipids Health Dis 2009 Aug 27;8:37 [FREE Full text] [doi: 10.1186/1476-511X-8-37] [Medline: 19712485]
64. Jonsson P, Wuolikainen A, Thysell E, Chorell E, Stattin P, Wikström P, et al. Constrained randomization and multivariate effect projections improve information extraction and biomarker pattern discovery in metabolomics studies involving dependent samples. Metabolomics 2015 Jun;11(6):1667-1678 [FREE Full text] [doi: 10.1007/s11306-015-0818-3] [Medline: 26491420]

65. Trygg J, Gullberg J, Johansson AI, Jonsson P, Antti H, Marklund SL, et al. Extraction and GC/MS analysis of the human blood plasma metabolome. Anal Chem 2005 Dec 15;77(24):8086-8094. [doi: 10.1021/ac051211v] [Medline: 16351159]
66. Nygren H, Seppänen-Laakso T, Castillo S, Hyötyläinen T, Orešič M. Liquid chromatography-mass spectrometry (LC-MS)-based lipidomics for studies of body fluids and tissues. Methods Mol Biol 2011;708:247-257. [doi: 10.1007/978-1-61737-985-7_15] [Medline: 21207295]
67. Woudberg NJ, Goedecke JH, Blackhurst D, Frias M, James R, Opie LH, et al. Association between ethnicity and obesity with high-density lipoprotein (HDL) function and subclass distribution. Lipids Health Dis 2016 May 11;15:92 [FREE Full text] [doi: 10.1186/s12944-016-0257-9] [Medline: 27169717]
68. Brulhart-Meynet M, Braunersreuther V, Brinck J, Montecucco F, Prost J, Thomas A, et al. Improving reconstituted HDL composition for efficient post-ischemic reduction of ischemia reperfusion injury. PLoS One 2015;10(3):e0119664 [FREE Full text] [doi: 10.1371/journal.pone.0119664] [Medline: 25781943]
69. Sankaranarayanan S, Kellner-Weibel G, de la Llera-Moya M, Phillips MC, Asztalos BF, Bittman R, et al. A sensitive assay for ABCA1-mediated cholesterol efflux using BODIPY-cholesterol. J Lipid Res 2011 Dec;52(12):2332-2340 [FREE Full text] [doi: 10.1194/jlr.D018051] [Medline: 21957199]
70. Goedecke JH, Utzschneider K, Faulenbach MV, Rizzo M, Berneis K, Spinas GA, et al. Ethnic differences in serum lipoproteins and their determinants in South African women. Metabolism 2010 Sep;59(9):1341-1350. [doi: 10.1016/j.metabol.2009.12.018] [Medline: 20096899]
71. Pesta D, Gnaiger E. High-resolution respirometry: OXPHOS protocols for human cells and permeabilized fibers from small biopsies of human muscle. Methods Mol Biol 2012;810:25-58. [doi: 10.1007/978-1-61779-382-0_3] [Medline: 22057559]
72. Kraunsøe R, Boushel R, Hansen CN, Schjerling P, Qvortrup K, Støckel M, et al. Mitochondrial respiration in subcutaneous and visceral adipose tissue from patients with morbid obesity. J Physiol 2010 Jun 15;588(Pt 12):2023-2032 [FREE Full text] [doi: 10.1113/jphysiol.2009.184754] [Medline: 20421291]
73. Jacobs RA, Flück D, Bonne TC, Bürgi S, Christensen PM, Toigo M, et al. Improvements in exercise performance with high-intensity interval training coincide with an increase in skeletal muscle mitochondrial content and function. J Appl Physiol (1985) 2013 Sep;115(6):785-793 [FREE Full text] [doi: 10.1152/japplphysiol.00445.2013] [Medline: 23788574]
74. Larsen S, Danielsen JH, Søndergård SD, Søgaard D, Vigelsoe A, Dybboe R, et al. The effect of high-intensity training on mitochondrial fat oxidation in skeletal muscle and subcutaneous adipose tissue. Scand J Med Sci Sports 2015 Feb;25(1):e59-e69. [doi: 10.1111/sms.12252] [Medline: 24845952]
75. Makrecka-Kuka M, Krumschnabel G, Gnaiger E. High-resolution respirometry for simultaneous measurement of oxygen and hydrogen peroxide fluxes in permeabilized cells, tissue homogenate and isolated mitochondria. Biomolecules 2015 Jun 29;5(3):1319-1338 [FREE Full text] [doi: 10.3390/biom5031319] [Medline: 26131977]
76. Andrews S. Bioinformatics. 2010. FastQC: a quality control tool for high throughput sequence data URL: http://www.bioinformatics.babraham.ac.uk/projects/fastqc/ [accessed 2018-02-14] [WebCite Cache ID 6xE6MVw1t]
77. Kuczynski J, Stombaugh J, Walters W, González A, Caporaso J, Knight R. Using QIIME to analyze 16S rRNA gene sequences from microbial communities. Curr Protoc Microbiol 2012 Nov;Chapter 1:Unit 1E.5 [FREE Full text] [doi: 10.1002/9780471729259.mc01e05s27] [Medline: 23184592]
78. Langille MG, Zaneveld J, Caporaso JG, McDonald D, Knights D, Reyes JA, et al. Predictive functional profiling of microbial communities using 16S rRNA marker gene sequences. Nat Biotechnol 2013 Sep;31(9):814-821 [FREE Full text] [doi: 10.1038/nbt.2676] [Medline: 23975157]
79. Ward T, Larson J, Meulemans J, Hillmann B, Lynch J, Sidiropoulos D, et al. BioRxiv. 2017. BugBase Predicts Organism Level Microbiome Phenotypes URL: https://www.biorxiv.org/content/early/2017/05/02/133462 [accessed 2018-02-19] [WebCite Cache ID 6xLJAfqyc]
80. Nordby P, Auerbach PL, Rosenkilde M, Kristiansen L, Thomasen JR, Rygaard L, et al. Endurance training per se increases metabolic health in young, moderately overweight men. Obesity (Silver Spring) 2012 Nov;20(11):2202-2212 [FREE Full text] [doi: 10.1038/oby.2012.70] [Medline: 22436841]
81. Ortega JF, Hamouti N, Fernández-Elías VE, Mora-Rodriguez R. Comparison of glucose tolerance tests to detect the insulin sensitizing effects of a bout of continuous exercise. Appl Physiol Nutr Metab 2014 Jul;39(7):787-792. [doi: 10.1139/apnm-2013-0507] [Medline: 24971679]
82. Ishwaran H, Kogalur U, Rao J. Spikeslab: prediction and variable selection using spike and slab regression. R Journal 2010;2(2):68-73.
83. Hastie T, Tibshirani R, Friedman J. The Elements of Statistical Learning: Data Mining, Inference, and Prediction. New York: Springer-Verlag; 2002.
84. Wadsworth WD, Argiento R, Guindani M, Galloway-Pena J, Shelbourne SA, Vannucci M. An integrative Bayesian Dirichlet-multinomial regression model for the analysis of taxonomic abundances in microbiome data. BMC Bioinformatics 2017 Feb 08;18(1):94 [FREE Full text] [doi: 10.1186/s12859-017-1516-0] [Medline: 28178947]
85. Holmes E, Li JV, Marchesi JR, Nicholson JK. Gut microbiota composition and activity in relation to host metabolic phenotype and disease risk. Cell Metab 2012 Nov 07;16(5):559-564 [FREE Full text] [doi: 10.1016/j.cmet.2012.10.007] [Medline: 23140640]

86. Tudor-Locke C, Craig CL, Brown WJ, Clemes SA, De Cocker K, Giles-Corti B, et al. How many steps/day are enough? For adults. Int J Behav Nutr Phys Act 2011 Jul 28;8:79 [FREE Full text] [doi: 10.1186/1479-5868-8-79] [Medline: 21798015]
87. Western Cape Provincial Aids Council. sanac. Western Cape: Western Cape Provincial Aids Council; 2016. Western Cape Provincial Aids Council Annual Progress Report 2014/2015 URL: http://sanac.org.za/wp-content/uploads/2016/04/WC_PSP-ANNUAL-PROGRESS-REPORT-Final.pdf [accessed 2018-02-14] [WebCite Cache ID 6xECS2Smh]

Abbreviations

DXA: dual energy X-ray absorptiometry
FA: fatty-acid
FFSTM: fat-free soft tissue mass
FGDs: focus group discussions
FSIGT: frequently sampled intravenous glucose tolerance test
GCP: Good Clinical Practice
GLUT: glucose transporter
HbA_{1c}: hemoglobin A_{1c}
HDL: high-density lipoprotein
HREC: Human Research Ethics Committee
HUVEC: human umbilical vein endothelial cells
LDL: low-density lipoprotein
MRI: magnetic resonance imaging
OPLS: Orthogonal Partial Least Squares
ORAC: oxygen radical capacity absorbance
OTUs: Operational Taxonomic Units
PARQ: physical activity readiness questionnaire
PCA: Principal Component Analysis
QC: quality control
ROS: reactive oxygen species
SA: South African
SAT: subcutaneous adipose tissue
SMC: Swedish Metabolomics Centre
SOD: superoxide dismutase
T2D: type 2 diabetes
TBARS: thiobarbituric acid reactive substance
VAT: visceral adipose tissue
VCAM: vascular cell adhesion molecule

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Protocol

Tailored Versus Generic Knowledge Brokering to Integrate Mood Management Into Smoking Cessation Interventions in Primary Care Settings: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Both tobacco smoking and depression are major public health problems associated with high morbidity and mortality. In addition, individuals with depression are almost twice as likely to smoke and less likely to achieve smoking cessation. In the Smoking Treatment for Ontario Patients program, an established smoking cessation program in Ontario, Canada, 38% of smokers in primary care settings have current or past depression with 6-month quit rates that are significantly lower than those without depression (33% versus 40%, $P<.001$). Integrating self-help mood management (eg, relaxation exercises and mood monitoring) with smoking cessation treatment increases long-term quit rates by 12%-20%. However, integration in real-world settings has not been reported. It is unclear which knowledge translation strategy would be more effective for motivating clinicians to provide resources on mood management to eligible patients.

Objective: The objectives of this study are to investigate the following comparisons among depressed smokers enrolled in a smoking cessation program: 1) the effectiveness of generalized, exclusively email-based prompts versus a personalized knowledge broker in implementing mood management interventions; 2) the effectiveness of the two knowledge translation strategies on smoking quit rates; and 3) the incremental costs of the two knowledge translation strategies on the implementation of mood management interventions.

Methods: The study design is a cluster randomized controlled trial of Family Health Teams participating in the Smoking Treatment for Ontario Patients program. Family Health Teams will be randomly allocated 1:1 to receive either generalized messages (related to depression and smoking) exclusively via email (group A) or be assigned a knowledge broker who provides personalized support through phone- and email-based check-ins (group B). The primary outcome, measured at the site level, is the proportion of eligible baseline visits that result in the provision of the mood management intervention to eligible patients.

Results: Recruitment for the primary outcome of this study will be completed in 2018/2019. Results will be reported in 2019/2020.

Conclusions: This study will address the knowledge gap in the implementation strategies (ie, email-based prompts versus a knowledge broker) of mood management interventions for smokers with depression in primary care settings.

Trial Registration: ClinicalTrials.gov NCT03130998; https://clinicaltrials.gov/ct2/show/NCT03130998 (Archived on WebCite at www.webcitation.org/6ylyS6RTe)

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KEYWORDS

tobacco; depression; health care practitioner; primary health care; knowledge broker; clinical decision support system; screening; brief intervention; integrated care pathways

Introduction

Background

Both tobacco smoking and depression are major public health problems with high morbidity and mortality [1-4]. Individuals with depression are almost twice as likely to be smokers [5-7], have lower long-term smoking abstinence (odds ratio [OR] 0.81, 95% CI 0.67-0.97) [1], and experience greater addiction severity and negative mood when quitting smoking [8-11].

Self-help mood management (eg, relaxation exercises and mood monitoring) integrated with smoking cessation treatment increases long-term quit rates by 12%-20% [3,4,12-15]. However, it remains unclear what knowledge translation (KT) strategy would be most effective in engaging practitioners to implement a mood management integrated care pathway (ICP) into primary care settings [16-20]. Two strategies that are commonly used in Canada to promote evidence-based practices include email communications and knowledge brokers (KBs) [17]. Emails provide targeted messages that connect relevant research evidence to specific practitioners, while KBs work one-on-one with practitioners to facilitate the implementation of an evidence-informed intervention [21] Several studies have shown that context where the intervention is being implemented is essential to take into account, in deciding which KT strategy to use [16,17]. Unfortunately, it is not known which of these KT strategies would be the most effective among Family Health Teams (FHTs) in Ontario, Canada. In Ontario, FHTs are primary health care organizations that include a team of family physicians, nurse practitioners, registered nurses, social workers, dietitians, and other professionals who work together to provide primary health care for their community [21].

Objective

This study aims to assess whether email updates versus a KB (who will communicate with health care providers on an as-needed basis) is more effective at enabling practitioners within FHTs to provide their patients with mood management resources when needed. In addition, it will explore which of these KT strategies has the greatest effect on smoking abstinence and depressive symptoms at time of follow-up. We will also examine the incremental cost effectiveness of the two KT strategies, the proportion of eligible smokers who report using the resources, smoking cessation outcomes compared to patients without depressive symptoms, and practitioner improvement in knowledge, attitudes, skills, and satisfaction in addressing depressive symptoms in smokers.

In this paper, we describe the protocol for a cluster randomized trial. This design was chosen because the intervention cannot be delivered to individual practitioners within a clinic without substantial risk of contamination across study arms. The trial will be operationalized through the Smoking Treatment for Ontario Patients (STOP) program, an established smoking cessation program in Ontario, Canada. The STOP program offers up to 26 weeks of smoking cessation treatment, consisting of nicotine replacement therapy and behavioral counseling, at no cost to the patient.

Methods

Inclusion Criteria

Site Level

Family Health Teams (FHTs) in Ontario, Canada implementing an existing smoking cessation program (ie, the STOP program) and using the STOP's online portal at the time of the study are eligible to participate. All FHTs operational in the STOP program as of November 2017 (n=153) will be eligible for randomization, except for those that do not use the online program portal at the time of patient enrollment (n=25). We anticipate that 128 FHTs will be randomized into the trial.

Patient Level

In order for a participant to be eligible for the trial, their baseline enrollment survey must be administered by the health care provider, in English, into the online portal in real time, so that the clinical interaction can be supported by the STOP portal. Therefore, those patients who are administered the baseline survey on paper, or in French, will be excluded. Patients, at the time of enrollment, must have depression (determined by a Patient Health Questionnaire [PHQ-9] score>9) or report a past diagnosis of depression.

Pre-Implementation

To understand the needs of the FHTs and the importance of treating depression in the smoking cessation program, we developed a survey which measures organizational readiness and the extent to which an organization is willing and able to implement a specific intervention [22]. The survey consists of 12 questions addressing the six components of The National Implementation Research Network's Hexagon Tool (ie, need, fit, resources, evidence, readiness, and capacity) [23], as well as the three readiness components described by Scaccia et al [24] (ie, motivation, general capacities, and specific capacities) [24]. Based on answers to this survey, organizations were grouped into two categories: most ready (n=44), and least ready (n=40). Organizations that did not answer the questionnaire (n=41) will be grouped together in a group labeled "unknown readiness." The detailed answers from this survey will be useful for developing a KT strategy that will allow the project team

to make informed decisions about their approach to change management.

In order to increase practitioners' competencies to deliver a brief mood management, two interactive webinars will be presented to communicate best practices for integrating evidence-based mood interventions into smoking cessation programming. The webinar audience will include the STOP Community of Practice (n=300) consisting of implementers, physicians, and executive directors, who interact through bi-weekly teleconferences to communicate updates, clarify procedures, address barriers or gaps in program delivery, and share experiences with other practitioners.

Trial Design

Study clusters (ie, FHTs) will receive either generalized messages (related to depression and smoking) exclusively through email (group A) or be assigned a KB who will provide personalized support through phone- and email-based check-ins (group B).

Practitioners from group A will receive one email per month for one year. The first email will provide an electronic copy of a relevant Cochrane review [15], and a short description of the new depression ICP that will be integrated into the STOP portal. Subsequent communications will be based on general needs identified throughout the study. Practitioners from group B will receive individualized support from a KB communicating through interactive technology (ie, Skype) on an as-needed basis. The KB will be certified in tobacco cessation counseling and will have completed a specialty course on tobacco addiction treatment for individuals with mental illness [25,26].

Clinics are the unit of randomization. Two stratification factors are defined: (1) organizational readiness (described previously) with three levels, and (2) clinic size with two levels, resulting in six strata. Expected clinic size will be estimated based on past STOP enrollment because the actual number of eligible trial participants clinics will enroll is not directly observable a priori. Within each readiness stratum, the two levels of clinic size were set such that expected total enrollment in the two levels would be balanced. Within each of the six combined strata, clinics were randomly allocated in a 1:1 allocation ratio to control (group A) or intervention (group B). Treatment allocation (randomization) for each clinic was determined for all operational clinics en masse. Any clinic that began implementing the STOP program after the randomization cut-off date (Nov 14, 2017) will not be eligible for participation in the trial. The random assignment of treatment to clinic was computer generated using the ralloc command of statistical computer software Stata V.14.

Blinding

This pragmatic, cluster trial is designed to evaluate an intervention to change practitioners' behavior. Blinding of the clinic through its practitioners will therefore not be possible as the practitioner will be aware of the presence or absence of the KB. Participating clinics will not be informed of their treatment allocation until the trial begins. Data analysis will be blinded to treatment allocation.

Interventions

Patient Screening and Brief Intervention

Across all sites, practitioners will receive the same depression ICP integrated into the STOP portal. Currently, patients are asked to self-report on past diagnosis of depression and screened for current depression using the PHQ-9. The PHQ-9 is a self-completed, 9-item instrument with each item aligning with the Diagnostic and Statistical Manual of Mental Disorders (version IV)'s criteria for depression, and developed specifically for use in primary care [27,28]. As part of the new ICP, the STOP portal will identify patients screened as having current or past depression, and prompt practitioners to provide a brief intervention and refer an evidence-based package of resources [29,30] (see Figure 1). Brief intervention messaging will be designed using the Canadian Network for Mood and Anxiety Treatments guidelines [31] and tailored to patients' depression levels based on their PHQ-9 score. Levels can range anywhere from low risk of depression, which would warrant the usual standard of care, to major depression with severe consequences [31]. If patients' screening results indicate risk of moderate or severe depression, practitioners will be prompted to consult with a team physician to determine next steps (eg, medication adjustment or psychiatric referral). For patients who endorse suicidal ideation, the ICP will guide practitioners to conduct an additional assessment. Whenever an intervention is warranted, practitioners will be encouraged to discuss other health risk behaviors that influence patient mood, including alcohol use and stress. Figure 1 presents a visual depiction of the study work flow.

The evidence-based resource package, which practitioners will be able to print or email it to patients, will include:

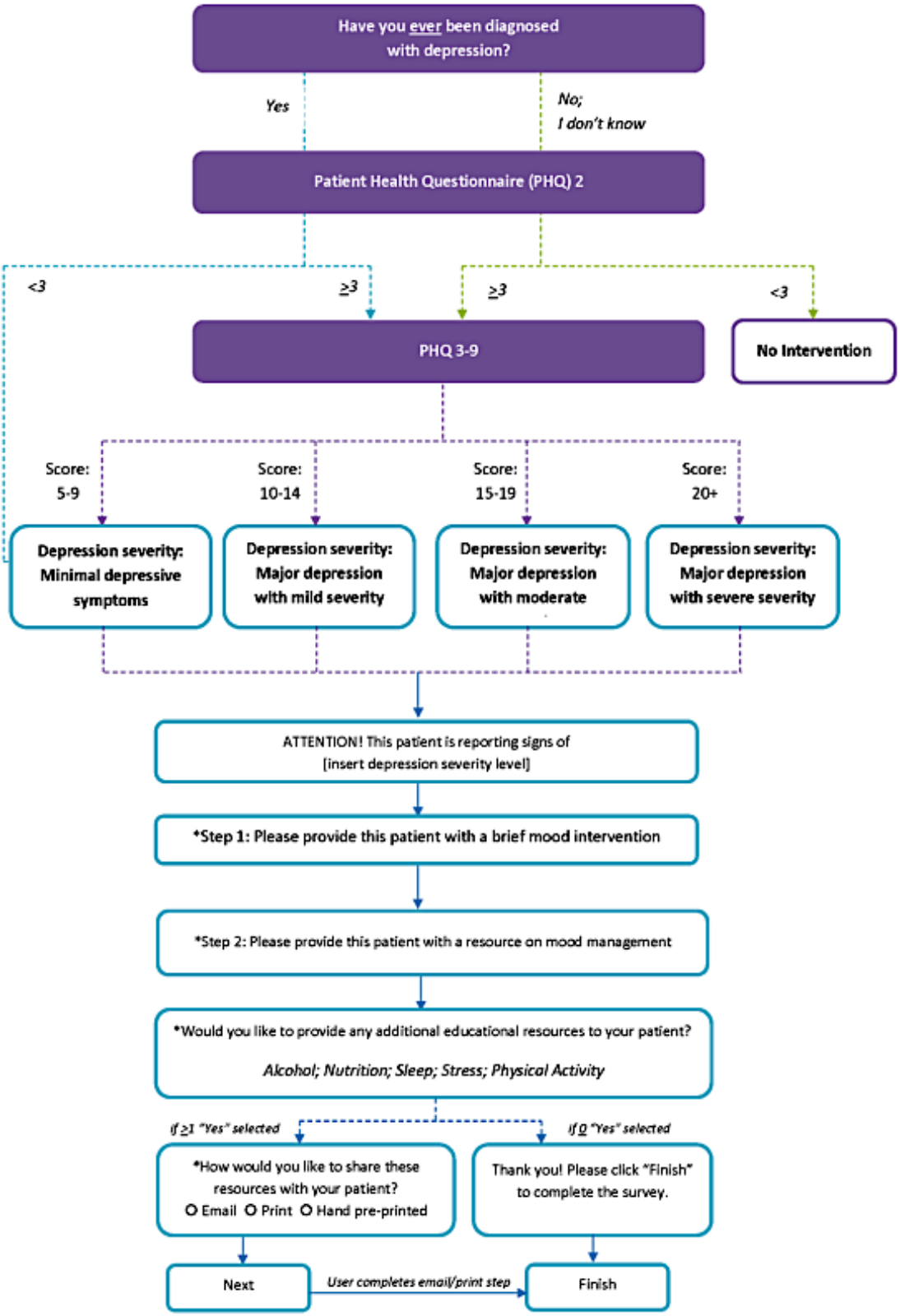
- Relaxation and mindfulness exercises
- Self-monitoring sheets to record each cigarette smoked, the activities they engaged in, and overall mood at the end of each day for 2 weeks
- Problem-solving attitudes and skills-building activities

Outcomes

The primary outcome will be the provision of the mood management intervention to eligible patients upon completion of the STOP smoking cessation program enrollment. This dichotomous outcome will be measured as positive by a response of "Patient accepted the resource" to the practitioner question "Did the patient accept or decline the resource?". In contrast, the outcome will be measured as negative if given a response of "Patient declined the resource" to the practitioner question "Did the patient accept or decline the resource?" or a response of "no" to the practitioner directive "Provide this patient with resources on mood management."

The secondary outcome will be patient smoking abstinence at the 6-month follow-up survey, as measured by a negative response to the seven-day point prevalence question "Have you had a cigarette, even a puff, in the last 7 days?". Self-reporting has been verified as a valid estimate of smoking status [32].

Figure 1. Study workflow diagram.



The tertiary outcome will be a cost-effectiveness analysis (CEA), evaluating the delivery of each intervention from the health care system, and societal perspectives. The CEA will include the costs of developing, maintaining, and running each intervention in addition to costs associated with personnel, training, supplies, and services. The incremental cost-effectiveness ratio (ICER) will be the primary outcome of the CEA. An additional measure of interest will be the 95% confidence interval for the ICER, which will be estimated using nonparametric bootstrap resampling techniques [33-36]. This method is commonly used when undertaking economic evaluations alongside clinical trials [37,38].

Other outcomes measured in this study will include change in PHQ-9 score between the baseline and 6-month follow-up surveys, the proportion of eligible smokers who report using the materials, smoking cessation outcomes compared to patients without depression, and practitioner improvement in knowledge, attitudes, skills, and satisfaction in addressing depression in smokers.

Covariates

Patient characteristics known to affect quit outcomes include age, gender, socioeconomic status, having a quit date, alcohol and other substance use, other mental health diagnosis and the Heaviness of Smoking Index [39]. Site and patient level covariates will be treated as potential confounders in the statistical analyses.

Sample Size

A sample size of 1224 patients per group (2446 total) was estimated using a method that accounts for intracluster correlation (ICC) within each FHT and uneven cluster sizes [40]. Using past STOP enrollment as a data source, we estimated an ICC of ρ=.032, cluster size variation coefficient of 1.24, an average annual enrolment of 24 patients, the proportion of control group patients who are provided the mood management intervention (p1) to be 0.08, and set alpha=.05 and power=.80. The minimum desired effect size was set at a risk difference=0.06. Based on enrollment in 2016-2017, we estimate the required sample size for the primary outcome will be achieved in less than 12 months.

Statistical Analysis

All analyses will adopt an intention-to-treat principle in which sites and patients will be analyzed in the trial arm to which they are randomized. Cluster specific methods will be used because the practices, rather than patients, will be randomized, and variance in how patients are managed, and in patient quit outcomes, will be partly explained by the practice.

Primary and Secondary Outcomes

The association between the KT intervention and the primary outcome (ie, delivery of mood management interventions) will be analyzed using a generalized estimating equation (GEE) fitted for logistic regression, using a population-averaged method. Stratification variables will be included as covariates. An exchangeable correlation matrix and robust standard errors will be specified. All outcomes are recoded by the STOP portal system and thus a full case analysis will be used.

The association between KT intervention and the secondary outcome (ie, smoking abstinence at 6-month follow-up) will be analyzed using a GEE as described above. All patients are invited to complete the 6-month follow-up survey, but not all do, so missing outcome data are expected. Therefore, we will conduct a single imputation of the best-case scenario (all patients not smoking) and a single imputation of the worst-case scenario (all patients smoking). If the analyses from the two case scenarios imply different conclusions, multiple imputations will be performed accounting for the clustered structure of the data. All study analyses will be performed in Stata 14 [41].

Tertiary Outcomes

In order to conduct a cost-effectiveness analysis, we will estimate an ICER for two outcomes: number of times resources are provided to patients (health provider side) and smoking quit rates (patient side). The ICER will be calculated as the difference in discounted mean costs between intervention groups A and B divided by the difference in the outcome, using the following formula: $ICER=(C_i–C_c)/(E_i–E_c)$, where C_i is the adjusted annual costs of group B, C_c is the adjusted annual costs of group A, E_i is the effect in group B, and E_c is the effect in group B. One-way deterministic sensitivity analyses will be performed to evaluate the robustness of our results.

Ethical Approval and Trial Status

The study was reviewed by the Research Ethics Board at the Centre for Addiction and Mental Health (approval number: 065-2016). The trail is registered with ClinicalTrials.gov (ID: NCT03130998). At the time of manuscript submission, the readiness survey was administered, but recruitment was not completed.

Results

Recruitment for the primary outcome of this study will be completed in 2018/2019. Results will be reported in 2019/2020.

Discussion

It is well known that the process of integrating research evidence into practice is slow and complex [42]. Even though there have been many strategies evaluated to improve how health care professionals care for their patients, there is still no clear answer as to which is the most effective, and cost-effective, strategy to use [16,17]. Two strategies that are commonly used to promote practice change include (1) tailored and targeted messages that connect relevant research evidence to practice users [43]; and (2) KBs who work one-on-one with decision makers to facilitate evidence-informed decision-making [16].

This clinical trial will address the knowledge gap in the implementation approach associated with the use of email-based prompts versus a KB in mood management interventions for smokers with depression in primary care settings. With at least one life saved from a tobacco-related death for every two smokers who quit [44], the potential patient-level impact will extend well beyond the study duration. Assuming both approaches are equally effective at achieving a modest probability (10%) of practice change and knowing there should be a 12%-20% improvement in the likelihood of quitting smoking due to use of a mood management intervention, we would expect 19 to 32 patients with depression to quit smoking. An additional benefit to patients will be a potential improvement in their depression scores as a result of the specialized care and resources provided by clinicians as part of this study.

In addition, the Web-based portal used by STOP overcomes the issue of compatibility across various electronic medical records in FHTs. Adding a depression intervention to this system could lead to a system-wide implementation of integrated depression care pathways at a relatively low cost, potentially reaching 2.25

million Ontarians registered at these FHTs. Moreover, a technology-based KB model will help reduce travel costs and expand the reach of KBs in the future.

Finally, rapid and efficient implementation in other settings participating in the STOP program, such as Community Health Centres, addiction agencies, Public Health Units, and Nurse Practitioner–Led Clinics, is possible at a relatively low cost. We will also have high quality data on these populations for planning and monitoring the effects of interventions in primary care settings.

Some potential limitations should be acknowledged. As noted earlier, health care practitioners will not be blinded to the treatment allocation. During this study, a health care practitioner might work in two different clinics, one assigned to group A, and one to group B. In this case, there is the possibility of contamination of knowledge, as the health care practitioner might apply knowledge obtained from the KB advice received while working in a group B clinic to patients in their group A clinic. This possible contamination could decrease the trial effect and lead to a more conservative effect estimate. However, we anticipate that this will be a rare occurrence. In addition, there is a risk that detecting change in the abstinence rates may be underpowered when estimating the ICER for the economic evaluation.

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Conflicts of Interest

None declared.

References

1. Hitsman B, Papandonatos G, McChargue D, DeMott A, Herrera M, Spring B, et al. Past major depression and smoking cessation outcome: a systematic review and meta-analysis update. Addiction 2013 Feb;108(2):294-306 [FREE Full text] [doi: 10.1111/add.12009] [Medline: 23072580]
2. Weinberger AH, Pilver CE, Desai RA, Mazure CM, McKee SA. The relationship of major depressive disorder and gender to changes in smoking for current and former smokers: longitudinal evaluation in the US population. Addiction 2012 Oct;107(10):1847-1856 [FREE Full text] [doi: 10.1111/j.1360-0443.2012.03889.x] [Medline: 22429388]
3. Blalock JA, Robinson JD, Wetter DW, Schreindorfer LS, Cinciripini PM. Nicotine withdrawal in smokers with current depressive disorders undergoing intensive smoking cessation treatment. Psychol Addict Behav 2008 Mar;22(1):122-128. [doi: 10.1037/0893-164X.22.1.122] [Medline: 18298238]
4. Kahler CW, Brown RA, Ramsey SE, Niaura R, Abrams DB, Goldstein MG, et al. Negative mood, depressive symptoms, and major depression after smoking cessation treatment in smokers with a history of major depressive disorder. J Abnorm Psychol 2002 Nov;111(4):670-675. [Medline: 12428781]
5. Hall SM, Prochaska JJ. Treatment of smokers with co-occurring disorders: emphasis on integration in mental health and addiction treatment settings. Annu Rev Clin Psychol 2009;5:409-431 [FREE Full text] [doi: 10.1146/annurev.clinpsy.032408.153614] [Medline: 19327035]
6. Kalman D, Morissette SB, George TP. Co-morbidity of smoking in patients with psychiatric and substance use disorders. Am J Addict 2005;14(2):106-123 [FREE Full text] [doi: 10.1080/10550490590924728] [Medline: 16019961]
7. Lasser K, Boyd J, Woolhandler S, Himmelstein D, McCormick D, Bor D. Smoking and mental illness: A population-based prevalence study. JAMA 2000;284(20):A.
8. Bolam B, West R. Gunnell D: Does smoking cessation cause depression and anxiety? Findings from the ATTEMPT cohort. Nicotine & Tobacco Research : Official Journal of the Society for Research on Nicotine and Tobacco 2011;13(3):209-214. [doi: 10.1093/ntr/ntq244]
9. Gierisch J, Bastian L, Calhoun P, McDuffie J, Williams J. Smoking cessation interventions for patients with depression: A systematic review and meta-analysis.. J Gen Inter Med 2012;27(3):A. [doi: 10.1007/s11606-011-1915-2]
10. Torres LD, Barrera AZ, Delucchi K, Penilla C, Pérez-Stable EJ, Muñoz RF. Quitting smoking does not increase the risk of major depressive episodes among users of Internet smoking cessation interventions. Psychol Med 2010 Mar;40(3):441-449 [FREE Full text] [doi: 10.1017/S0033291709990560] [Medline: 19627638]
11. Weinberger A, Mazure C, Morlett A, McKee SA. Two decades of smoking cessation treatment research on smokers with depression: 1990-2010. Nicotine Tob Res 2013 Jun;15(6):1014-1031 [FREE Full text] [doi: 10.1093/ntr/nts213] [Medline: 23100459]
12. Prochaska J, Hall S, Tsoh J, Eisendrath S, Rossi J, Redding C, et al. Treating tobacco dependence in clinically depressed smokers: effect of smoking cessation on mental health functioning. Am J Public Health 2008 Mar;98(3):446-448. [doi: 10.2105/AJPH.2006.101147] [Medline: 17600251]

13. Thorsteinsson HS, Gillin JC, Patten CA, Golshan S, Sutton LD, Drummond S, et al. The effects of transdermal nicotine therapy for smoking cessation on depressive symptoms in patients with major depression. Neuropsychopharmacology 2001 Apr;24(4):350-358 [FREE Full text] [doi: 10.1016/S0893-133X(00)00217-7] [Medline: 11182530]
14. Tsoh JY, Humfleet GL, Muñoz RF, Reus VI, Hartz DT, Hall SM. Development of major depression after treatment for smoking cessation. Am J Psychiatry 2000 Mar;157(3):368-374. [doi: 10.1176/appi.ajp.157.3.368] [Medline: 10698811]
15. van DMR, Willemsen M, Smit F, Cuijpers P. Smoking cessation interventions for smokers with current or past depression. Cochrane Database Syst Rev 2013 Aug 21;8(8):CD006102. [doi: 10.1002/14651858.CD006102.pub2] [Medline: 23963776]
16. Dobbins M, Robeson P, Ciliska D, Hanna S, Cameron R, O'Mara L, et al. A description of a knowledge broker role implemented as part of a randomized controlled trial evaluating three knowledge translation strategies. Implement Sci 2009 Apr 27;4:23 [FREE Full text] [doi: 10.1186/1748-5908-4-23] [Medline: 19397820]
17. Dobbins M, Hanna S, Ciliska D, Manske S, Cameron S, Mercer S, et al. A randomized controlled trial evaluating the impact of knowledge translation and exchange strategies. Implementation Sci 2009 Sep 23;4(1):A. [doi: 10.1186/1748-5908-4-61]
18. Grimshaw J, Eccles MP. Is evidence-based implementation of evidence-based care possible? Med J Aust 2004 Mar 15;180(6 Suppl):S50-S51. [Medline: 15012580]
19. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. The Lancet 2003 Oct;362(9391):1225-1230. [doi: 10.1016/S0140-6736(03)14546-1]
20. Lavis J, Davies H, Oxman A, Denis J, Golden-Biddle K, Ferlie E. Towards systematic reviews that inform health care management and policy-making. J Health Serv Res Policy 2005 Jul;10 Suppl 1:35-48. [doi: 10.1258/1355819054308549] [Medline: 16053582]
21. Government of Canada. Family Health Teams. URL: http://www.health.gov.on.ca/en/pro/programs/fht/ [accessed 2018-04-18] [WebCite Cache ID 6ymGiU3yS]
22. Drzensky F, Egold N, van Dick R. Ready for a Change? A Longitudinal Study of Antecedents, Consequences and Contingencies of Readiness for Change. Journal of Change Management 2012 Mar;12(1):95-111. [doi: 10.1080/14697017.2011.652377]
23. Blase K, Kiser L, Van Dyke M. The Hexagon Tool: Exploring Context. Chapel Hill, NC: National Implementation Research Network; 2013.
24. Scaccia JP, Cook BS, Lamont A, Wandersman A, Castellow J, Katz J, et al. A practical implementation science heuristic for organizational readiness: R=MC. J Community Psychol 2015 Apr;43(4):484-501 [FREE Full text] [doi: 10.1002/jcop.21698] [Medline: 26668443]
25. Herie M, Connolly H, Voci S, Dragonetti R, Selby P. Changing practitioner behavior and building capacity in tobacco cessation treatment: the TEACH project. Patient Educ Couns 2012 Jan;86(1):49-56 [FREE Full text] [doi: 10.1016/j.pec.2011.04.018] [Medline: 21612884]
26. Nicotine Dependence Clinic. Training Enhancement in Applied Cessation Counselling and Health. TEACH 2011.
27. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 1999 Nov 10;282(18):1737-1744. [Medline: 10568646]
28. Spitzer RL, Williams JB, Kroenke K, Hornyak R, McMurray J. Validity and utility of the PRIME-MD patient health questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. Am J Obstet Gynecol 2000 Sep;183(3):759-769. [Medline: 10992206]
29. Muñoz RF, Barrera AZ, Delucchi K, Penilla C, Torres LD, Pérez-Stable EJ. International Spanish/English Internet smoking cessation trial yields 20% abstinence rates at 1 year. Nicotine Tob Res 2009 Sep 10;11(9):1025-1034 [FREE Full text] [doi: 10.1093/ntr/ntp090] [Medline: 19640833]
30. Muñoz RF, Lenert LL, Delucchi K, Stoddard J, Perez JE, Penilla C, et al. Toward evidence-based Internet interventions: A Spanish/English Web site for international smoking cessation trials. Nicotine Tob Res 2006 Feb;8(1):77-87. [doi: 10.1080/14622200500431940] [Medline: 16497602]
31. Patten SB. Updated CANMAT Guidelines for Treatment of Major Depressive Disorder. Can J Psychiatry 2016 Sep;61(9):504-505 [FREE Full text] [doi: 10.1177/0706743716660034] [Medline: 27534886]
32. Wong SL, Shields M, Leatherdale S, Malaison E, Hammond D. Assessment of validity of self-reported smoking status. Health Rep 2012 Mar;23(1):47-53 [FREE Full text] [Medline: 22590805]
33. Drummond MF, Sculpher MJ, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2005.
34. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials. Oxford: Oxford University Press; 2007.
35. Campbell MK, Torgerson DJ. Bootstrapping: estimating confidence intervals for cost-effectiveness ratios. QJM:monthly journal of the Association of Physicians 1999;92(3):177-182. [doi: 10.1093/qjmed/92.3.177]
36. Bachmann MO, Fairall L, Clark A, Mugford M. Methods for analyzing cost effectiveness data from cluster randomized trials. Cost Eff Resour Alloc 2007 Sep 06;5:12 [FREE Full text] [doi: 10.1186/1478-7547-5-12] [Medline: 17822546]

37. Salize HJ, Merkel S, Reinhard I, Twardella D, Mann K, Brenner H. Cost-effective primary care-based strategies to improve smoking cessation: more value for money. Arch Intern Med 2009 Feb 09;169(3):230-5; discussion 235. [doi: 10.1001/archinternmed.2008.556] [Medline: 19204212]
38. Smit ES, Evers SMAA, de VH, Hoving C. Cost-effectiveness and cost-utility of Internet-based computer tailoring for smoking cessation. J Med Internet Res 2013 Mar 14;15(3):e57 [FREE Full text] [doi: 10.2196/jmir.2059] [Medline: 23491820]
39. Borland R, Yong H, O'Connor R, Hyland A, Thompson M. The reliability and predictive validity of the Heaviness of Smoking Index and its two components: Findings from the International Tobacco Control Four Country study. Nicotine & Tobacco Research 2010 Sep 30;12(Supplement 1):S45-S50. [doi: 10.1093/ntr/ntq038] [Medline: 19204212]
40. Rutterford C, Copas A, Eldridge S. Methods for sample size determination in cluster randomized trials. Int J Epidemiol 2015 Jun 14;44(3):1051-1067 [FREE Full text] [doi: 10.1093/ije/dyv113] [Medline: 26174515]
41. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp; 2011. URL: https://www.stata.com/support/faqs/resources/citing-software-documentation-faqs/ [WebCite Cache ID 6ym5ZNdfV]
42. Haynes B, Haines A. Barriers and bridges to evidence based clinical practice. BMJ 1998 Jul 25;317(7153):273-276 [FREE Full text] [Medline: 9677226]
43. Kreuter MW, Wray RJ. Tailored and targeted health communication: strategies for enhancing information relevance. Am J Health Behav 2003;27 Suppl 3:S227-S232. [Medline: 14672383]
44. West R. The clinical significance of “small” effects of smoking cessation treatments. Addiction 2007 Apr 25;102(4):506-509 [FREE Full text] [doi: 10.1111/j.1360-0443.2007.01750.x] [Medline: 17362283]
45. Kreuter MW, Wray RJ. Tailored and targeted health communication: strategies for enhancing information relevance. Am J Health Behav 2003;27 Suppl 3:S227-S232. [Medline: 14672383]
46. West RTCSO'EOSCT. The clinical significance of “small” effects of smoking cessation treatments. Addiction 2007 Apr;102(4):506-509. [doi: 10.1111/j.1360-0443.2007.01750.x] [Medline: 17362283]

Abbreviations

CEA: cost-effectiveness analysis
FHT: Family Health Team
GEE: generalized estimating equation
ICC: intracluster correlation
ICER: incremental cost-effectiveness ratio
ICP: integrated care pathway
KB: knowledge broker
KT: knowledge translation
OR: odds ratio
PHQ-9: Patient Health Questionnaire
STOP: Smoking Treatment for Ontario Patients

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Protocol

Intervention to Increase HIV Testing Among Substance-Using Young Men Who Have Sex With Men: Protocol for a Randomized Controlled Trial

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Abstract

Background: Young men who have sex with men (YMSM) and transgender people in the Detroit Metro Area are the only risk group for whom the incidence of HIV and sexually transmitted infections (STI) has increased since 2000, with HIV incidence nearly doubling among youth. Substance use (including alcohol), which is relatively frequent among YMSM and transgender people, creates barriers to the optimal delivery of HIV prevention and care services. Standard HIV counseling, testing, and referral (CTR) is limited in providing strategies to identify and address substance use. Hence, in its current form, CTR may not be serving the prevention needs of substance-using YMSM and transgender people. Brief counseling interventions, grounded in principles of motivational interviewing, may offer a mechanism to meet the HIV prevention and care needs of substance-using YMSM and transgender people.

Objective: This prospective, 4-arm, factorial randomized controlled trial aims to examine the efficacy of an motivational interviewing–based substance use brief intervention (SUBI) on participants' substance use and engagement in HIV prevention.

Methods: The research implements a prospective randomized controlled trial (Project Swerve) of 600 YMSM and transgender people recruited both online and in person. Eligibility criteria include participants who (1) are between the ages of 15 to 29 years, (2) live in the Detroit Metro Area, (3) self-identify as a man or transgender man or woman, (4) have had sexual contact with a man in the 6 months before enrollment, (5) self-report binge drinking or any substance use in the 3 months before enrollment, and (6) self-report an unknown or negative HIV status upon enrollment. Participants are randomized to receive, 3-months apart starting at baseline, 2 individual sessions. Sessions are CTR-only, SUBI-only, CTR followed by SUBI, or SUBI followed by CTR.

Results: Project Swerve was launched in April 2017 and enrollment is ongoing.

Conclusions: Incorporating a SUBI that utilizes the principles of motivational interviewing into HIV CTR provides an opportunity to tailor counseling services for YMSM and transgender people to address additional client barriers to HIV and STI testing.

Trial Registration: ClinicalTrials.gov NCT02945436; http://clinicaltrials.gov/ct2/show/NCT02945436 (Archived by WebCite at http://www.webcitation.org/6yFyOK57w)

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KEYWORDS

HIV; men who have sex with men; drug abuse; substance use disorders; motivational interviewing

Introduction

Background

Young men who have sex with men (YMSM) and transgender people (TG; herein collectively referred to as YMSMTG) are at heightened risk for HIV and other sexually transmitted infections (STI) [1,2]. The 3 major cities in the Detroit Metro Area (DMA)—Detroit, Flint, and Ann Arbor—are represented in the top 5 Michigan counties with greatest increases of new HIV, chlamydia, gonorrhea, and syphilis infections [1]. Consistent with the national epidemic, YMSMTG in the DMA are the only risk groups for whom HIV and STI incidence has increased since 2000, with HIV incidence among YMSM between the ages of 13 and 25 years nearly doubling [1,2]. YMSM accounted for 72% of new HIV infections and over 80% of new syphilis diagnoses among people aged 13-24 years. Over 75% of gonorrhea-HIV coinfections were among YMSM [1,3].

The Centers for Disease Control and Prevention (CDC) have recommended that HIV and STI testing be repeated frequently (3-6 month intervals) for high-risk YMSMTG (ie, having multiple or anonymous partners with whom they have condomless anal intercourse [CAI] and who report engaging in illicit drug use) [2]. Recent recommendations from a CDC working group on HIV testing for men who have sex with men (MSM) suggest that clinicians can consider the benefits of offering more frequent screening (eg, once every 3 or 6 months) to individual MSM at increased risk for acquiring HIV infection, weighing their patients' individual risk factors, local HIV epidemiology, and local testing policies [2]. Consistent with national trends, YMSM living in the DMA report low adherence to these testing guidelines; data are scant on whether TG in this context are adhering to testing guidelines. In 3 prior studies conducted between 2011 and 2014 with YMSM in this community [4-6], a large proportion of YMSM (15%-36%) had never tested for HIV. Among those who did test for HIV, over 65% reported that they had not tested in the past 12 months. YMSM living with HIV also account for the largest drop-off across the HIV/AIDS continuum of care in the DMA, particularly if they are racial or ethnic minorities and live in neighborhoods characterized by socioeconomic disadvantage [1].

Changes in the use of alcohol, tobacco, and other drugs (ATOD) during adolescence and young adulthood are developmentally noteworthy because they can have short- and long-term consequences that affect one's adult life trajectory including HIV/STI acquisition [7], development of substance use disorders (SUDs), and disruptions in school and job performance [8-14]. Alcohol and marijuana are the most common substances used by youth. National Survey on Drug Use and Health [15] data for the DMA demonstrated that 12.1% of 18- to 25-year-olds needed, but did not receive, treatment for alcohol use and 6.8% of 18- to 25-year-olds needed, but did not receive, treatment for drug use. Given the known synergy between AOD use and HIV risk among YMSMTG [16-21], there is a need to develop HIV prevention interventions that also recognize and tackle issues of substance use [22].

AIDS Service Organizations (ASOs) often serve and are sensitive to the HIV-related needs of underserved YMSMTG. Delivery of HIV services through ASOs has been an efficient rollout mechanism because they reach and affect large numbers of people efficiently; create and establish grassroots policies and procedures that maximize the adoption and diffusion of interventions while considering the community's social context; increase program sustainability and advocacy; and incorporate the needs of specific communities into tailored services. At present, however, HIV test counselors situated in ASOs are not trained to comprehensively and systematically screen for and address ATOD use in counseling, testing, and referral (CTR) sessions—the routine procedure used to test for HIV. Preliminary data from our community partners indicate that lack of AOD screening and counseling within CTR is a missed opportunity. The authors of this study [23] and others [7,24,25] have also documented that HIV-positive persons with problematic patterns of alcohol and stimulant use experience difficulties with HIV disease management and display elevated HIV viral load, demonstrating a need for reducing substance use early to avoid complicating disease management.

Consistent with the National HIV/AIDS Strategy's call [26] to reduce new HIV infections by intensifying prevention efforts in highly impacted communities and increasing rates of routine HIV testing, this protocol outlines an intervention that targets high-risk YMSMTG by including a substance use brief intervention (SUBI) as part of CTR. The intervention builds on prior SUBI research [27-34] and also meets the recommendations of the CDC working group on HIV testing among MSM that recommended more frequent testing among high-risk groups: substance using YMSMTG are clearly at an elevated risk of HIV acquisition and currently underutilize HIV prevention services. Using a consensus approach to conceptualize health behavior change, the model guiding our intervention [35-38] synthesizes social cognitive theories [39], along with the trans-theoretical model of change [40,41] and self-determination theory [42,43]. These theories emphasize social cognitive factors that impact behavior change and have informed ATOD and HIV interventions [12,44-46]. Motivational interviewing (MI) [36], the primary approach used to deliver SUBI, is consistent with these theories [47], focusing on resolving ambivalence about problem behaviors, increasing self-efficacy for change, and enhancing motivation moving toward action [48]. This protocol describes the methods for the testing of the intervention below.

Objective

The prospective, 4-arm factorial randomized controlled trial (RCT) aims to examine the efficacy of Project Swerve, an MI-based SUBI (intervention) compared with the current standard of care CTR (control) on participants' substance use and engagement in HIV prevention.

Methods

Trial Registration, Ethics, Consent, and Institutional Board Approval

The research and ethics presented in this study has been reviewed and approved by the University of Michigan Institutional Review Board (HUM00105125), in addition to the Data Safety Monitoring Board. The study is also registered on ClinicalTrials.gov (NCT02945436).

Trial Design

The research activities involve a 4-arm factorial RCT of approximately 600 AOD-using YMSMTG aged 15-29 years in the DMA. We will follow participants for 18 months, with follow-up assessments collected every 3 months.

The intervention comprises 2 visits separated by 3 months. Participants are randomized to receive either CTR (control) or a SUBI-adapted version of CTR (referred to as SUBI; intervention) in each visit. To examine how the sequencing and dosing of interventions impacts efficacy, we randomize at baseline into a factorial RCT. The control arm will receive CTR-only at both study visits 1 and 2. Experimental arm 1 (CTR+SUBI) will receive CTR at visit 1 and SUBI at visit 2. Experimental arm 2 (SUBI+CTR) will receive SUBI at visit 1 and CTR at visit 2. Experimental arm 3 (SUBI+SUBI) will receive the intervention condition at visits 1 and 2. Individuals who test HIV-positive at study visits 1 or 2 will receive case management and linkage to care, as offered routinely by each ASO where study activities take place.

This 4-arm factorial randomized design will help answer 3 important questions: (1) what is the impact of adapting current CTR to include SUBI on HIV engagement in care and sexual- and substance-related risk-taking behaviors among high-risk YMSMTG; (2) what combination of services (CTR-only, CTR+SUBI, SUBI+CTR, SUBI+SUBI) has the greatest impact on engagement in HIV prevention (where engagement in care is defined as routine HIV testing for seronegative YMSMTG and linkage and retention in care for seropositive YMSMTG); and (3) if effective, what are the costs of delivering SUBI compared with those of delivering CTR?

Participants

Eligible participants are: (1) between 15 and 29 years old, (2) identify as a cisgender man or as transgender man or woman, (3) have had sexual contact with a man (oral or anal) in the last 6 months, (4) live in the DMA, (5) have unknown or negative HIV status, (6) and report binge drinking or using any illicit substance or nonmedical use of prescription drugs in the prior 3 months. The ATOD eligibility criteria are measured using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) [49] to assess frequency of AOD use in the prior 3 months.

Recruitment

Participants are recruited using Web-based advertisements on social media websites (eg, Facebook, Grindr), which will be tailored to target YMSMTG in the DMA. Recruitment will also occur in person at local venues and community outreach events in the region.

Screening

Eligible participants will be invited for their baseline visit at the ASO closest to them: offices are available in Ann Arbor, Ypsilanti, Detroit, and Flint, allowing access by participants from across the DMA. Participants who present for participation in the trial will have already set up a study account online and completed an online baseline survey with informed consent given online. When they arrive for their first visit, they will be reconsented verbally and offered a physical copy of the consent form. A study counselor will be available to answer any questions that the participants may have about the study before they decide to participate. Participants who do not consent to participate in the trial will be offered free HIV testing and counseling. Resources will be readily available for providing tools to avoid ATOD-related risks (eg, reducing ATOD use or consequences), and referrals to community resources as needed (eg, psychosocial services, leisure activities not involving substance use).

Randomization

Participants will be randomly assigned to 1 of the 4 conditions using a 1:1:1:1 treatment allocation. The treatment assignments will be generated with the use of a pseudo-random-number generator with permutated blocks that will be used to ensure balance between the numbers of YMSMTG assigned to each treatment. Assignments to the control or intervention arms will use concealment of allocation techniques designed to minimize assignment bias including generating, in advance, the sequence of assignment in sealed envelopes, which will be opened by the counselor at the time of randomization. When YMSM are randomized to receive CTR-only at a visit, they will receive standard CTR (30 min). YMSM randomized to SUBI at a study visit will receive the CTR that has been adapted to include the SUBI. On average, both conditions will last approximately 30 min.

Incentives

Participants will receive US $25 at each ASO visit and US $30 for each follow-up, making the total potential incentives (if all assessment visits are completed) US $200 per participant.

Intervention

Study interventionists will be trained to deliver SUBI and will offer YMSMTG the opportunity to explore and strengthen motivations for changing their ATOD use during session. Interventionists are trained in CTR and typically have a Master's degree in Public Health, Social Work, or a health-related discipline. The SUBI intervention consists of 2 components. Similar in style to other MI-based brief interventions for substance use and related risk behaviors [50-54], Component 1 focuses on employing MI to explore substance use (illicit drugs, misuse of prescription drugs, alcohol) and co-occurring sexual risk-taking with cultural and developmental tailoring for YMSMTG. There are 7 steps to Component 1 (see Table 1). To maintain the MI spirit, participants are asked for permission to begin the session and also when transitioning through different steps of each component.

Table 1. Steps taken during Component 1 of the Swerve intervention compared with standard counseling, testing, and referral (CTR) steps.

Steps	Swerve intervention (SUBI[a]) Component 1: Alcohol, drugs, and sex	CTR: HIV prevention counseling
1	Rapport-building, exploring participants' strengths and near-term goals	Introduce and orient the participant/client to the session and conduct of HIV test
2	Review of alcohol and substance use and conduct of HIV test	Identify risk behaviors and circumstances
3	Psychoeducation about alcohol/drugs and HIV risk	Identify safer goal behavior
4	Explore benefits to reducing substance use/harm reduction	Identify action steps
5	Build commitment to change	Provide referrals and support
6	Summary of Steps 1-6	Summarize and close
7	Explore possible reactions to HIV test results	—

[a]SUBI: substance use brief intervention.

In Step 1, counselors focus on MI-based engagement strategies to explore areas of strength and aspirations that the participant holds. Affirming these areas allows counselors to build rapport with participants and begin to uncover potential sources of motivation to change risky behaviors.

Step 2 invokes the MI process of focusing by reviewing participants' recent substance use. Counselors explore participants' frequency of current substance use, their motivations for use, and elicit any consequences to using substances. Possible links between substance use and risky sexual behaviors are examined by querying the potential role of substance use in having sex or hooking up and use of condoms. Counselors are trained to listen for, elaborate on, and evoke change talk as it begins to occur in Step 2 and throughout the remainder of the session. In Step 2, the counselor conducts the rapid HIV test.

In Step 3, counselors provide basic psychoeducation about how substance use and/or risky sex can impact risk for HIV infection, tailored to the participant's own high-risk behaviors.

Step 4 seeks to elicit from participants any potential benefits to changing their substance use (eg, reducing use, ceasing use, or employing harm reduction), with a specific emphasis on how changing use can impact the risk for HIV transmission.

In Step 5, counselors reflect on participants' perceived benefits and assess the importance of and readiness to change using the visual of a ruler in order to elicit their current stage of change. If participants are interested in changing, the counselor uses evocative questions to elicit a potential first step; for those not interested in making changes currently, the counselor elicits participants' views on what might prompt them to consider a change in the future.

In Step 6, the counselor provides a strategic summary of what was discussed during Component 1. Here, counselors are beginning to transition into disclosing the HIV results from the test that was conducted in Step 2 and it is important for participants to think about what was discussed in each step as a whole.

Finally, in Step 7, counselors elicit and reflect how participants would react to a positive (reactive) or negative (nonreactive) result before disclosing the HIV results.

Component 2 varies based on the HIV test results (see Table 2), with the focus across intervention arms including either risk reduction counseling for HIV-negative participants or linkage and retention to HIV care among newly HIV-diagnosed individuals. Throughout Component 2, counselors remain grounded in the MI spirit and use MI skills to engage the participant in a collaborative conversation.

If participants' results are nonreactive, repeat HIV testing and pre-exposure prophylaxis (PrEP) are the focal points of Steps 8 through 12. In Step 8, counselors elicit and reflect participants' responses to receiving a nonreactive result.

Step 9 explores the benefits of repeat testing. Counselors discuss the window period, recommendation for testing every 3-6 months, and how participants feel about repeat testing, particularly eliciting concerns regarding the window period. As with change talk regarding substance use, counselors are trained to reflect selectively and affirm statements favoring repeat testing.

PrEP referrals are discussed in Step 10. Participants are asked what they know about PrEP, and counselors provide additional information and/or referrals to PrEP providers.

In Step 11, counselors tie the goals and strengths from Component 1 into encouraging repeat testing and PrEP evaluation. Possible barriers to repeat testing and PrEP evaluation are discussed along with strategies to overcome these barriers.

Step 12 summarizes what was talked about during Component 2 while affirming the strengths and goals from Component 1. Here, counselors elicit goals with regard to repeat testing and/or PrEP uptake and elicit steps to achieve these goals that are achievable, clear, and have a distinguishable end point. Barriers to achieving the goal are elicited and problem-solved, and strengths are affirmed as a means of supporting follow-through with the goals established. Counselors then thank the participants for their time and end the session. Alternatively, if participants' HIV test results are preliminary reactive, linkage to HIV care is encouraged in Steps 8 through 11. Step 8 focuses on participants' reactions to the test result. Counselors allow the participants to process their emotions and use empathic reflections in response and offering statements of hope.

Table 2. Steps taken during Component 2 of the Swerve intervention.

Steps	Swerve intervention (SUBI[a]) Component 2a: Repeat HIV testing and PrEP[b] (nonreactive results)	CTR[c]: HIV test counseling and partner services (nonreactive results)	Swerve intervention (SUBI) Component 2b: Linkage to HIV care (reactive results)	CTR: HIV test counseling and partner services (reactive results)
8	Response to testing nonreactive result	Meaning of test results	Response to testing HIV positive	Meaning of test results
9	Focus on repeat HIV testing	Cost and benefit analysis of testing	Focus on linkage to HIV care	Cost and benefit analysis of testing
10	PrEP referral	Interpretation of HIV test results	Links to Component 1 (goals, strengths, and substance use as a barrier)	Interpretation of HIV test results
11	Links to Component 1 (goals, strengths, and substance use as a barrier)	Reinforce plan for reducing risk based on test results	Summary and plan for action	Renegotiate risk reduction plan
12	Summary and plan for action	—	—	Discuss disclosure, partner services, appropriate referrals for medical evaluations, and early intervention services
13	—	—	—	Collect specimen for confirmatory testing[d]

[a]SUBI: substance use brief intervention.

[b]PrEP: pre-exposure prophylaxis.

[c]CTR: counseling, testing, and referral.

[d]Each ASO has specific procedure for confirmatory testing. Detroit-Blood draw for confirmatory testing: results in 3 days. Ypsilanti-Rapid test for confirmatory testing: results in 1 min. Flint-Rapid test for confirmatory testing: results in 20 min.

With permission, counselors begin to discuss the importance of linkage to HIV care in Step 9. Counselors explain how people with HIV can live healthy lives provided that they attend medical appointments and take medications while also exploring the participant's perceived benefits of seeing a HIV medical provider.

Step 10 links the strengths and goals from Component 1 as a tool to continue to encourage linkage to care. Possible barriers to linkage to care are explored, with an emphasis on the potential impact of substance use.

Step 11 reflects on the participants' goals for next steps toward linkage to care with an emphasis on eliciting goal-setting with goals that are achievable, clear, and have a defined end point. Counselors provide support to participants by affirming their strengths to meet these goals. Counselors thank the participants for their time and end the session.

Substance Use Brief Intervention at Study Visit 2

For those who received a nonreactive HIV test result at visit 1 and who are randomized to receive SUBI at study visit 2, the same intervention components and steps are delivered, as described above. For those who received a reactive test result at visit 1, the SUBI session focuses employing MI skills to address adherence with HIV care and the role of substance use.

Sample Size and Power

The primary outcome for the proposed trial is successful engagement in care. For those who test seronegative at baseline, we define engagement in care as participation in routine HIV testing. For those who test seropositive at baseline, we define engagement in HIV care as linkage and retention in HIV care (per the Institute of Medicine guidelines of linkage within 30 days of diagnosis and at least 2 physician visits with a CD4 and viral load test in 12 months) and achievement of viral suppression. We define power as correctly identifying the difference in the proportions of YMSM with serospecific engagement in HIV care within 15 months of each active treatment condition (3 arms: SUBI-CTR, SUBI-SUBI, CTR-SUBI) to the control arm (CTR-CTR), thus powering for 3 independent hypothesis tests. Our sample size calculations are based on a 2-sample test of proportions using a 2-sided significance level of $P<.05$ altered by the number of comparisons using a Bonferroni adjustment (significance level is $P=.02$ for 3 comparisons). To have 80% power to compare each active treatment to the control group in a 4-arm trial, we require at least 500 participants to find a 20% difference between each treatment and control and 228 participants to find a 30% difference. To allow for 20% loss to follow-up (our previous trials have each achieved retention rates of >90%), we estimate a sample of 600 YMSMTG to be enrolled.

Participants may continue the study even if they miss follow-ups or visits intermittently over the data collection period. We will compare those who completed different follow-up interviews with those who did not on key predictors from the baseline assessment to check for possible sampling bias due to missing data. Missing data will be minimized by the computer-based entry for all measures. The use of Expectation-Maximization algorithm and multiple imputation approach in longitudinal analyses will help overcome missing data concerns when appropriate.

Outcomes

The trial focuses on 3 sets of outcomes: engagement in HIV prevention and care services; AOD use; and sexual risk. The trial will also measure satisfaction with the intervention.

Engagement in HIV Prevention and Care Services

We will ask YMSMTG having unknown or negative HIV status to indicate the date of any recent HIV and STI tests. At baseline, we will ask participants to note if they have ever been medically diagnosed as having one or more STIs. Among those diagnosed, we will ask if the STI diagnosis occurred in the prior 12 months. In follow-up surveys, we will ask participants to report if they tested for STIs in the prior 3 months and whether any of their tests were reactive.

At each follow-up session (visits 3-7), we will measure the primary outcome of repeat HIV testing. For anyone who tested in each intersurvey period, we will assess the test result and motivations for testing (exposure-related vs regular health checking). For seropositives, the survey will assess the incidence of HIV-related physician visits, including whether CD4 counts and viral load tests were conducted and prescriptions for antiretroviral therapy (ART) were given. We will also ask participants to self-report their adherence to ART using an abbreviated 6-item questionnaire based on the AIDS Clinical Trial Group assessment. Participants are asked to note, using a scale ranging from “never” to “often,” if they missed their HIV medication over the past month for one of the listed reasons. Seropositives will also provide a blood sample for a viral load test. Viral load testing will be done every 6 months. We prioritize viral load tests over a biomarker of adherence, given that adherence is the primary pathway to viral suppression.

Biomarkers for HIV Prevention and Care

In addition to self-reported behavioral measures, the study will also collect biomarkers to test for HIV and STIs. At the intervention visits, HIV testing will be performed as part of CTR. STI screening: For syphilis screening, participants will undergo a blood draw for subsequent unheated serum regain test and, for chlamydia and gonorrhea screening, participants will provide a urine sample and pharyngeal, rectal, and/or vaginal swab cultures. Hepatitis C will be assessed using the OraQuick rapid test. Although we expect prevalence of hepatitis C to be low in an AOD population that has low levels of injection drug use (and thus hepatitis C will not be a secondary outcome), we will include hepatitis C testing to assess prevalence in this population. Those who are asymptomatic and test positive will be referred by study staff to local health care providers for further evaluation and treatment. All other STI tests will be processed by the Michigan Department of Health and Human Services. As required by state law, all new positive STI results will be reported to the State Health Department for the purposes of disease surveillance. The requirement for reporting of confidential test results to the health department will be explained in the informed consent. Condoms and water-based lubricant will be provided to all participants. We will screen for STIs at the final study assessment.

Alcohol and Other Drugs Use, Misuse, and Consequences

We use the ASSIST [49] to assess frequency of AOD use in prior 3 months, a validated measure to screen for the presence of possible alcohol and other substance use disorders. For each substance, the ASSIST assesses frequency of use, cravings, impact of use on key life domains, expressed concern from others, and failed quit attempts to derive a Specific Substance Involvement Score. If respondents indicate alcohol use, we ask the respondent’s frequency with which they had had 5 or more drinks in a row during the last 2 weeks (binge drinking), and how often the respondent drinks to get drunk. We also assess respondents’ use of alcohol and/or illicit drugs during or before condomless sex. We use the Alcohol Use Disorders Identification Test [55], a 10-item screening questionnaire with 3 questions on the amount and frequency of drinking, 3 questions on alcohol dependence, and 4 on problems caused by alcohol.

Biomarkers for Use of Alcohol and Other Drugs

In addition to self-reported behavioral measures of drug and alcohol use, the study will also collect biomarkers of drug and alcohol use. Participants will provide urine samples for on-site toxicology screening using an EZ split key test kit (Redwood Toxicology Laboratory, Inc.). In our prior clinical research with methamphetamine-using MSM, urine samples were obtained for toxicology testing in 98% of study visits. The on-site urine screening kits are designed to test for recent amphetamine, barbiturates, benzodiazepines, buprenorphine, cocaine, marijuana, methadone, methamphetamine, oxycodone, propoxyphene, morphine, and ecstasy. Urine toxicology screening will be used to provide information regarding recent substance use and will be conducted each study visit. Alcohol screening will be used where ethyl glucuronide (EtG) a direct metabolite of ethanol indicates that ethanol has been ingested within the last 3-4 days (80 hours). EtG will be analyzed using the 1-step EtG test dip card. Urine will be collected in a urine specimen cup and the tip of the EtG dip card will be submerged into the urine sample for 15 seconds. EtG will allow us to adjust for under-reporting of recent unhealthy drinking on participants’ surveys and will also be screened at each study visit.

Sexual Behaviors

Sexual behaviors will be assessed using a modified version of the Sexual Practices Assessment Schedule (SPAS) used in previous studies with YMSMTG [56] to explore different sexual acts (oral, vaginal, and anal) with different partner types. SPAS estimates the number of sexual partners and occasions across partner types, as well as the proportion of instances when condoms were not used. We also assess how frequently they report using drugs or alcohol immediately before or during sex. SPAS also ascertains YMSMTG’s HIV status disclosure practices with each partner.

Intervention Acceptability and Satisfaction

YMSMTG will report data on the acceptability of the intervention after completing each intervention session. We will use 2 different assessments: (1) Self-Evaluation Forms (SEF) and (2) Client Satisfaction Questionnaires (CSQ-8). The SEF

is a brief 12-item questionnaire that elicits information about the experience with the intervention (ie, was the intervention interesting, was it relevant to their life, and did they learn from the intervention). The CSQ-8 will be used at the completion of the intervention to assess satisfaction with the intervention. The CSQ-8 has demonstrated high internal consistency across a large number of studies [57]. The SEF and CSQ will take approximately 10 min to complete and will be completed at the ASO on a tablet immediately after intervention delivery at visits 1 and 2.

Statistical Analysis

Descriptive statistics of the clinical and demographic characteristics of the participants will described for all and by treatment group. 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. We will conduct primary analyses of our pooled successful engagement measure using logistic regression analyses to compare each active treatment group with the control in pairwise comparison tests at an adjusted significance level of .017 to reduce Type-I errors in our 4-arm trial. We will then conduct exploratory logistic regression analyses by sero-status. For seronegative YMSMTG, the proportion of participants who obtain at least 2 tests at least 3 months apart within 15 months will be calculated and presented with corresponding 95% exact binomial CIs. Among seropositive YMSMTG, we will examine how intervention conditions influence HIV linkage and retention in care per IOM guidelines. We will also examine for all participants the pursuit of substance use treatment services (if necessary). Hence, for seronegative participants, the outcome will be repeat HIV testing at regular intervals, and for seropositive participants, the outcome will be linkage and retention in care. We will not consider viral suppression in the regression analysis due to the short time period available to achieve suppression. However, we will present descriptive statistics on viral load and suppression across the 4 treatment arms. The regression will be run with group assignment in the model while controlling for patient, structural, and agency characteristics. Interactions between group assignment and these characteristics will be tested to explore potential moderators of treatment effect. We will repeat these analyses for STI/ATOD biomarkers conducted during the trial. Additional analyses include comparing groups in (1) the average number of tests obtained using Poisson regression and (2) time to getting tested using repeated events survival analysis.

We will test for intervention effects over time on sexual risk (eg, CAI events) and drug use (eg, reduction in ATOD use and ATOD-related consequences) outcomes. We will use the general framework of generalized linear mixed models [58-60] to model the longitudinal outcome trajectories [61-63]. Note that some of our outcomes are measured as binary, some as count, and some as continuous measures and thus need to be treated differently. Assuming a linear time trend, visit can be coded from 0 to 7, or it can be simply coded as a categorical variable representing the distinct effect of each visit compared with the baseline. The interaction coefficients are of interest here, measuring the difference in the rate of change in outcomes across the 4 treatment groups. 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. To ensure robustness, we will also apply an exchangeable working correlation structure to its corresponding generalized estimating equation model [64].

Intervention Fidelity and Supervision

The study team balanced the clinical and ecological validity of the design and procedures of project Swerve as the intervention was developed for YMSMTG in the DMA. First, we recognize that the CTR and SUBI treatments may have different amounts of contact time with participants. Although it is possible that contact time may influence intervention effects across CTR and SUBI conditions, the control sessions may actually last longer than often expected during CTR, given the high-risk characteristics of our study participants. In our analyses, we will also examine whether length of sessions differ statistically across treatment arms and include time spent in each session as a covariate due to its potential confounder. Second, we recognize that there may be variability in how counselors deliver CTR and SUBI sessions, which could confound our ability to measure the intervention's strength. We have put in place several procedures to minimize potential biases including training counselors using 2-day training with boosters and ongoing group and individual supervision, allowing counselors at each site—who are not trained in the intervention—to deliver CTR, and monitoring and addressing treatment fidelity for both conditions throughout the trial using the Motivational Interviewing Treatment Integrity-4 rating system [65].

Examine Cost-Effectiveness and Sustainability

The study team will collect information on: (1) time spent by study staff for training, supervision, and technical assistance of counselors; (2) time participants spent in a counseling session; and (3) costs associated with test counselor delivery of the intervention. Capital equipment cost (eg, computer) and facility cost (eg, rent, telephone) at the study sites that are attributable to our intervention will be obtained from each site's accounting records. Capital equipment cost will be distributed over a 4-year period with a 3% discount rate. Cost items that are not directly divisible between participants will be spread across relevant individuals (eg, spreading capital equipment and facility cost across all participants tested at each agency). A flat rate covering the cost of CTR materials for each intervention group will be estimated. No costs associated with research data collection will be included. These components of cost will be summed over the 15-month study period for each participant to generate an estimated per person cost. Effectiveness will be measured by examining relevant substance use and HIV-related outcomes reported by each YMSMTG over the 15-month period. Incremental cost effectiveness ratio (ICER) across treatment arms will be defined as $\Delta C/\Delta E$, where ΔC denotes the estimated difference in mean cost per intervention and ΔE reflects the estimated difference in mean effectiveness between the intervention and control group. ICER indicates the additional costs associated with the intervention for each new HIV

infection avoided. Nonparametric bootstrap resampling will be used to estimate the 95% CI of ICER [63]. Primary analysis will be performed on participants with complete data. Sensitivity analysis will be conducted by including all participants with multiple imputation for those with missing data.

Results

Project Swerve launched in April 2017 and is currently recruiting YMSMTG into the trial. Current recruitment strategies combine online and in-person (venue-based sampling) approaches. As of February 22, 2018, 5183 people began the screener survey, of which 3178 (61.32%) completed it. In total, 594 (18.70%), people successfully screened were eligible to participate in the study, of which 378 (63.6%) provided consent and 223 of these (58.9%) enrolled into the study. Of these, 160 (71.7%) have completed the baseline survey and 18 dropped from the study; the remaining 142 participants have been randomized into study arms as follows: 36 SUBI-SUBI; 36 SUBI-CTR; 34 CTR-SUBI; and 36 CTR-CTR.

Discussion

SUBI is a promising approach to address AOD use as part of HIV prevention and care services for YMSMTG. Efficacious SUBI approaches are typically delivered on-site to clients and have the advantage of being reimbursable [66] and cost-effective [67]. For nontreatment-seeking samples, SUBI has strong support in the alcohol literature [68-74], and some promising effects have been observed with respect to other substances, including heroin, cocaine, amphetamine, and marijuana use [68-73,75]. Few SUBI trials have considered whether the dosage or sequence of SUBI may result in differential risk-reduction outcomes, particularly among youth. In a 2012 meta-analysis, Eaton and colleagues [74] showed that one-time, brief interventions were a suitable and efficacious strategy for HIV and STI prevention. Pooling together 29 intervention trials (n=52,465), the authors found that single-session interventions (1) were associated with a reduction in STI incidence and risk behaviors when compared with standard-of-care; (2) were as effective as multisession interventions; (3) and were particularly effective in trials involving racial and ethnic minorities. In a recent study among drug-using adults in the DMA, Bonar and colleagues [50] found that a brief MI-focused intervention targeting drug use resulted in postintervention changes in psychological precursors of drug use behavior change (eg, confidence and intentions to reduce drug use), reduced drug use, and increased intentions to use condoms with sexual partners.

At present, few RCTs have examined the efficacy of brief interventions targeting ATOD use as a strategy to reduce sexual-risk taking behavior or to increase engagement in HIV care and prevention among high-risk YMSMTG who, compared with heterosexual adults or older MSM, may not have yet developed sustained drug use and abuse patterns. Furthermore, distinct developmental considerations including the use of ATOD before the legal age for use, the high prevalence and visibility of ATOD within YMSMTG's social networks, and the influence of these social networks' norms on YMSMTG's behavior may require particular attention when developing a SUBI for YMSMTG [76-80]. In addition to targeting an often overlooked barrier to successful engagement in HIV prevention and care, our intervention may offer structural opportunities to offset the decreases in HIV prevention funds across ASOs in the region. In light of shrinking HIV prevention and care funds, the Swerve program could increase ASO revenue by billing for substance use screening and referrals. Consequently, if efficacious, our theoretically-guided intervention may provide HIV and substance use risk reduction strategies that recognize the developmental needs specific to YMSMTG.

Conflicts of Interest

None declared.

References

1. Michigan Department of Community Health. Michigan. Annual HIV Surveillance Report, Michigan 2017 URL: http://www.michigan.gov/documents/mdch/January_2014_ALL_446611_7.pdf [accessed 2018-03-28] [WebCite Cache ID 6yFpSQxFt]
2. DiNenno EA, Prejean J, Irwin K, Delaney KP, Bowles K, Martin T, et al. Recommendations for HIV screening of gay, bisexual, and other men who have sex with men - United States, 2017. MMWR Morb Mortal Wkly Rep 2017 Aug 11;66(31):830-832 [FREE Full text] [doi: 10.15585/mmwr.mm6631a3] [Medline: 28796758]
3. Michigan Department of Community Health. Michigan 2012 Sexually Transmitted Diseases Report. Lansing: Michigan Department of Community Health; 2014.
4. Meadowbrooke CC, Veinot TC, Loveluck J, Hickok A, Bauermeister JA. Information behavior and HIV testing intentions among young men at risk for HIV/AIDS. J Assoc Inf Sci Technol 2014 Mar;65(3):609-620 [FREE Full text] [doi: 10.1002/asi.23001] [Medline: 25346934]
5. Bauermeister JA, Pingel ES, Jadwin-Cakmak L, Harper GW, Horvath K, Weiss G, et al. Acceptability and preliminary efficacy of a tailored online HIV/STI testing intervention for young men who have sex with men: the Get Connected! program. AIDS Behav 2015 Oct;19(10):1860-1874 [FREE Full text] [doi: 10.1007/s10461-015-1009-y] [Medline: 25638038]
6. Meanley S, Gale A, Harmell C, Jadwin-Cakmak L, Pingel E, Bauermeister JA. The role of provider interactions on comprehensive sexual healthcare among young men who have sex with men. AIDS Educ Prev 2015 Feb;27(1):15-26. [doi: 10.1521/aeap.2015.27.1.15] [Medline: 25646727]

7. Ellis RJ, Childers ME, Cherner M, Lazzaretto D, Letendre S, Grant I, HIV Neurobehavioral Research Center Group. Increased human immunodeficiency virus loads in active methamphetamine users are explained by reduced effectiveness of antiretroviral therapy. J Infect Dis 2003 Dec 15;188(12):1820-1826. [doi: 10.1086/379894] [Medline: 14673760]
8. Arnett J. The developmental context of substance use in emerging adulthood. J Drug Issues 2016 Aug 03;35(2):235-254 [FREE Full text] [doi: 10.1177/002204260503500202]
9. Chassin L, Pitts SC, DeLucia C. The relation of adolescent substance use to young adult autonomy, positive activity involvement, and perceived competence. Dev Psychopathol 1999;11(4):915-932. [Medline: 10624732]
10. Bauermeister JA, Zimmerman MA, Barnett TE, Caldwell CH. Working in high school and adaptation in the transition to young adulthood among African American youth. J Youth Adolesc 2007 Jun 15;36(7):877-890. [doi: 10.1007/s10964-007-9196-0]
11. Maggs JL, Schulenberg J, Hurrelmann K. Developmental transitions during adolescence: health promotion implications. In: Health Risks and Developmental Transitions during Adolescence. New York: Cambridge University Press; 1997:522-546.
12. Stone AL, Becker LG, Huber AM, Catalano RF. Review of risk and protective factors of substance use and problem use in emerging adulthood. Addict Behav 2012 Jul;37(7):747-775. [doi: 10.1016/j.addbeh.2012.02.014] [Medline: 22445418]
13. Braun BL, Hannan P, Wolfson M, Jones-Webb R, Sidney S. Occupational attainment, smoking, alcohol intake, and marijuana use: ethnic-gender differences in the CARDIA study. Addict Behav 2000;25(3):399-414. [Medline: 10890293]
14. Dariotis JK, Sonenstein FL, Gates GJ, Capps R, Astone NM, Pleck JH, et al. Changes in sexual risk behavior as young men transition to adulthood. Perspect Sex Reprod Health 2008 Dec;40(4):218-225. [doi: 10.1363/4021808] [Medline: 19067935]
15. Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: SAMHSA; 2014.
16. Koblin BA, Husnik MJ, Colfax G, Huang Y, Madison M, Mayer K, et al. Risk factors for HIV infection among men who have sex with men. AIDS 2006 Mar 21;20(5):731-739. [doi: 10.1097/01.aids.0000216374.61442.55] [Medline: 16514304]
17. Plankey MW, Ostrow DG, Stall R, Cox C, Li X, Peck JA, et al. The relationship between methamphetamine and popper use and risk of HIV seroconversion in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr 2007 May 01;45(1):85-92 [FREE Full text] [doi: 10.1097/QAI.0b013e3180417c99] [Medline: 17325605]
18. Ostrow DG, Stall R. Alcohol, tobacco, drug use among gay bisexual men. In: Wolitski RJ, Stall R, Valdiserri RO, editors. Unequal Opportunity: Health Disparities Affecting Gay and Bisexual Men in the United States. Oxford: Oxford University Press; 2008:121-158.
19. Ostrow DG, Plankey MW, Cox C, Li X, Shoptaw S, Jacobson LP, et al. Specific sex drug combinations contribute to the majority of recent HIV seroconversions among MSM in the MACS. J Acquir Immune Defic Syndr 2009 Jul 01;51(3):349-355 [FREE Full text] [doi: 10.1097/QAI.0b013e3181a24b20] [Medline: 19387357]
20. Mustanski B. Moderating effects of age on the alcohol and sexual risk taking association: an online daily diary study of men who have sex with men. AIDS Behav 2008 Jan;12(1):118-126. [doi: 10.1007/s10461-007-9335-3] [Medline: 18034298]
21. Mustanski BS, Newcomb ME, Du Bois SN, Garcia SC, Grov C. HIV in young men who have sex with men: a review of epidemiology, risk and protective factors, and interventions. J Sex Res 2011 Mar;48(2-3):218-253 [FREE Full text] [doi: 10.1080/00224499.2011.558645] [Medline: 21409715]
22. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet 2009 Jun 27;373(9682):2223-2233. [doi: 10.1016/S0140-6736(09)60746-7] [Medline: 19560604]
23. Carrico AW, Riley ED, Johnson MO, Charlebois ED, Neilands TB, Remien RH, et al. Psychiatric risk factors for HIV disease progression: the role of inconsistent patterns of antiretroviral therapy utilization. J Acquir Immune Defic Syndr 2011 Feb 01;56(2):146-150 [FREE Full text] [doi: 10.1097/QAI.0b013e318201df63] [Medline: 21116186]
24. Carrico AW. Substance use and HIV disease progression in the HAART era: implications for the primary prevention of HIV. Life Sci 2011 May 23;88(21-22):940-947. [doi: 10.1016/j.lfs.2010.10.002] [Medline: 20934437]
25. Hendershot CS, Stoner SA, Pantalone DW, Simoni JM. Alcohol use and antiretroviral adherence: review and meta-analysis. J Acquir Immune Defic Syndr 2009 Oct 01;52(2):180-202 [FREE Full text] [doi: 10.1097/QAI.0b013e3181b18b6e] [Medline: 19668086]
26. The White House. National HIV/AIDS Strategy for the United States. Washington, DC: The White House; 2010.
27. Madras BK, Compton WM, Avula D, Stegbauer T, Stein JB, Clark HW. Screening, brief interventions, referral to treatment (SBIRT) for illicit drug and alcohol use at multiple healthcare sites: comparison at intake and 6 months later. Drug Alcohol Depend 2009 Jan 01;99(1-3):280-295 [FREE Full text] [doi: 10.1016/j.drugalcdep.2008.08.003] [Medline: 18929451]
28. Bazargan-Hejazi S, Bing E, Bazargan M, Der-Martirosian C, Hardin E, Bernstein J, et al. Evaluation of a brief intervention in an inner-city emergency department. Ann Emerg Med 2005 Jul;46(1):67-76. [doi: 10.1016/j.annemergmed.2004.10.014] [Medline: 15988430]
29. Havard A, Shakeshaft A, Sanson-Fisher R. Systematic review and meta-analyses of strategies targeting alcohol problems in emergency departments: interventions reduce alcohol-related injuries. Addiction 2008 Mar;103(3):368-376. [doi: 10.1111/j.1360-0443.2007.02072.x] [Medline: 18190671]

30. Longabaugh R, Woolard RE, Nirenberg TD, Minugh AP, Becker B, Clifford PR, et al. Evaluating the effects of a brief motivational intervention for injured drinkers in the emergency department. J Stud Alcohol 2001 Nov;62(6):806-816. [Medline: 11838918]
31. Monti PM, Barnett NP, Colby SM, Gwaltney CJ, Spirito A, Rohsenow DJ, et al. Motivational interviewing versus feedback only in emergency care for young adult problem drinking. Addiction 2007 Aug;102(8):1234-1243. [doi: 10.1111/j.1360-0443.2007.01878.x] [Medline: 17565560]
32. Blow FC, Barry KL, Walton MA, Maio RF, Chermack ST, Bingham CR, et al. The efficacy of two brief intervention strategies among injured, at-risk drinkers in the emergency department: impact of tailored messaging and brief advice. J Stud Alcohol 2006 Jul;67(4):568-578. [Medline: 16736077]
33. Walton MA, Chermack ST, Shope JT, Bingham CR, Zimmerman MA, Blow FC, et al. Effects of a brief intervention for reducing violence and alcohol misuse among adolescents: a randomized controlled trial. J Am Med Assoc 2010 Aug 04;304(5):527-535 [FREE Full text] [doi: 10.1001/jama.2010.1066] [Medline: 20682932]
34. Walton MA, Chermack ST, Blow FC, Ehrlich PF, Barry KL, Booth BM, et al. Components of brief alcohol interventions for youth in the emergency department. Subst Abus 2015 Sep;36(3):339-349 [FREE Full text] [doi: 10.1080/08897077.2014.958607] [Medline: 25222484]
35. Rollnick S, Heather N, Bell A. Negotiating behaviour change in medical settings: the development of brief motivational interviewing. J Ment Health 2009 Jul 06;1(1):25-37. [doi: 10.3109/09638239209034509]
36. Miller WR, Rollnick S. Motivational Interviewing: Helping People Change. New York, NY: The Guildford Press; 2012.
37. Rollnick S, Miller WR. What is motivational interviewing? Behav Cogn Psychother 2009 Jun 16;23(4):325-334. [doi: 10.1017/S135246580001643X]
38. Burke BL, Arkowitz H, Menchola M. The efficacy of motivational interviewing: a meta-analysis of controlled clinical trials. J Consult Clin Psychol 2003 Oct;71(5):843-861. [doi: 10.1037/0022-006X.71.5.843] [Medline: 14516234]
39. Havard A, Shakeshaft A, Sanson-Fisher R. Systematic review and meta-analyses of strategies targeting alcohol problems in emergency departments: interventions reduce alcohol-related injuries. Addiction 2008 Mar;103(3):368-376. [doi: 10.1111/j.1360-0443.2007.02072.x] [Medline: 18190671]
40. Prochaska JO, Velicer WF, Rossi JS, Goldstein MG, Marcus BH, Rakowski W, et al. Stages of change and decisional balance for 12 problem behaviors. Health Psychol 1994 Jan;13(1):39-46. [Medline: 8168470]
41. Prochaska JO, Redding CA, Evers KE. The transtheoretical model stages of change. In: Glanz K, Rimer BK, Viswanath K, editors. Health Behavior and Health Education: Theory Research and Practice. San Francisco: Jossey-Bass; 2008:97-121.
42. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol 2000;55(1):68-78. [doi: 10.1037/0003-066X.55.1.68]
43. Deci EL, Eghrari H, Patrick BC, Leone DR. Facilitating internalization: the self-determination theory perspective. J Pers 1994 Mar;62(1):119-142. [doi: 10.1111/j.1467-6494.1994.tb00797.x]
44. Herbst JH, Kay LS, Passin WF, Lyles CM, Crepaz N, Marín BV, HIV/AIDS Prevention Research Synthesis (PRS) Team. A systematic review and meta-analysis of behavioral interventions to reduce HIV risk behaviors of Hispanics in the United States and Puerto Rico. AIDS Behav 2007 Jan;11(1):25-47. [doi: 10.1007/s10461-006-9151-1] [Medline: 16917668]
45. Naar-King S, Parsons JT, Johnson AM. Motivational interviewing targeting risk reduction for people with HIV: a systematic review. Curr HIV/AIDS Rep 2012 Dec;9(4):335-343. [doi: 10.1007/s11904-012-0132-x] [Medline: 22890780]
46. Noar SM, Palmgreen P, Chabot M, Dobransky N, Zimmerman RS. A 10-year systematic review of HIV/AIDS mass communication campaigns: have we made progress? J Health Commun 2009 Feb;14(1):15-42. [doi: 10.1080/10810730802592239] [Medline: 19180369]
47. Resnicow K, DiIorio C, Soet JE, Ernst D, Borrelli B, Hecht J. Motivational interviewing in health promotion: it sounds like something is changing. Health Psychol 2002 Sep;21(5):444-451. [Medline: 12211511]
48. Resnicow K, McMaster F. Motivational interviewing: moving from why to how with autonomy support. Int J Behav Nutr Phys Act 2012 Mar 02;9:1-9 [FREE Full text] [doi: 10.1186/1479-5868-9-19] [Medline: 22385702]
49. Khan R, Chatton A, Nallet A, Broers B, Thorens G, Achab-Arigo S, et al. Validation of the French version of the alcohol, smoking and substance involvement screening test (ASSIST). Eur Addict Res 2011 Apr;17(4):190-197. [doi: 10.1159/000326073] [Medline: 21494047]
50. Bonar EE, Walton MA, Cunningham RM, Chermack ST, Bohnert AS, Barry KL, et al. Computer-enhanced interventions for drug use and HIV risk in the emergency room: preliminary results on psychological precursors of behavior change. J Subst Abuse Treat 2014 Jan;46(1):5-14 [FREE Full text] [doi: 10.1016/j.jsat.2013.08.005] [Medline: 24035142]
51. Monti PM, Mastroleo NR, Barnett NP, Colby SM, Kahler CW, Operario D. Brief motivational intervention to reduce alcohol and HIV/sexual risk behavior in emergency department patients: a randomized controlled trial. J Consult Clin Psychol 2016 Jul;84(7):580-591 [FREE Full text] [doi: 10.1037/ccp0000097] [Medline: 26985726]
52. Colby SM, Nargiso J, Tevyaw TO, Barnett NP, Metrik J, Lewander W, et al. Enhanced motivational interviewing versus brief advice for adolescent smoking cessation: results from a randomized clinical trial. Addict Behav 2012 Jul;37(7):817-823 [FREE Full text] [doi: 10.1016/j.addbeh.2012.03.011] [Medline: 22472523]

53. Saitz R, Palfai TP, Cheng DM, Alford DP, Bernstein JA, Lloyd-Travaglini CA, et al. Screening and brief intervention for drug use in primary care: the ASPIRE randomized clinical trial. J Am Med Assoc 2014 Aug 06;312(5):502-513 [FREE Full text] [doi: 10.1001/jama.2014.7862] [Medline: 25096690]
54. Bernstein E, Ashong D, Heeren T, Winter M, Bliss C, Madico G, et al. The impact of a brief motivational intervention on unprotected sex and sex while high among drug-positive emergency department patients who receive STI/HIV VC/T and drug treatment referral as standard of care. AIDS Behav 2012 Jul;16(5):1203-1216. [doi: 10.1007/s10461-012-0134-0] [Medline: 22261830]
55. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption--II. Addiction 1993 Jun;88(6):791-804. [Medline: 8329970]
56. Bauermeister JA. Sexual partner typologies among single young men who have sex with men. AIDS Behav 2014 Oct 31;19(6):1116-1128. [doi: 10.1007/s10461-014-0932-7] [Medline: 25358726]
57. Attkisson CC, Greenfield TK. The UCSF Client Satisfaction Scales: I. The Client Satisfaction Questionnaire-8. In: Maruish ME, editor. The Use of Psychological Testing for Treatment Planning and Outcome Assessment. 2nd Edition. Mahwah, NJ: Lawrence Erlbaum Associates Publishers; 1999.
58. Breslow NE, Clayton DG. Approximate inference in generalized linear mixed models. J Am Stat Assoc 1993 Mar;88(421):9-25. [doi: 10.2307/2290687]
59. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986 Mar;42(1):121-130. [doi: 10.2307/2531248]
60. Zeger SL, Liang KY. An overview of methods for the analysis of longitudinal data. Stat Med 1992;11(14-15):1825-1839. [Medline: 1480876]
61. Luborsky MR. The identification and analysis of themes and patterns. In: Gubrium J, Sankar A, editors. Qualitative Methods in Aging Research. Thousand Oaks, CA: Sage Publications; 1994:189-210.
62. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
63. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ 1997;6(4):327-340. [Medline: 9285227]
64. Zeger SL, Liang K, Albert PS. Models for longitudinal data: a generalized estimating equation approach. Biometrics 1988 Dec;44(4):1049-1060. [doi: 10.2307/2531734]
65. Moyers T, Manuel J, Ernst D. Casaa.unm.edu.: Unpublished Manual; 2014. Motivational Interviewing Treatment Integrity Coding Manual 4.1 URL: https://casaa.unm.edu/download/miti4_1.pdf [accessed 2018-03-28] [WebCite Cache ID 6yFsO0SRt]
66. Fussell HE, Rieckmann TR, Quick MB. Medicaid reimbursement for screening and brief intervention for substance misuse. Psychiatr Serv 2011 Mar;62(3):306-309. [doi: 10.1176/ps.62.3.pss6203_0306] [Medline: 21363904]
67. Barbosa C, Cowell A, Bray J, Aldridge A. The cost-effectiveness of alcohol screening, brief intervention, and referral to treatment (SBIRT) in emergency and outpatient medical settings. J Subst Abuse Treat 2015 Jun;53:1-8. [doi: 10.1016/j.jsat.2015.01.003] [Medline: 25648375]
68. Walton MA, Resko S, Barry KL, Chermack ST, Zucker RA, Zimmerman MA, et al. A randomized controlled trial testing the efficacy of a brief cannabis universal prevention program among adolescents in primary care. Addiction 2014 May;109(5):786-797 [FREE Full text] [doi: 10.1111/add.12469] [Medline: 24372937]
69. Walton MA, Bohnert K, Resko S, Barry KL, Chermack ST, Zucker RA, et al. Computer and therapist based brief interventions among cannabis-using adolescents presenting to primary care: one year outcomes. Drug Alcohol Depend 2013 Oct 01;132(3):646-653 [FREE Full text] [doi: 10.1016/j.drugalcdep.2013.04.020] [Medline: 23711998]
70. Bernstein E, Ashong D, Heeren T, Winter M, Bliss C, Madico G, et al. The impact of a brief motivational intervention on unprotected sex and sex while high among drug-positive emergency department patients who receive STI/HIV VC/T and drug treatment referral as standard of care. AIDS Behav 2012 Jul;16(5):1203-1216. [doi: 10.1007/s10461-012-0134-0] [Medline: 22261830]
71. Bernstein J, Bernstein E, Tassiopoulos K, Heeren T, Levenson S, Hingson R. Brief motivational intervention at a clinic visit reduces cocaine and heroin use. Drug Alcohol Depend 2005 Jan 07;77(1):49-59. [doi: 10.1016/j.drugalcdep.2004.07.006] [Medline: 15607841]
72. Field CA, Baird J, Saitz R, Caetano R, Monti PM. The mixed evidence for brief intervention in emergency departments, trauma care centers, and inpatient hospital settings: what should we do? Alcohol Clin Exp Res 2010 Dec;34(12):2004-2010 [FREE Full text] [doi: 10.1111/j.1530-0277.2010.01297.x] [Medline: 20860610]
73. Blow FC, Walton MA, Bohnert AS, Ignacio RV, Chermack S, Cunningham RM, et al. A randomized controlled trial of brief interventions to reduce drug use among adults in a low-income urban emergency department: the HealthiER You study. Addiction 2017 Aug;112(8):1395-1405. [doi: 10.1111/add.13773] [Medline: 28127808]
74. Eaton LA, Huedo-Medina TB, Kalichman SC, Pellowski JA, Sagherian MJ, Warren M, et al. Meta-analysis of single-session behavioral interventions to prevent sexually transmitted infections: implications for bundling prevention packages. Am J Public Health 2012 Nov;102(11):e34-e44 [FREE Full text] [doi: 10.2105/AJPH.2012.300968] [Medline: 22994247]

75. Academic ED SBIRT Research Collaborative. The impact of screening, brief intervention, and referral for treatment on emergency department patients' alcohol use. Ann Emerg Med 2007 Dec;50(6):699-710, 710.e1. [doi: 10.1016/j.annemergmed.2007.06.486] [Medline: 17870206]
76. Rosario M, Schrimshaw EW, Hunter J. Disclosure of sexual orientation and subsequent substance use and abuse among lesbian, gay, and bisexual youths: critical role of disclosure reactions. Psychol Addict Behav 2009 Mar;23(1):175-184 [FREE Full text] [doi: 10.1037/a0014284] [Medline: 19290704]
77. Corliss HL, Rosario M, Wypij D, Wylie SA, Frazier AL, Austin SB. Sexual orientation and drug use in a longitudinal cohort study of U.S. adolescents. Addict Behav 2010 May;35(5):517-521 [FREE Full text] [doi: 10.1016/j.addbeh.2009.12.019] [Medline: 20061091]
78. VanDevanter N, Duncan A, Burrell-Piggott T, Bleakley A, Birnbaum J, Siegel K, et al. The influence of substance use, social sexual environment, psychosocial factors, and partner characteristics on high-risk sexual behavior among young Black and Latino men who have sex with men living with HIV: a qualitative study. AIDS Patient Care STDS 2011 Feb;25(2):113-121 [FREE Full text] [doi: 10.1089/apc.2010.0100] [Medline: 21235387]
79. Bauermeister JA. It's all about “connecting”: reasons for drug use among Latino gay men living in the San Francisco Bay Area. J Ethn Subst Abuse 2007;6(1):109-129. [doi: 10.1300/J233v06n01_07] [Medline: 17430819]
80. Cook SH, Bauermeister JA, Gordon-Messer D, Zimmerman MA. Online network influences on emerging adults' alcohol and drug use. J Youth Adolesc 2013 Nov;42(11):1674-1686 [FREE Full text] [doi: 10.1007/s10964-012-9869-1] [Medline: 23212348]

Abbreviations

AOD: alcohol and other drugs
ASO: AIDS Service Organization
CAI: condomless anal intercourse
CDC: Centers for Disease Control and Prevention
CSQ: Client Satisfaction Questionnaires
CTR: counseling, testing, and referral
DMA: Detroit Metro Area
ICER: incremental cost effectiveness ratio
MI: motivational interviewing
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SUBI: substance use brief intervention
SUDs: substance use disorders
SEF: Self-Evaluation Forms
STI: sexually transmitted infections
TG: transgender people
YMSM: young men who have sex with men
YMSMTG: young men who have sex with men and transgender people

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Protocol

A Novel Mobile App and Population Management System to Manage Rheumatoid Arthritis Flares: Protocol for a Randomized Controlled Trial

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Abstract

Background: Rheumatoid arthritis flares have a profound effect on patients, causing pain and disability. However, flares often occur between regularly scheduled health care provider visits and are, therefore, difficult to monitor and manage. We sought to develop a mobile phone app combined with a population management system to help track RA flares between visits.

Objective: The objective of this study is to implement the mobile app plus the population management system to monitor rheumatoid arthritis disease activity between scheduled health care provider visits over a period of 6 months.

Methods: This is a randomized controlled trial that lasts for 6 months for each participant. We aim to recruit 190 patients, randomized 50:50 to the intervention group versus the control group. The intervention group will be assigned the mobile app and be prompted to answer daily questionnaires sent to their mobile devices. Both groups will be assigned a population manager, who will communicate with the participants via telephone at 6 weeks and 18 weeks. The population manager will also communicate with the participants in the intervention group if their responses indicate a sustained increase in rheumatoid arthritis disease activity. To assess patient satisfaction, the primary outcomes will be scores on the Treatment Satisfaction Questionnaire for Medication as well as the Perceived Efficacy in Patient-Physician Interactions questionnaire at 6 months. To determine the effect of the mobile app on rheumatoid arthritis disease activity, the primary outcome will be the Clinical Disease Activity Index at 6 months.

Results: The trial started in November 2016, and an estimated 2.5 years will be necessary to complete the study. Study results are expected to be published by the end of 2019.

Conclusions: The completion of this study will provide important data regarding the following: (1) the assessment of validated outcome measures to assess rheumatoid arthritis disease activity with a mobile app between routinely scheduled health care provider visits, (2) patient engagement in monitoring their condition, and (3) communication between patients and health care providers through the population management system.

Trial Registration: ClinicalTrials.gov NCT02822521, http://clinicaltrials.gov/ct2/show/NCT02822521 (Archived by WebCite at http://www.webcitation.org/6xed3kGPd)

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KEYWORDS

arthritis, rheumatoid; symptom flare up; telemedicine; mobile applications

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease that causes stiffness, swelling, and pain, resulting from inflammation in the joints [1]. Individuals with RA may experience occasional increases in inflammation that are associated with worsening symptoms called flares [2]. In focus groups, RA patients characterized flares as unpredictable, intense episodes that render them feeling helpless [3].

It is important for health care providers (HCPs) to monitor flares because frequent, long-lasting increases in inflammation can result in a permanent damage to joints and negatively impact quality of life [4,5]. The assessment of flares, however, is complicated. Flares are often unreported or inaccurately reported as RA patients may no longer recall flares that occurred between HCP visits. A study reported that 65% of RA patients who experienced flares were no longer facing issues by the time of their routine clinic visit [2]. In addition, patients and their HCPs frequently differ in what they call a flare. A qualitative research study, involving semistructured interviews and a Delphi exercise, revealed that, of the 10 domains identified as important by patients in the assessment of flare, only 4 overlapped with the domains considered important by their HCPs [6]. Although several research groups are working on the development of validated RA flare criteria, additional work is needed to develop appropriate scoring criteria and thresholds for flare severity and change [7,8].

To help HCPs and their patients better manage flares, better methods of tracking RA symptoms are needed. One potential method is through the use of mobile app. Nearly 64% of adults in the United States owned mobile phones in 2015, and 58.23% of mobile phone owners downloaded at least 1 health app [9,10]. Many types of apps have been developed to explore ways of helping people with chronic illnesses, such as diabetes and heart disease, and to monitor, understand, and manage symptoms [11]. Fewer apps have focused on the management of chronic autoimmune conditions, such as RA.

A research group in Japan recently created an app that enables RA patients to measure disease activity through patient-reported tender joints, a modified health assessment questionnaire, and measurement of gait balance using an accelerometer. In a pilot study of 65 RA patients, Nishiguchi et al demonstrated that patient-reported assessment of disease activity, via the mobile app, correlated with a validated measure of disease activity, the Disease Activity Score in 28 Joints, which includes physician-assessed joint counts and C-reactive protein, a serum inflammatory disease marker [12]. In a follow-up study in 2016 conducted by the same group, participants were surveyed about their opinions using the app. Overall, participants were favorable, stating that they had no or little difficulty recording their self-assessments [13]. Limitations, however, included the small sample size (N=9) and the limited length of follow-up (3 months). In addition, no information was provided regarding the use of these data by HCPs in medical decision making.

The *overall objective* of this proposal is to implement a mobile app plus a population management system to monitor RA disease activity between scheduled HCP visits over 6 months. The essential components in this system are as follows: (1) the mobile app, (2) the Web-based dashboard, and (3) the population manager. The Web-based dashboard consolidates incoming patient-reported data using preprogrammed algorithms to identify increases in disease activity, and the population manager is a trained individual who monitors the Web-based dashboard and connects patients with their HCPs. Our *hypothesis* is that the combination of mobile app and the population management system will improve patient satisfaction and management of RA disease activity by identifying RA flares as they occur and providing this information to the HCP through a trained population manager. The *rationale* is that the mobile app will increase patient involvement in disease assessment, whereas the population management system will support the integration of patient-reported data into the workflow of a busy clinical practice, enabling improved disease activity management between scheduled clinic visits.

Methods

Infrastructure

The setting for this study is the outpatient rheumatology clinic of an academic medical center in Boston, MA. This site was chosen because it is the home institution of the researchers involved in this study. The institution supports the development of mobile interventions through the Digital Health Innovation Group, which offers advice and assistance to ensure that the important standards for mHealth research (eg, cybersecurity, software design, and software maintenance) are met. The city of Boston, MA, is an ideal location for this study because it is one of the top 50 mobile-friendly cities in the United States [14]. In 2016, the availability of carrier networks in Boston was 51% above the national average of 81%. Upload and download speeds were 6.26 mbps and 8.74 mbps, respectively, and there were 2.12 mobile phone stores per 10,000 residents, enabling in-person customer service for mobile devices.

Study Visit Design

General Schematic

This is a randomized controlled trial (RCT) of a mobile app plus the population management system. All participants will be assigned a population manager to serve as a contact person with whom participants can communicate regarding their flares. Participants randomized to receive the app will answer daily questions about their RA disease activity, using a validated self-report measure, Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), and the Patient-Reported Outcomes Measurement Information System (PROMIS) depression,

fatigue, pain interference, physical function, and sleep impairment short forms [15,16]. The RADAI-5 was chosen because it is a short, 5-item questionnaire based only on patient-reported measures, whereas other common disease activity measures, such as the Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index, require in-person assessment of joints by a health care professional [17,18]. Studies have shown that patient-reported measures have similar, possibly greater, sensitivity in detecting treatment effects in RA [19].

The app will record the answers and summarize them in a graphical form to enable the visualization of trends. Population managers will have access to this information in real-time via a secure Web-based dashboard.

Inclusion and Exclusion Criteria

To be included in this study, participants must: (1) be diagnosed with RA by a board-certified rheumatologist, (2) be taking a disease-modifying antirheumatic drug (DMARD), (3) own a mobile device with an Android or iOS operating system, (4) be at least 18 years old, and (5) be able to speak English. Participants who do not plan on receiving follow-up care at this academic medical center will be excluded.

Randomization (Disease Activity Levels)

Participants will be randomized 1:1 using a publicly available Web-based randomization tool. Randomization will occur within categories stratified by disease activity, assessed by the CDAI: remission (≤2.8), low (>2.8-10), moderate (>10-22), and high (>22) [17].

Study Visits

Study visits will occur at baseline, 3 months, and 6 months and will coincide with regularly scheduled visits to the participants' rheumatology HCP. A trained research assistant will perform all assessments, including the joint examinations and tender point counts. Participants will also complete self-administered questionnaires to assess disease activity, flares, treatment satisfaction, and perceived efficacy of the patient-physician relationship. Specific data collection instruments are outlined in the section Data Collection. The research assistant will be blinded to the study arms to which the participants are assigned. This role is distinct from that of the population manager described in the section Population Management and Web-Based Dashboard (Figure 1).

Rheumatoid Arthritis Flare Study App

The mobile app was designed by the principal investigator and coinvestigators and custom developed by the ADK Group (Boston, MA), with guidance on the visual display from experienced app developers. Although RA patients were not involved in the design of this specific study or app, we incorporated information obtained from another study of a mobile phone app for RA patients, which was designed and led by one of the study co-investigators [20].

Figure 1. Study schematic showing the roles of research assistants at study visits versus the roles of population managers who communicate with subjects between study visits. Research assistants are blinded to the randomization, whereas population managers are not blinded. Pt = patient.

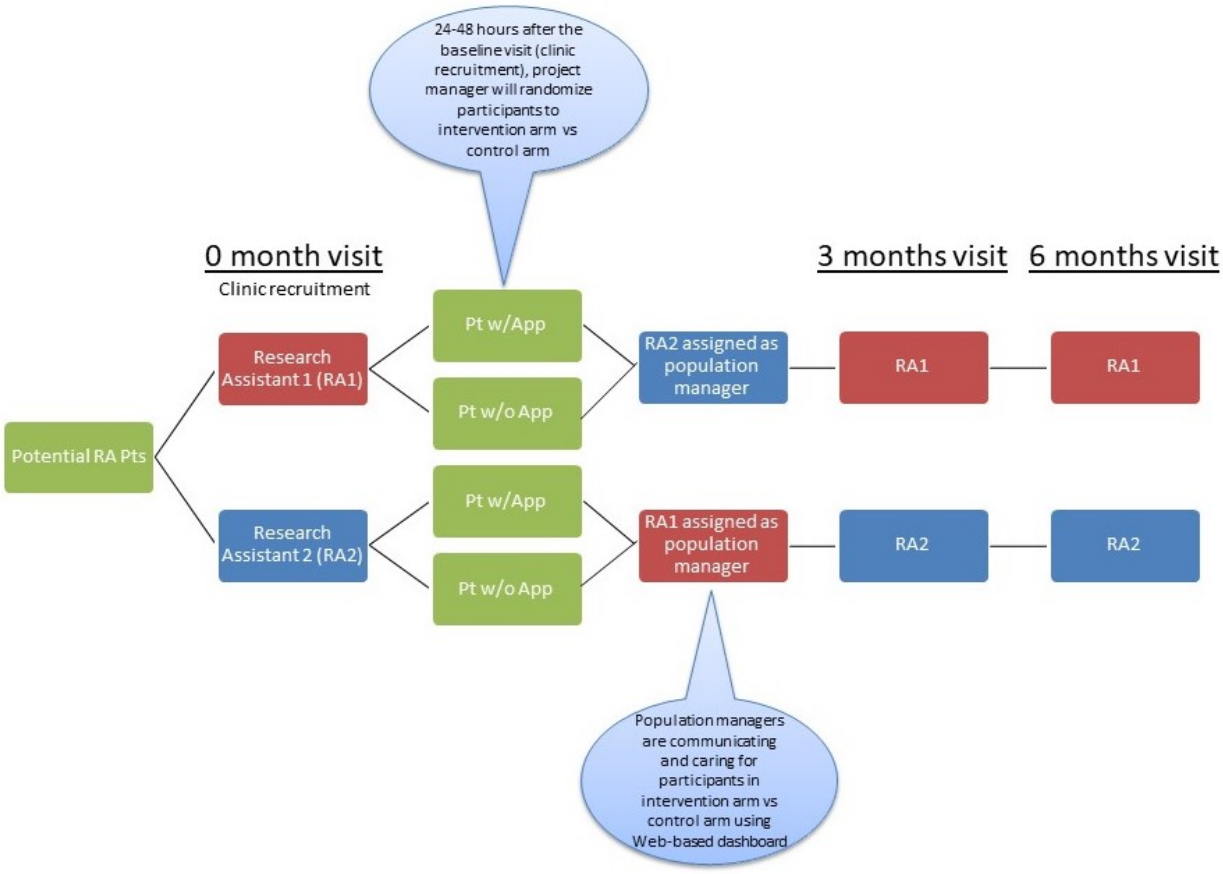
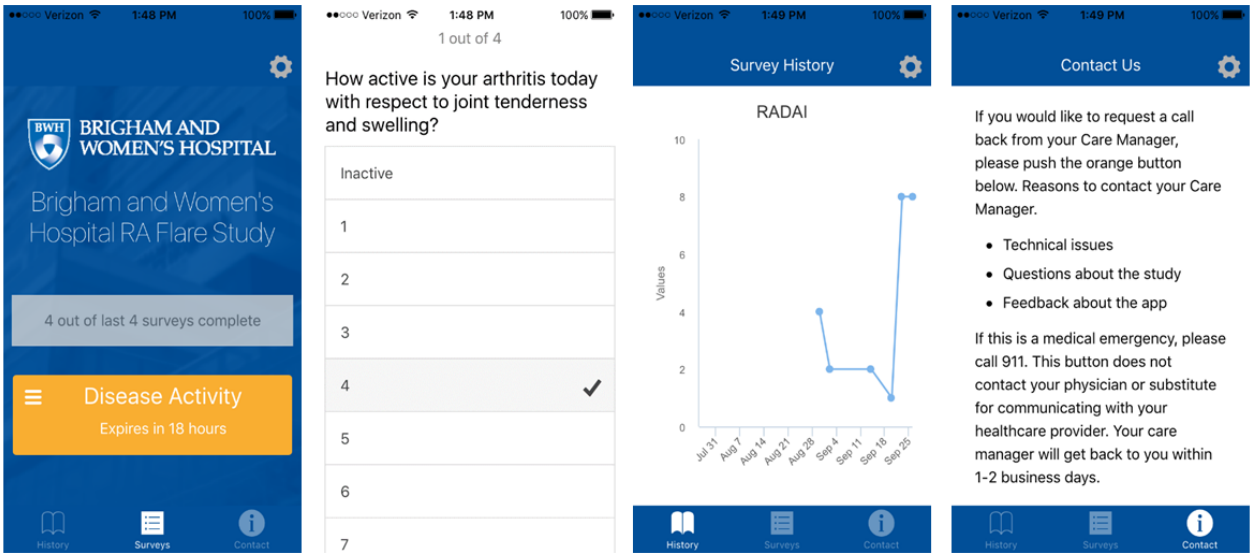


Figure 2. Screenshots of interface of RA Flare Mobile App.



All questionnaires used in the app have been validated and used in other studies including RA patients [15,16]. The app was designed to function on both the Android and iOS systems and met all guidelines for submission to the US Google Play and Apple App stores. Screenshots of the app are provided to show the visual interface (Figure 2).

At the first study visit, all study participants will be informed that, if they are randomized to receive the app, they will receive an email containing links to download the app from Google Play or the Apple App store. They will also receive a phone call from a trained study staff member, acting as a population manager, who will confirm that they were randomized to the intervention arm and take the participant through the process of downloading and using the app. Participants will register their account using a username, a password, and 5-digit pin number. After the app is downloaded, participants will be guided through a short interactive tutorial outlining important features of the app.

The app will send users a notification at 9:00 AM every day, prompting them to login using their username and 5-digit pin number to answer questions related to RA. If users have not answered their daily questions by 9:00 PM, they will receive another notification to remind them to complete the questions by 9:00 AM the next day. Once logged in, an option on the home screen will enable participants to select the daily survey. A table listing the surveys is provided in the section Data collection. Study participants will be able to view their responses in a graphic form on their apps if they are connected to the internet. However, no data will be stored on the app itself. Data will be transmitted securely and stored on secure servers at the study site. Data will be viewable by study staff on a password-protected Web-based dashboard, which includes graphs of all survey scores, as well as a table that shows the numerical scores. Additionally, the app will include a "Contact Us" button, which sends an email to the population manager, requesting further contact.

Population Management and Web-Based Dashboard

Each participant, regardless of study arm assignment, will be assigned to a population manager. The population manager is a trained study staff member who, unlike the research assistant performing visits, is not blinded to study group assignment. The population manager is responsible for communicating with participants during the course of the study. The initial call will occur immediately after the first study visit. The population manager will call to introduce him or herself and offer to assist participants with troubleshooting procedures to successfully download and register the app on the mobile device. The population manager will also call participants at weeks 6 and 18 to check in on participants and ask if they are experiencing an RA flare. These calls also serve to encourage participants to stay engaged in the study. If participants endorse a flare, an additional set of structured questions will be asked to assess the specific joints involved, as well as other symptoms and medication adherence.

For participants randomized to receive the mobile app, the population manager will also monitor responses to the daily questionnaires on the Web-based dashboard (Figure 3). An algorithm will be used to identify potential RA flares by comparing the mean RADAI-5 score over the past 2 weeks to the mean RADAI-5 score over the previous 2 weeks.

If the participants' RADAI-5 score increases by more than 30% from the previous 2 weeks' reading and their current RADAI-5 score is >3, the dashboard will generate an alert to the population manager (Figure 4). The study team decided on this threshold after 1:1 conversations with board-certified rheumatologists at the study site. The appropriateness of this threshold will be evaluated as a part of this study.

Figure 3. Web-based dashboard interface used by population managers to monitor participants' responses to the app.

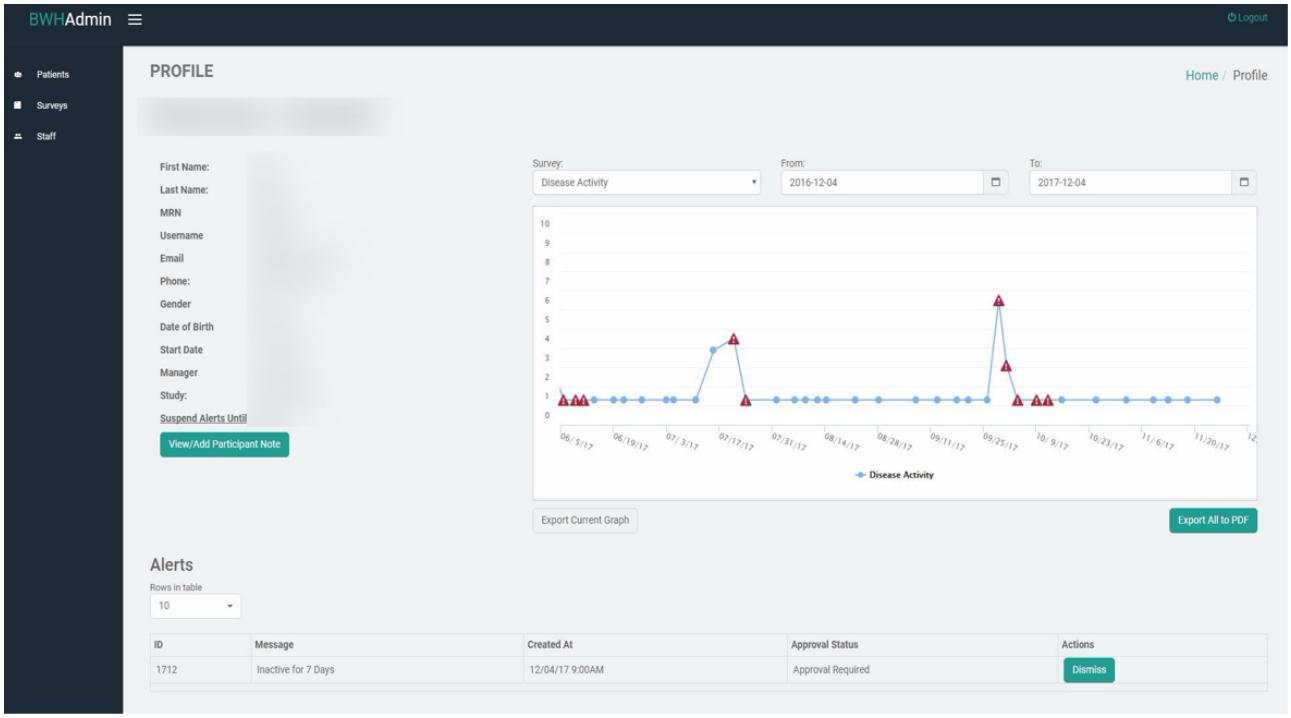
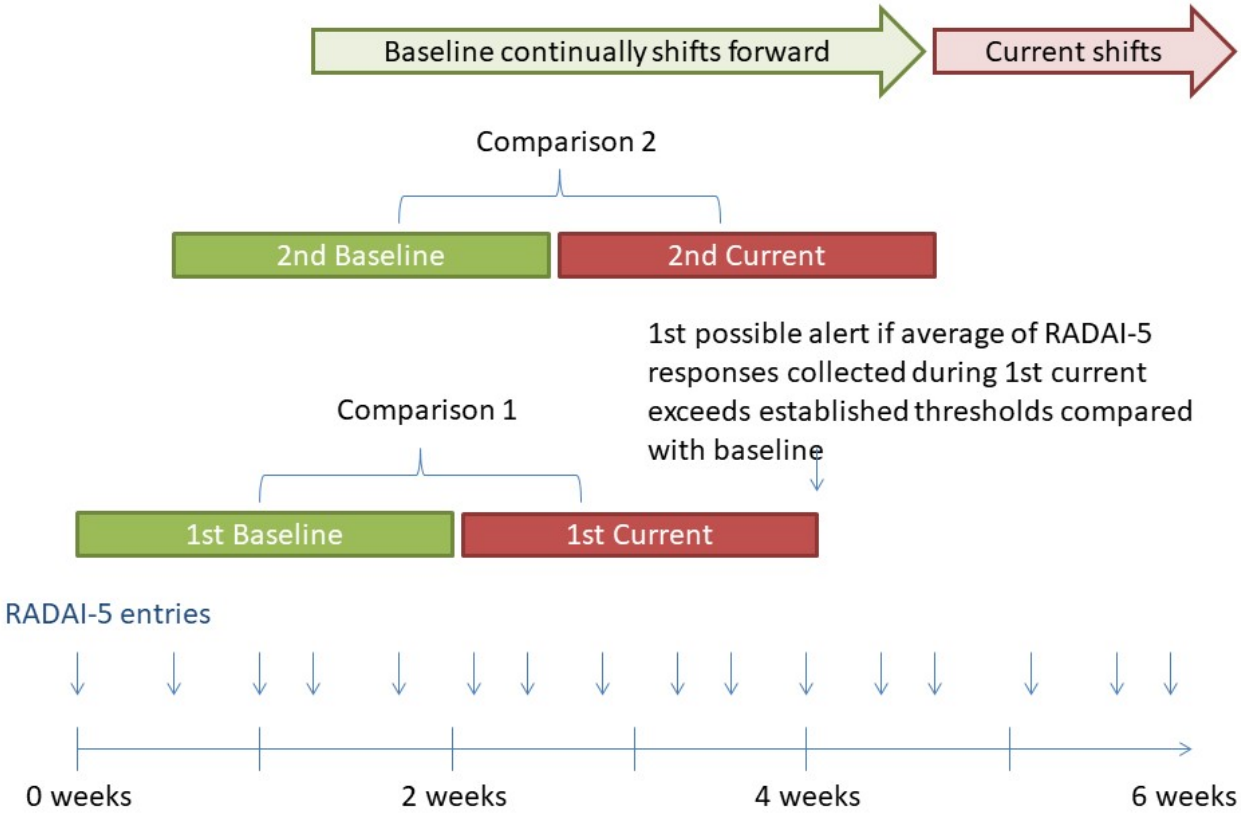


Figure 4. The flare algorithm compares Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5) responses over a period of 2 weeks compared with the previous 2 weeks' average. If the participant's RADAI-5 score increases by more than 30% from the previous 2 weeks' reading, the dashboard will generate an alert to the population manager.



The population manager will be responsible for communicating with study participants when the app algorithm identifies possible flares. The participant will be contacted and asked a structured set of follow-up questions about the possible flare, associated symptoms, and medication adherence. A 1-page summary will be compiled to send to the referring rheumatology HCP. Population managers will remind participants that their HCP is not required to respond to the summary, and it is up to their HCP to decide on appropriate follow-up procedures.

Although we considered prescribing a specific algorithm for HCPs to follow to address RA flares, we ultimately decided to allow each rheumatology HCP to respond to the notifications according to his or her own practice patterns. Our decision was based on 3 considerations: (1) there are no accepted guidelines regarding the treatment of RA flares, (2) surveys with the site's HCPs indicated that physician participation would be negatively impacted by a rigid paradigm, and (3) we believe the mobile app plus the population management system will have broad applicability, independent of the specific management paradigm.

If participants do not answer any survey questions for 7 consecutive days, the population manager will contact the participant after the 7th day. Participants will be asked a set of questions to better understand the reasons underlying their lack of responses for the past week.

Data Collection

Data will be collected using the following methods: (1) all participants in the study will complete validated, self-reported questionnaires at study visits using paper forms (Table 1) and (2) participants in the intervention arm will also provide data daily through the app (Table 2). Rheumatology HCPs will also complete questionnaires at every study visit. Specifically, they will provide the physician global assessment of disease activity by answering the question, "Please rate your patient's disease activity on a scale of 0-10 with 0 being very good and 10 being very bad" at every visit. At every visit following the baseline visit, HCPs will also be asked to complete the Physician Flare Questionnaire, which assesses their responses to flare notifications (eg, called patient, saw patient in person, changed medications; Multimedia Appendix 1). After the subject's final study visit, his or her HCP will complete a Physician Exit Survey to provide feedback regarding his or her experiences with the mobile app and the population management system, including questions about its impact on patient-physician communication, overall management of RA disease activity, and physician workload (Multimedia Appendix 2).

Table 1. Evaluations occurring at all study visits among all study participants.

Type of assessment and instrument	Description
Self-administered questionnaires	
Basic demographics (only during baseline visit)	Gender, age, ethnicity, race, education, and marital status
Treatment Satisfaction Questionnaire for Medication (TSQM)	The TSQM asks participants about their level of satisfaction with their medications [21]
Perceived Efficacy in Patient-Physician Interactions Questionnaire (PEPPI)	The PEPPI consists of 10 items asking participants about their self-efficacy in interacting with their health care providers [22]
Patient global assessment of disease activity	Participants will be asked, "Considering all the ways in which illness and health conditions may affect you at this time, please rate how you are doing on a scale of 0-100 with 0 being very well and 100 being very poorly."
Brigham Rheumatoid Arthritis Sequential Study flare questions	Participants will be asked "During the past 3 months, have you had a flare in your rheumatoid arthritis (RA)?" If a participant answers yes, the participant will be queried about flare frequency, and how he or she treated the flare(s) [2]
Flare Assessment of Rheumatoid Arthritis Questionnaire	This 13-item questionnaire was developed through a Delphi exercise to detect RA flares between medical visits [6]
Patient Activity Scale II (PAS-II)	This is a validated index that assesses 3 American College of Rheumatology (ACR) Core Data Set patient-reported outcomes—physical function, pain, and global health [23]
Assessments by trained study staff members	
Clinical Disease Activity Index (CDAI)	The CDAI is a measurement of RA disease activity calculated from the 28 joint count examination in addition to the physician global assessment and patient global assessment scores [17]
Tender point examination	The tender point examination assesses tenderness at 18 sites and is used in the 1990 ACR Criteria for the Classification of Fibromyalgia [24]

Table 2. Self-administered questionnaires delivered through the mobile app between study visits among participants in the intervention group.

Instruments	Description	Frequency of administration
Mobile Entry Questionnaire	This module includes 4 items about how subjects feel about their connection with their health care team	Once at the beginning of the study
Modified Rheumatoid Arthritis Disease Activity Index (RADAI-5)	The RADAI-5 is a validated survey consisting of 5 items in a Likert format from 0 to 10 [15]: (1) How active was your arthritis in the last 6 months?; (2) How active is your arthritis today with respect to joint tenderness and swelling?; (3) How severe is your arthritis pain today?; (4) How would you describe your general health today?; and (5) Did you experience joint (hand) stiffness on awaking yesterday morning? If yes, how long was this stiffness?	The first question regarding arthritis activity in the last 6 months will be asked once a month. The last 4 questions regarding joint tenderness and swelling, pain severity, global health, and joint stiffness will be asked 3 times during an 8-day rotation
PROMIS[a] Pain Interference Short Form	4 questions about the extent to which pain hinders engagement with activities [25]	Once every 8 days
PROMIS Physical Function Short Form	4 questions about the ability to perform basic activities [26]	Once every 8 days
PROMIS Fatigue Short Form	4 questions about tiredness and exhaustion [27]	Once every 8 days
PROMIS Depression Short Form	4 questions about negative mood and views of self [28]	Once every 8 days
PROMIS Sleep Disturbance Short Form	4 questions about sleep quality and restoration associated with sleep [29]	Once every 8 days
Flare treatment strategies	This module is based on questions asked in the Brigham Rheumatoid Arthritis Sequential Study preliminary study of flares in rheumatoid arthritis (RA). Specifically, this module will ask participants whether they had an RA flare in the 14 days and how they treated this flare [2]	Monthly

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

Recruitment

The recruitment goal is 190 participants. Potential participants will be identified by searching for ICD-9 diagnosis codes for RA (714.x) in the Brigham Integrated Computing System scheduling database. Every week, study staff will generate lists of potential participants and prescreen patients via medical record review. Study staff will provide weekly lists to clinicians for their approval to contact the patients. Study staff will also be present in clinic during the busiest clinic sessions to remind HCPs of potential participants and to facilitate referrals. Every eligible participant will review the informed consent document approved by Partners Institutional Review Board, and written informed consent will be obtained by a trained research assistant. All study staff will complete training in HIPAA and Ethics in Human Subjects Research. Approximately 50.0% (95/190) will be randomized to receive the mobile app (intervention group). On the basis of attrition rates from previous studies, we expect ≥61.0% (122/190) of subjects to complete the study.

Outcome Measures

To assess patient satisfaction, the primary outcomes will be scores on the TSQM and PEPPI questionnaire at 6 months [21,22]. To determine the effect of the mobile app on RA disease activity, the primary outcome will be CDAI at 6 months [17].

The TSQM is a validated questionnaire that assesses medication satisfaction [21]. The different components of medication satisfaction are the following: side effects, effectiveness, convenience, and overall satisfaction. There are 14 questions, scored on a 5- or 7-point Likert scale. Responses to each question are assigned a score between 0 and 100, with 0 being extremely dissatisfied to 100 being extremely satisfied. The TSQM was initially validated in a national study of chronic disease, including patients with arthritis, asthma, depression, hyperlipidemia, hypertension, migraine, and psoriasis. It was subsequently validated in separate populations of patients with multiple sclerosis, cystic fibrosis, and coronary disease [30-32]. In one study, ceiling and floor effects were observed in the side effects domain [32]. Of note, if these effects are a problem, a separate score (TSQM-9) can be calculated, removing the 5 items in the side effects domain. This abbreviated score was shown to have good construct and convergent validity, along with high internal consistency and good test-retest reliability [33]. In a study of individuals with chronic illnesses including 25.6% (44/172) RA patients, representative scores on the TSQM were 77.1 (SD 25.2) for side effects, 61.6 (SD 24.16) for effectiveness, 66.1 (SD 17.1) for convenience, and 68.8 (SD 20.6) for overall satisfaction [34]. Although no studies have specifically examined the responsiveness of the TSQM in RA, a study of osteoarthritis patients revealed that perceptions of convenience, effectiveness, and overall satisfaction increased with treatment with a nonsteroidal anti-inflammatory drug [35]. The TSQM has also been used in clinical trials of RA patients to compare patient satisfaction with the effects of different DMARDs [36].

The PEPPI is a validated questionnaire that assesses self-efficacy in the patient-physician interaction [22]. It consists of 10 questions, scored on 5-point Likert scales, reflecting very confident to not confident at all. In multiple studies of elderly individuals and patients with osteoarthritis, the PEPPI showed construct, convergent, discriminant, and structural validity [22,37,38]. Although a ceiling effect was noted in the PEPPI 10-item scale, no ceiling effects were noted using the abbreviated 5-item scale, and no floor effects were noted for

either scale [37-39]. Of note, the PEPPI was recently used in a 12-month RCT of an eHealth interactive self-assessment website (Sanoia) in RA [40]. The 320 participants in this study were similar in age, sex, and disease duration to the population we are recruiting. The mean baseline PEPPI score was 39.2 (SD 7.8). Participants randomized to receive the active intervention had small increases in their PEPPI score (mean 0.6, SD 5.2), whereas participants randomized to the control arm had concurrent decreases in their PEPPI score (mean -0.91, SD 6.08). Although the magnitude of change was small, the difference between the 2 groups was statistically significant (P=.01), indicating that this instrument is able to detect differences between an active self-monitoring intervention and control.

Statistical Analysis

The primary analysis will be a completer analysis. Summary statistics (eg, frequencies, means, and medians) of the baseline variables will be calculated to assess the effectiveness of randomization. Treatment effects (mean differences in outcomes between the 2 groups at 3 and 6 months) will be estimated with mixed models. This model includes the interaction of treatment and time and allows adjustment for baseline scores. For each outcome measure, we will also adjust for age, sex, race, disease duration, and any variables that are statistically different from each other in unadjusted analyses (P<.10). A 2-tailed P value of .05 will be considered significant. All analyses will be conducted by a blinded statistician using SAS 9.3 (SAS Institute).

On the basis of previous studies performed by this research group within this population, we do not expect a large amount of missing data in the primary outcome measures and covariates. These data are obtained during in-person study visits. A research assistant is present during all study visits and checks forms for completion. When necessary, multiple imputation by chained equations will be used to impute missing variables.

Sample Size Calculation

A total of 2920 RA patients were seen at the site of recruitment between April 30, 2013, and May 1, 2014. Of these patients, 1980 were prescribed at least one DMARD between April 30, 2013, and May 1, 2014, and approximately 60.00% (1188/1980) had moderate-to-high disease activity. From the 2013 Pew Internet Tracking Survey, we estimate that 50% of these patients (594/1980) own mobile phones [41]. Of these 594 individuals, we expect 80.1% (476/594) to meet the remainder of the inclusion criteria (≥18 years old, English speaking), and 40.0% (190/476) to agree to participate.

On the basis of previous studies examining differences in patient satisfaction, the expected difference between groups is 9.4 (SD 18.4) in TSQM scores [42,43]. No data exist regarding the expected difference in CDAI scores for this intervention. However, the minimal clinically important difference in CDAI scores is 12 [44,45]. On the basis of attrition rates from previous studies, we expect ≥61% (122/190, 64.2%) subjects to complete the study. Given a sample size of 122 subjects and an alpha level of .05, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.80 to 0.99.

Fidelity of the Intervention

In addition to the assessments of satisfaction and efficacy described above, we will also assess the fidelity of the intervention. Systems are in place to monitor survey completion rates, and an alert is issued to the population manager if participants have not answered a survey in the past 7 days. Information is also obtained on the exit survey to determine whether participants were able to download the app.

Results

Recruitment is currently underway. We started patient recruitment in November 2016 and will continue until the recruitment goal of 190 participants has been achieved. Findings on the study's primary outcomes are expected to be finalized by September 2019. Thus far, user feedback from both RA patients and HCPs has been positive. RA patients have particularly enjoyed the ability to track their disease activity and symptoms and to share these results, using the app's graphic interface, with their family members. HCPs have appreciated receiving information about their patients between regularly scheduled clinic visits.

Discussion

Summary and Strengths

The findings from this study will represent the first randomized trial to test the effects of a combined mobile app and the population management system on a patient population with RA. Although several mobile apps exist to monitor symptoms of chronic disease, none have incorporated the use of a population management system for the management of disease activity in RA. This manuscript was written meeting the checklist to report health interventions using mobile phones [46].

In a systematic review of mobile apps to assist RA patients in disease management, Grainger et al reported that high-quality apps, including monitoring tools that assess disease activity using validated instruments, are lacking [47]. They also noted the importance of delivering the tools via a user-friendly interface. Our medical team collaborated with the local app developer, as well as other experienced developers, to address these 2 issues. First, we worked with the local app developer to incorporate a validated measure of self-reported RA, the RADAI-5, and PROMIS assessments of pain interference, physical function, fatigue, depression, and sleep disturbance. Second, we met experienced app developers to get advice regarding the user interface during the development stages. The developers provided valuable feedback, including suggestions to create large menu buttons at the bottom of the screen rather than to rely on a list of menu options as a dropdown box along the side. As a result, we were able to develop a mobile app that incorporates useful information for physicians, while also being easy for patients to enter and visualize data.

We foresee tangible benefits to both patients and HCPs. For patients, an app can be beneficial by providing tools to easily track and record their disease trajectories. If successful, this system may spark greater patient engagement in self-management of RA. People with chronic diseases have been more engaged in using mobile apps in managing their diseases than people managing other aspects of their health [48]. For HCPs, an app and a population management system may be beneficial by providing a more complete picture of their patients, beyond the snapshots they currently see during scheduled clinic visits. We specifically created the combined app and population management system so that it does not create a large amount of work for busy HCPs. Instead, we maximize the use of other trained staff members (eg, population managers) and only involve HCPs when clinically significant events are identified by flare alerts. This increased reservoir of information may then serve as a catalyst for more effective patient-HCP communication. A formal cost assessment was not performed as this is a research study designed to assess feasibility and efficacy, and the costs involved in this endeavor will likely differ from actual implementation in the clinic setting.

Barriers and Limitations

Many barriers have occurred during app development and study implementation. Specifically, beta-testing took more time than we planned, and, as a result of beta-testing, additional revisions were required. After the app was developed, regular maintenance and updates were required. These included testing and updates for new releases of the iOS and Android operating systems and cross-device and browser testing for new device and browser versions. In addition, implementation of the study was disrupted for a period of 2-6 days when surveys were not sent to participants due to disruptions in server access. These difficulties highlight the importance of ensuring that timelines include appropriate consideration for beta-testing, and budgets include appropriate resources for support and maintenance activities.

A major limitation is that this system is not integrated with the existing electronic medical record (EMR). Although we originally sought to integrate this system, multiple factors intervened. Specifically, the hospital system changed EMRs during the planning phase of this study. Thus, the institution's information technology priorities were focused on the clinical implementation of the new EMR, not on research endeavors. In addition, as a result of the transition in EMRs, HCPs were required to complete multiple training sessions and change their workflow to accommodate the new EMR. As a result, additional meetings with HCPs to discuss the best strategies for integration into the EMR were not possible at this time. The ability to translate this pilot study to a large-scale clinical implementation will depend on integration with the EMR. Although technically possible, integration with the EMR will require much negotiation with hospital administration and HCP groups, as well as an appropriate budget to fund the processes to support this integration.

In addition, we expect a fair amount of missing data from the app due to varying engagement from participants. However, our primary objective is not to use these data in statistical analyses; rather, our intention is that these data be useful to patients in monitoring and understanding their disease. Even if patients do not enter 50% of the data, they will still, on average, have at least 1 data point for disease activity per week and at least 1 data point for each of the other symptoms every 2 weeks. These data, in themselves, can be helpful and are more than is normally obtained without the aid of a disease activity and/or symptom tracker. We will also analyze the completion rates of daily surveys as proxies for patient engagement and overall feasibility.

Other limitations include the following: (1) the possibility of a ceiling effect if most participants have low disease activity and score well on the primary outcome measures, even at baseline; (2) the study being available only to English speakers, as not all of the surveys have been validated in other languages; and (3) limited generalizability, as we are only enrolling individuals who own a mobile device and, therefore, are likely receptive to mobile technology. In a study of 9183 participants in the Arthritis Internet Registry, older age and lower income were significantly associated with lower rates of mobile phone ownership [20]. However, recent studies suggest that mobile phone ownership is growing at a rapid rate, even among individuals over 50 years. On the basis of a 2016 report by the Pew Research Center, 74% of individuals between 50 and 64 years of age now own a mobile phone, a number which is up from approximately 50% in 2013 [49,50]. Similarly, mobile phone ownership in low-income households (<US $30,000/year) now exceeds 50% and continues to rise [51].

Conclusions

The successful implementation of a mobile device and population management system may help integrate patient-reported data into the workflow of a busy clinical practice. We expect this model to be easily adaptable to other rheumatic conditions, as well as nonrheumatic chronic illnesses. The PROMIS questionnaires used in this study were specifically developed to be relevant across different conditions for the assessment of symptoms and functions, and we anticipate that a mobile app combined with a population management system will have broad applicability in helping patients better understand their disease, improving patient-HCP communication and, ultimately, improving disease management and overall satisfaction in their care.

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Conflicts of Interest

This project was funded by an Independent Grant for Learning and Change from Pfizer, Inc. YLC has stock in Express Scripts. ABL is a Senior Advisor for Ranked Health, a nonprofit organization that evaluates digital health apps.

Multimedia Appendix 1

Physician exit form.

[PDF File (Adobe PDF File), 319KB - resprot_v7i4e84_app1.pdf]

Multimedia Appendix 2

Physician study visit follow-up questions.

[PDF File (Adobe PDF File), 291KB - resprot_v7i4e84_app2.pdf]

References

1. Tanaka Y. Current concepts in the management of rheumatoid arthritis. Korean J Intern Med 2016 Mar;31(2):210-218 [FREE Full text] [doi: 10.3904/kjim.2015.137] [Medline: 26932398]
2. Bykerk VP, Shadick N, Frits M, Bingham CO, Jeffery I, Iannaccone C, et al. Flares in rheumatoid arthritis: frequency and management. A report from the BRASS registry. J Rheumatol 2014 Feb;41(2):227-234. [doi: 10.3899/jrheum.121521] [Medline: 24334643]
3. Hewlett S, Sanderson T, May J, Alten R, Bingham CO, Cross M, et al. 'I'm hurting, I want to kill myself': rheumatoid arthritis flare is more than a high joint count--an international patient perspective on flare where medical help is sought. Rheumatology (Oxford) 2012 Jan;51(1):69-76. [doi: 10.1093/rheumatology/keq455] [Medline: 21565901]
4. Sanderson T, Kirwan J. Patient-reported outcomes for arthritis: time to focus on personal life impact measures? Arthritis Rheum 2009 Jan 15;61(1):1-3 [FREE Full text] [doi: 10.1002/art.24270] [Medline: 19116964]
5. Sanderson T, Morris M, Calnan M, Richards P, Hewlett S. What outcomes from pharmacologic treatments are important to people with rheumatoid arthritis? Creating the basis of a patient core set. Arthritis Care Res (Hoboken) 2010 May;62(5):640-646 [FREE Full text] [doi: 10.1002/acr.20034] [Medline: 20461785]
6. Berthelot JM, De Bandt M, Morel J, Benatig F, Constantin A, Gaudin P, STPR group of French Society of Rheumatology. A tool to identify recent or present rheumatoid arthritis flare from both patient and physician perspectives: the 'FLARE' instrument. Ann Rheum Dis 2012 Jul;71(7):1110-1116. [doi: 10.1136/ard.2011.150656] [Medline: 22072015]
7. Bykerk VP, Bingham CO, Choy EH, Lin D, Alten R, Christensen R, et al. Identifying flares in rheumatoid arthritis: reliability and construct validation of the OMERACT RA Flare Core Domain Set. RMD Open 2016;2(1):e000225 [FREE Full text] [doi: 10.1136/rmdopen-2015-000225] [Medline: 27252895]
8. Fautrel B, Morel J, Berthelot JM, Constantin A, De Bandt M, Gaudin P, STPR Group of the French Society of Rheumatology. Validation of FLARE-RA, a self-administered tool to detect recent or current rheumatoid arthritis flare. Arthritis Rheumatol 2017 Feb;69(2):309-319. [doi: 10.1002/art.39850] [Medline: 27636400]
9. Krebs P, Duncan DT. Health app use among US mobile phone owners: a national survey. JMIR Mhealth Uhealth 2015;3(4):e101 [FREE Full text] [doi: 10.2196/mhealth.4924] [Medline: 26537656]
10. Smith A. Pew Research Center. 2015. U.S. Smartphone Use in 2015 URL: http://www.pewinternet.org/files/2015/03/PI_Smartphones_0401151.pdf [WebCite Cache ID 6skGaCGAL]
11. Singh K, Drouin K, Newmark LP, Filkins M, Silvers E, Bain PA, et al. Patient-Facing Mobile Apps to Treat High-Need, High-Cost Populations: A Scoping Review. JMIR Mhealth Uhealth 2016 Dec 19;4(4):e136 [FREE Full text] [doi: 10.2196/mhealth.6445] [Medline: 27993761]
12. Nishiguchi S, Ito H, Yamada M, Yoshitomi H, Furu M, Ito T, et al. Self-assessment of rheumatoid arthritis disease activity using a smartphone application. Development and 3-month feasibility study. Methods Inf Med 2016;55(1):65-69. [doi: 10.3414/ME14-01-0106] [Medline: 26391694]
13. Nishiguchi S, Ito H, Yamada M, Yoshitomi H, Furu M, Ito T, et al. Self-assessment tool of disease activity of rheumatoid arthritis by using a smartphone application. Telemed J E Health 2014 Mar;20(3):235-240. [doi: 10.1089/tmj.2013.0162] [Medline: 24404820]
14. Ramirez V, Todd J. Nerdwallet. 2016. Top mobile-friendly U.S. Cities URL: https://www.nerdwallet.com/blog/utilities/top-mobile-friendly-cities-2016/ [accessed 2018-03-03] [WebCite Cache ID 6xerHMNDu]
15. Leeb BF, Haindl PM, Maktari A, Nothnagl T, Rintelen B. Patient-centered rheumatoid arthritis disease activity assessment by a modified RADAI. J Rheumatol 2008 Jul;35(7):1294-1299. [Medline: 18484698]
16. Witter JP. Introduction: PROMIS a first look across diseases. J Clin Epidemiol 2016 May;73:87-88. [doi: 10.1016/j.jclinepi.2016.02.014] [Medline: 26931294]

17. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7(4):R796-R806 [FREE Full text] [doi: 10.1186/ar1740] [Medline: 15987481]
18. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003 Feb;42(2):244-257. [Medline: 12595618]
19. Pincus T, Amara I, Segurado OG, Bergman M, Koch GG. Relative efficiencies of physician/assessor global estimates and patient questionnaire measures are similar to or greater than joint counts to distinguish adalimumab from control treatments in rheumatoid arthritis clinical trials. J Rheumatol 2008 Feb;35(2):201-205. [Medline: 18050378]
20. Michaud K, Schumacher R, Wahba K, Moturu S. Are rheumatic disease patient reported outcomes collected passively and directly through smart phones feasible? Early results from a nation-wide pilot study. Ann Rheum Dis 2014 Jun 10;73(Suppl 2):455-456. [doi: 10.1136/annrheumdis-2014-eular.4581]
21. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes 2004 Feb 26;2:12 [FREE Full text] [doi: 10.1186/1477-7525-2-12] [Medline: 14987333]
22. Maly RC, Frank JC, Marshall GN, DiMatteo MR, Reuben DB. Perceived efficacy in patient-physician interactions (PEPPI): validation of an instrument in older persons. J Am Geriatr Soc 1998 Jul;46(7):889-894. [Medline: 9670878]
23. Wolfe F, Michaud K, Pincus T. A composite disease activity scale for clinical practice, observational studies, and clinical trials: the patient activity scale (PAS/PAS-II). J Rheumatol 2005 Dec;32(12):2410-2415. [Medline: 16331773]
24. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. Arthritis Rheum 1990 Feb;33(2):160-172. [Medline: 2306288]
25. Amtmann D, Cook KF, Jensen MP, Chen W, Choi S, Revicki D, et al. Development of a PROMIS item bank to measure pain interference. Pain 2010 Jul;150(1):173-182 [FREE Full text] [doi: 10.1016/j.pain.2010.04.025] [Medline: 20554116]
26. Fries JF, Cella D, Rose M, Krishnan E, Bruce B. Progress in assessing physical function in arthritis: PROMIS short forms and computerized adaptive testing. J Rheumatol 2009 Sep;36(9):2061-2066. [doi: 10.3899/jrheum.090358] [Medline: 19738214]
27. Reeve BB, Hays RD, Bjorner JB, Cook KF, Crane PK, Teresi JA, PROMIS Cooperative Group. Psychometric evaluation and calibration of health-related quality of life item banks: plans for the Patient-Reported Outcomes Measurement Information System (PROMIS). Med Care 2007 May;45(5 Suppl 1):S22-S31. [doi: 10.1097/01.mlr.0000250483.85507.04] [Medline: 17443115]
28. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D, PROMIS Cooperative Group. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS®): depression, anxiety, and anger. Assessment 2011 Sep;18(3):263-283 [FREE Full text] [doi: 10.1177/1073191111411667] [Medline: 21697139]
29. Buysse DJ, Yu L, Moul DE, Germain A, Stover A, Dodds NE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. Sleep 2010 Jun;33(6):781-792 [FREE Full text] [Medline: 20550019]
30. Vermersch P, Hobart J, Dive-Pouletty C, Bozzi S, Hass S, Coyle PK. Measuring treatment satisfaction in MS: Is the Treatment Satisfaction Questionnaire for Medication fit for purpose? Mult Scler 2017 Apr;23(4):604-613 [FREE Full text] [doi: 10.1177/1352458516657441] [Medline: 27364322]
31. Regnault A, Balp M, Kulich K, Viala-Danten M. Validation of the Treatment Satisfaction Questionnaire for Medication in patients with cystic fibrosis. J Cyst Fibros 2012 Dec;11(6):494-501 [FREE Full text] [doi: 10.1016/j.jcf.2012.04.007] [Medline: 22583743]
32. Liberato AC, Rodrigues RC, São-João TM, Alexandre NM, Gallani MC. Satisfaction with medication in coronary disease treatment: psychometrics of the Treatment Satisfaction Questionnaire for Medication. Rev Lat Am Enfermagem 2016 Jun 07;24:e2705 [FREE Full text] [doi: 10.1590/1518-8345.0745.2705] [Medline: 27276018]
33. Bharmal M, Payne K, Atkinson MJ, Desrosiers M, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes 2009;7:36 [FREE Full text] [doi: 10.1186/1477-7525-7-36] [Medline: 19397800]
34. Delestras S, Roustit M, Bedouch P, Minoves M, Dobremez V, Mazet R, et al. Comparison between two generic questionnaires to assess satisfaction with medication in chronic diseases. PLoS One 2013;8(2):e56247 [FREE Full text] [doi: 10.1371/journal.pone.0056247] [Medline: 23437104]
35. Lin HY, Cheng TT, Wang JH, Lee CS, Chen MH, Lei V, et al. Etoricoxib improves pain, function and quality of life: results of a real-world effectiveness trial. Int J Rheum Dis 2010 May;13(2):144-150. [doi: 10.1111/j.1756-185X.2010.01468.x] [Medline: 20536599]
36. Jobanputra P, Maggs F, Deeming A, Carruthers D, Rankin E, Jordan AC, et al. A randomised efficacy and discontinuation study of etanercept versus adalimumab (RED SEA) for rheumatoid arthritis: a pragmatic, unblinded, non-inferiority study of first TNF inhibitor use: outcomes over 2 years. Br Med J Open 2012;2(6) [FREE Full text] [doi: 10.1136/bmjopen-2012-001395] [Medline: 23148339]

37. ten Klooster PM, Oostveen JC, Zandbelt LC, Taal E, Drossaert CH, Harmsen EJ, et al. Further validation of the 5-item Perceived Efficacy in Patient-Physician Interactions (PEPPI-5) scale in patients with osteoarthritis. Patient Educ Couns 2012 Apr;87(1):125-130. [doi: 10.1016/j.pec.2011.07.017] [Medline: 21889864]
38. Zhao H, Luo W, Maly RC, Liu J, Lee J, Cui Y. Validation of the Chinese version 10-item Perceived Efficacy in Patient-Physician Interactions scale in patients with osteoarthritis. Patient Prefer Adherence 2016;10:2189-2195 [FREE Full text] [doi: 10.2147/PPA.S110883] [Medline: 27822020]
39. Eyles JP, Hunter DJ, Meneses SR, Collins NJ, Dobson F, Lucas BR, et al. Instruments assessing attitudes toward or capability regarding self-management of osteoarthritis: a systematic review of measurement properties. Osteoarthritis Cartilage 2017;25(8):1210-1222. [Medline: 28263899]
40. Gossec L, Cantagrel A, Soubrier M, Berthelot JM, Joubert JM, Combe B, et al. An e-health interactive self-assessment website (Sanoia®) in rheumatoid arthritis. A 12-month randomized controlled trial in 320 patients. Joint Bone Spine Dec 2017. [Medline: 29246532]
41. Smith A. Wall Street Journal. 2013. Smartphone Ownership - 2013 Update URL: https://www.wsj.com/articles/how-apps-can-help-manage-chronic-diseases-1498443120 [WebCite Cache ID 6wSGq7JjL]
42. Regnault A, Balp MM, Kulich K, Viala-Danten M. Validation of the Treatment Satisfaction Questionnaire for Medication in patients with cystic fibrosis. J Cyst Fibros 2012 Dec;11(6):494-501 [FREE Full text] [doi: 10.1016/j.jcf.2012.04.007] [Medline: 22583743]
43. Hanson KA, Agashivala N, Stringer SM, Balantac Z, Brandes DW. A cross-sectional survey of patient satisfaction and subjective experiences of treatment with fingolimod. Patient Prefer Adherence 2013 Apr 16;7:309-318. [Medline: 23620662]
44. Ward MM, Guthrie LC, Alba MI. Clinically important changes in individual and composite measures of rheumatoid arthritis activity: thresholds applicable in clinical trials. Ann Rheum Dis 2015 Sep;74(9):1691-1696. [Medline: 24794149]
45. Curtis JR, Yang S, Chen L, Pope JE, Keystone EC, Haraoui B, et al. Determining the minimally important difference in the clinical disease activity index for improvement and worsening in early rheumatoid arthritis patients. Arthritis Care Res (Hoboken) 2015 Oct;67(10):1345-1353 [FREE Full text] [doi: 10.1002/acr.22606] [Medline: 25988705]
46. Agarwal S, LeFevre AE, Lee J, L'Engle K, Mehl G, Sinha C, et al. Guidelines for reporting of health interventions using mobile phones: mobile health (mHealth) evidence reporting and assessment (mERA) checklist. Br Med J 2016;352:i1174. [Medline: 26988021]
47. Grainger R, Townsley H, White B, Langlotz T, Taylor WJ. Apps for people with rheumatoid arthritis to monitor their disease activity: a review of apps for best practice and quality. JMIR Mhealth Uhealth 2017 Feb 21;5(2):e7 [FREE Full text] [doi: 10.2196/mhealth.6956] [Medline: 28223263]
48. Landro L. WSJ. 2017. How Apps Can Help Manage Chronic Diseases URL: https://www.wsj.com/articles/how-apps-can-help-manage-chronic-diseases-1498443120 [accessed 2018-01-14] [WebCite Cache ID 6wSGq7JjL]
49. Pewinternet. Mobile Fact Sheet URL: http://www.pewinternet.org/fact-sheet/social-media/ [accessed 2017-08-15] [WebCite Cache ID 6skGlzurf]
50. Deloitte. 2014. The smartphone generation gap: over-55? There’s no app for that URL: https://www2.deloitte.com/content/dam/Deloitte/au/Documents/technology-media-telecommunications/deloitte-au-tmt-smartphone-generation-gap-011014.pdf [WebCite Cache ID 6skGttO6U]
51. Anderson M. Pewinternet. 2015. The Demographics of Device Ownership URL: http://www.pewinternet.org/2015/10/29/the-demographics-of-device-ownership/ [WebCite Cache ID 6skH6AtQz]

Abbreviations

CDAI: Clinical Disease Activity Index
DMARD: disease-modifying antirheumatic drug
EMR: electronic medical record
HCP: health care provider
PEPPI: Perceived Efficacy in Patient-Physician Interactions
PROMIS: Patient-Reported Outcomes Measurement Information System
RA: rheumatoid arthritis
RADAI-5: Rheumatoid Arthritis Disease Activity Index-5
RCT: randomized controlled trial
TSQM: Treatment Satisfaction Questionnaire for Medication

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Protocol

A Web-Based Decision Tool to Improve Contraceptive Counseling for Women With Chronic Medical Conditions: Protocol For a Mixed Methods Implementation Study

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Abstract

Background: Women with chronic medical conditions, such as diabetes and hypertension, have a higher risk of pregnancy-related complications compared with women without medical conditions and should be offered contraception if desired. Although evidence based guidelines for contraceptive selection in the presence of medical conditions are available via the United States Medical Eligibility Criteria (US MEC), these guidelines are underutilized. Research also supports the use of decision tools to promote shared decision making between patients and providers during contraceptive counseling.

Objective: The overall goal of the *MiHealth*, *MiChoice* project is to design and implement a theory-driven, Web-based tool that incorporates the US MEC (provider-level intervention) within the vehicle of a contraceptive decision tool for women with chronic medical conditions (patient-level intervention) in community-based primary care settings (practice-level intervention). This will be a 3-phase study that includes a predesign phase, a design phase, and a testing phase in a randomized controlled trial. This study protocol describes phase 1 and aim 1, which is to determine patient-, provider-, and practice-level factors that are relevant to the design and implementation of the contraceptive decision tool.

Methods: This is a mixed methods implementation study. To customize the delivery of the US MEC in the decision tool, we selected high-priority constructs from the Consolidated Framework for Implementation Research and the Theoretical Domains Framework to drive data collection and analysis at the practice and provider level, respectively. A conceptual model that incorporates constructs from the transtheoretical model and the health beliefs model undergirds patient-level data collection and analysis and will inform customization of the decision tool for this population. We will recruit 6 community-based primary care practices and conduct quantitative surveys and semistructured qualitative interviews with women who have chronic medical conditions, their primary care providers (PCPs), and clinic staff, as well as field observations of practice activities. Quantitative survey data will be summarized with simple descriptive statistics and relationships between participant characteristics and contraceptive recommendations (for PCPs), and current contraceptive use (for patients) will be examined using Fisher exact test. We will conduct thematic analysis of qualitative data from interviews and field observations. The integration of data will occur by comparing, contrasting, and synthesizing qualitative and quantitative findings to inform the future development and implementation of the intervention.

Results: We are currently enrolling practices and anticipate study completion in 15 months.

Conclusions: This protocol describes the first phase of a multiphase mixed methods study to develop and implement a Web-based decision tool that is customized to meet the needs of women with chronic medical conditions in primary care settings. Study findings will promote contraceptive counseling via shared decision making and reflect evidence-based guidelines for contraceptive selection.

Trial Registration: ClinicalTrials.gov NCT03153644; https://clinicaltrials.gov/ct2/show/NCT03153644 (Archived by WebCite at http://www.webcitation.org/6yUkA5lK8)

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KEYWORDS

contraception; mobile apps; birth control; primary care physicians; implementation science; decision support techniques; chronic disease; multiple chronic conditions; qualitative research

Introduction

Quality Gaps in Contraceptive Care

Access to family planning services to prevent unintended pregnancies is one of the leading health indicators for Healthy People 2020 [1]. Unintended pregnancies account for half of all US pregnancies [2] and are associated with adverse outcomes for women and children, such as maternal depression and low birth weight, respectively [3,4]. In 2008, US expenditures for live births resulting from unintended pregnancies were US $12.5 billion [5]. In 2014, the Centers for Disease Control and Prevention (CDC) and the US Office of Population Affairs jointly recommended an increase in the volume and quality of family planning services across all health care sectors, including primary care, to address this unmet public health need [6]. The Office of Population Affairs subsequently released contraceptive quality measures that assess the percentage of reproductive-aged fertile women who are provided moderately effective and highly effective contraceptive methods [7]. The National Quality Forum formally endorsed these measures in 2017, and the development of a patient-reported measure of contraceptive care is in progress [7]. There is a timely and critical need to disseminate and implement evidence-based interventions to meet these contraceptive quality measures and improve reproductive health outcomes.

Implications for Women With Chronic Medical Conditions

Women with chronic medical conditions (eg, diabetes and hypertension) have a higher rate of pregnancy-related complications [8-11] and death compared with women without these conditions [12,13]. The most prevalent chronic medical conditions (hereafter called “chronic conditions”) among reproductive-age women have risen over the last 10 years and include obesity (24.7%), asthma (16.2%), high cholesterol (13%), hypertension (10%), and diabetes (2.9%) [14]. Expanded definitions of chronic conditions that include psychiatric conditions estimate that women with chronic conditions comprise up to 45% of reproductive age women seen in primary care [15,16]. Studies have raised concerns that adult women with chronic conditions are at greater risk for unplanned pregnancy [17] as they are more likely to not use any contraceptive method, underutilize the most effective methods, and rely upon the least effective methods compared with the general population of reproductive-aged women [18-21]. Women with chronic conditions are often prescribed medications that can cause fetal defects [22,23], and those who do not desire pregnancy should be offered contraceptive options. Contraceptive counseling should include an explanation of potential beneficial or adverse impact of a method on their conditions and interactions with ongoing drug therapy.

Missed Opportunities and Barriers to Contraceptive Care in Primary Care

Women with chronic conditions most frequently see primary care providers (PCPs) for their health management [24]; these visits are windows of opportunity to address contraception within the context of ongoing medical care [25]. PCPs are well situated to address the contraceptive needs of women with chronic conditions, but the time constraints of office visits and incomplete provider knowledge are commonly cited barriers to doing so [26-28]. Although family planning is a required part of training for most PCPs, contraceptive knowledge is lower among PCPs compared with obstetrics and gynecology providers [27,28]; this is not surprising given the greater intensity of training and exposure to women’s health care among obstetrics and gynecology providers.

Implementation of Evidence-Based Contraceptive Guidelines From the Centers for Disease Control and Prevention

In 2010, the CDC released the United States Medical Eligibility Criteria (US MEC), which was adapted directly from the World Health Organization’s MEC to meet the unique needs of US patients. The US MEC provides guidance to clinicians regarding the selection of contraceptive methods in the presence of specific chronic conditions (eg, seizures) and personal characteristics (eg, age) [29] and is revised on a continual basis. In 2011, the American Congress of Obstetricians and Gynecologists formally endorsed use of the US MEC for “clinicians providing family planning services for women, especially women with chronic conditions” [30] as an effort to promote national-level dissemination and implementation of evidence-based contraceptive practices. However, there is a significant gap between the US MEC and reported clinical recommendations, particularly with respect to the intrauterine device and the implant—the most effective long-acting reversible contraceptives (LARC) [26,28,31-34]. LARC methods are estrogen-free and safe for the vast majority of women, including

those with conditions that may preclude the use of estrogen (eg, cardiac disease) [35-37]. It is critical to correct PCP misconceptions about LARC eligibility so that they do not unnecessarily prevent LARC use among women with chronic conditions, who are otherwise appropriate candidates [36], thus placing them at risk for unintended pregnancy.

Evidence-Based Contraceptive Counseling With Electronic Decision Aids

Studies have shown that provider recommendations have a significant and positive impact on patient initiation and selection of a contraceptive method [38-40]. However, the provision of generic contraceptive information alone is insufficient. Prior literature highlights the importance of individualized contraceptive counseling [41-43] via a shared decision-making process [44-47], defined as an interactive process through which providers and patients communicate and arrive at a mutually agreeable decision [48]. Decisions aids are clinical tools designed to support patient-centered communication via shared decision making rather than provide paternalistic or generic information [41,49]. Prior contraceptive decision aids have been developed for use on electronic tablet or computer-based platforms across multiple geographic regions, practice settings, and patient populations and have been associated with improved patient involvement [50], decreased decisional conflict, increased patient knowledge [51], and increased contraceptive use [45,52]. Patients have reported numerous advantages to a Web-based platform over paper, including the interactive nature of the interface and the ability to compare contraceptive methods using filters and sorting options [53,54]. Furthermore, patients appreciated the use of a decision tool before a clinical visit to help them narrow down their contraception options and prepare questions for their providers [53].

Rationale for Mixed Methods Study Design

The underlying rationale for collecting, integrating, and analyzing both qualitative and quantitative data are multifold: (1) quantitative data collected from self-administered survey items will provide descriptive statistics to allow for comparison with other practice settings and populations, (2) qualitative interviews will provide a deeper understanding of the lived experiences of women with chronic conditions and their primary care teams with respect to receiving and providing contraceptive services, respectively, (3) qualitative interviews provide an opportunity to immediately expand upon close-ended quantitative survey items that warrant further investigation [55], (4) leveraging the complementary nature of quantitative data and qualitative data maximizes our capacity to assess a broader range of theoretical constructs and contextual factors than if quantitative or quantitative methods were used alone [56], (5) collecting data via multiple methods (observations, interviews, surveys) improves the robustness and credibility of our findings [57].

The Use of Theory and Implementation Science to Develop a Patient-Centered Intervention for Use in Usual Care Settings

To ensure the development of a patient-centered tool that explicitly upholds patient autonomy in decision making, we created a conceptual model that draws upon principles from reproductive justice theory and health behavior theories. This conceptual model will provide a preliminary prototype for the decision tool, which will be modified iteratively during this study phase. To develop an intervention that is contextualized for use in real-world clinical practices, our study design is informed by implementation science, an emerging field of methods and approaches that address the challenges of implementing health interventions in usual practice settings.[58] We use selected constructs from 2 frameworks commonly used in implementation science: the Consolidated Framework for Implementation Research (CFIR) [59] and the Theoretical Domains Framework, to guide data collection and analysis on the practice and provider level, respectively.

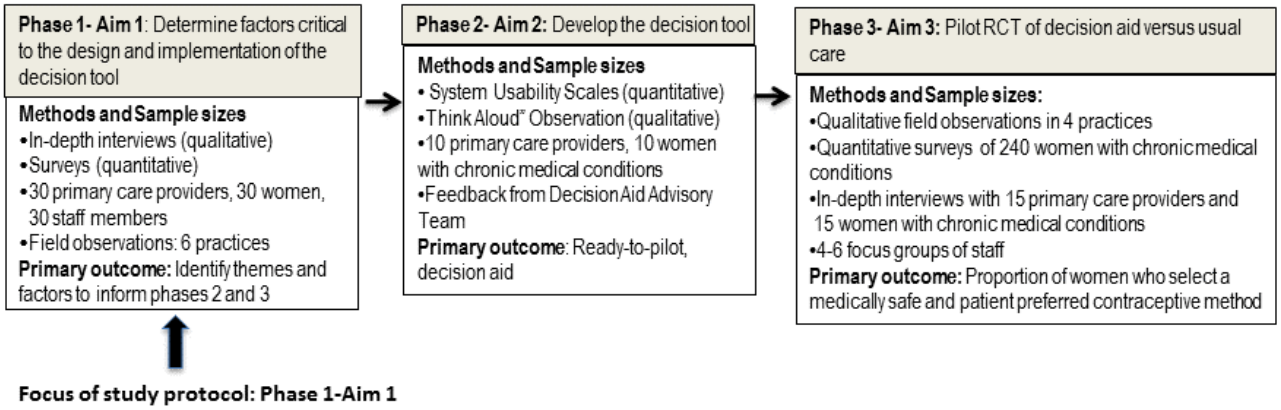
The overall goal of this mixed methods implementation project, the *MiHealth MiChoice study*, is to design and implement a theory-driven, Web-based contraceptive decision tool that can be accessed on an electronic tablet or computer before a clinical visit by women with chronic conditions who are seen in primary care settings. The feature of this tool that sets it apart from prior decision aids is that it will be tailored to factor in the personal preferences and medical history of a specific individual in a manner that also reflects evidence-based guidelines. The development and testing of this tool will occur over 3 phases (a predevelopment, development, and testing phase). The aim of this study protocol for phase 1 is to identify multilevel contextual factors that should drive the design and implementation of the contraceptive decision tool and explain subsequent study outcomes [60].

Methods

Overall Study Design

This mixed methods implementation study consists of 3 phases. This protocol focuses on phase 1, which is to identify the most critical patient-, provider-and practice-level factors that should inform the design and implementation of the decision-support tool. In phase 2, we will work with an expert health informatics team and an advisory council comprising patients, providers, and decision aid experts to build the Web-based decision tool that is accessible via a secured weblink from a computer or handheld tablet. Findings from phase 1 and a novel conceptual model (described in Figure 1 below) will inform iterative prototypes of the decision tool. In phase 3, the decision tool will be compared with usual care in a randomized controlled trial. We have received ethics approval for this study protocol by the University of Michigan Institutional Review Board (HUM00128060).

Figure 1. Multiphase mixed methods design. PCP: primary care provider; RCT: randomized controlled trial; CC: chronic condition.



Phase 1 Study Design

This is a convergent mixed methods design phase that focuses primarily on qualitative data collection and analysis with concurrent quantitative data collection and analysis. We will conduct semistructured, qualitative interviews of patients, PCPs, and practice staff members. All study participants will complete quantitative written surveys or electronic surveys via Qualtrics (Qualtrics, Provo, UT) before their qualitative interviews. The quantitative survey items complement the qualitative interview guide with the goal of obtaining maximal depth and breadth of understanding of each construct. Semistructured field observations in practices and collection of practice artifacts (eg, clinical protocols and patient intake forms) will further diversify our data sources and optimize data triangulation, which in turn will reduce the risk of systematic biases based on reported behaviors and experiences alone [61].

Sampling Strategy, Eligibility, and Recruitment

Practices

To balance similarity and variation across practices, providers, and patients, we will use a combination of purposeful sampling techniques as described by Palinkas and colleagues [62]. Eligible practices include practices that identify as family medicine, internal medicine, internal medicine-pediatric, or any combination of these. First, we will use criterion sampling to select individuals who have experiences that are relevant to the phenomenon of interest [62]; for this study, we aim to select practices for which a contraceptive intervention is both clinically relevant and feasible to implement. Because LARC methods (intrauterine device and implant) are the most effective reversible methods and medically appropriate for the vast majority of women with chronic conditions [36,37,63], we will recruit practices that either provide LARC or assist with referrals for LARC. Therefore, eligible practices must have: (1) one or more providers who currently offer prescription contraception (eg, oral contraceptive pills), and (2) informal or formal processes to refer patients who desire LARC methods to another site *or* provide LARC methods on site. To achieve maximum variation in practice attributes that are associated with variations in contraceptive practice [31,64], clinical sites will be sampled to reflect a range of location (urban, suburban, and rural practices), a balance between private practices and practices with federal designations (federally qualified health centers, rural health center, medically underserved areas), and diversity in the racial/ethnic background of patients. Thus, maximum variation sampling aims to achieve breadth in sampling and can highlight differences between practices. To complement this approach, we will also use snowball sampling such that participating practices suggest other practices for recruitment; this approach tends to select practices that share characteristics and thus will help to achieve depth of understanding of similar practices [62]. We will recruit practices through The Great Lakes Research Into Practice Network, a statewide practice-based research network that is recognized by the Agency for Healthcare Research and Quality [65].

Sample Size

To achieve the depth and variation in practices as described above, we aim to enroll 6 clinical sites. For individual qualitative interviews, prior literature has documented that 6 to 12 interviews per homogeneous group provide sufficient qualitative data to reach saturation, the point at which analysis produces no new information, or disconfirming or confirming evidence [55,66]. On the basis of the sampling strategy described, we aim to enroll 30 patients, 30 PCPs, and 30 staff members (nurses, medical assistants, and administrative staff). Our definitions of homogenous groups are summarized below and in Multimedia Appendix 1. Purposeful sampling will be driven by this matrix such that the perspectives of individuals in each category are represented in qualitative interview data with the goal of data saturation. We expect this category to evolve based upon patient population characteristics in recruited practices.

Practice Members (Primary Care Practices and Staff)

Eligible practice members must be aged 18 years or older, English-speaking, able to give informed consent, and be indirectly or directly involved with patient care. PCPs must be physicians, nurse practitioners, physician assistants, or certified nurse midwives, who currently provide preventive health and management of chronic conditions to reproductive-aged women [62]. To complement criterion sampling as described above, we seek maximal variation [62] in PCPs' contraceptive practices and will sample individuals who: (1) do not provide prescription contraception (eg, oral contraceptive pills), (2) provide prescription contraception but *do not* insert LARC devices, or (3) provide prescription contraception *and* insert LARC devices. For practice staff members other than PCPs, we aim to gather

staff perspectives regarding contraceptive services and interventions that may differ based upon their primary responsibilities and context of patient interaction: (1) director or manager (clinical director, administrative director, nurse manager), (2) work with PCPs during clinical visits (nurses, medical assistants, licensed practical nurses), and (3) other services (social work, complex care management, pharmacist, behavioral counselor). A designated practice liaison (eg, medical director, office manager) will assist the study team to identify eligible practice members and extend invitations for study participation.

Patients

Eligible patients must be women aged 18 to 50 years, fertile, English-speaking, and able to provide informed consent. They must also meet at least one of the following criteria: (1) a documented medical condition or multiple medical conditions being *actively managed* (on medication or requiring at least 2 visits a year), (2) a documented past medical condition or multiple medical conditions which would pose a significant risk to health during pregnancy (eg, past lung clot), or (3) current use of any drugs that are Pregnancy Category D or Category X medications. This definition expands upon guidance provided by the Department of Health and Human Services [67] as well as informed by pilot interviews with 15 PCPs (unpublished data). To obtain a range of perspectives, we aim to sample approximately equal numbers of women in the following groups that consist of conditions commonly encountered in primary care [68], conditions that frequently coexist together, or are managed with similar behavioral approaches and medications. Furthermore, we will focus on conditions for which there is evidence-based guidance regarding contraceptive selection in the CDC US MEC [69]. The following groups are described in detail in Multimedia Appendix 1: (1) psychiatric conditions, (2) metabolic and endocrine conditions, and (3) neurologic conditions. We will include an *other* group to capture women with less common conditions that nevertheless have a significant impact on pregnancy-related morbidity and mortality and contraceptive eligibility. The principal investigator (JW), who is a primary care specialist and a family planning expert, will review each participant's medical history and medications, in conjunction with the designated practice liaison, to ensure that eligibility criteria have been met.

The designated practice liaison in each practice will assist the study team in identifying patients who meet the eligibility criteria. With the permission of their PCPs, recruitment letters will be sent to potentially eligible patients followed up by up to 3 phone calls.

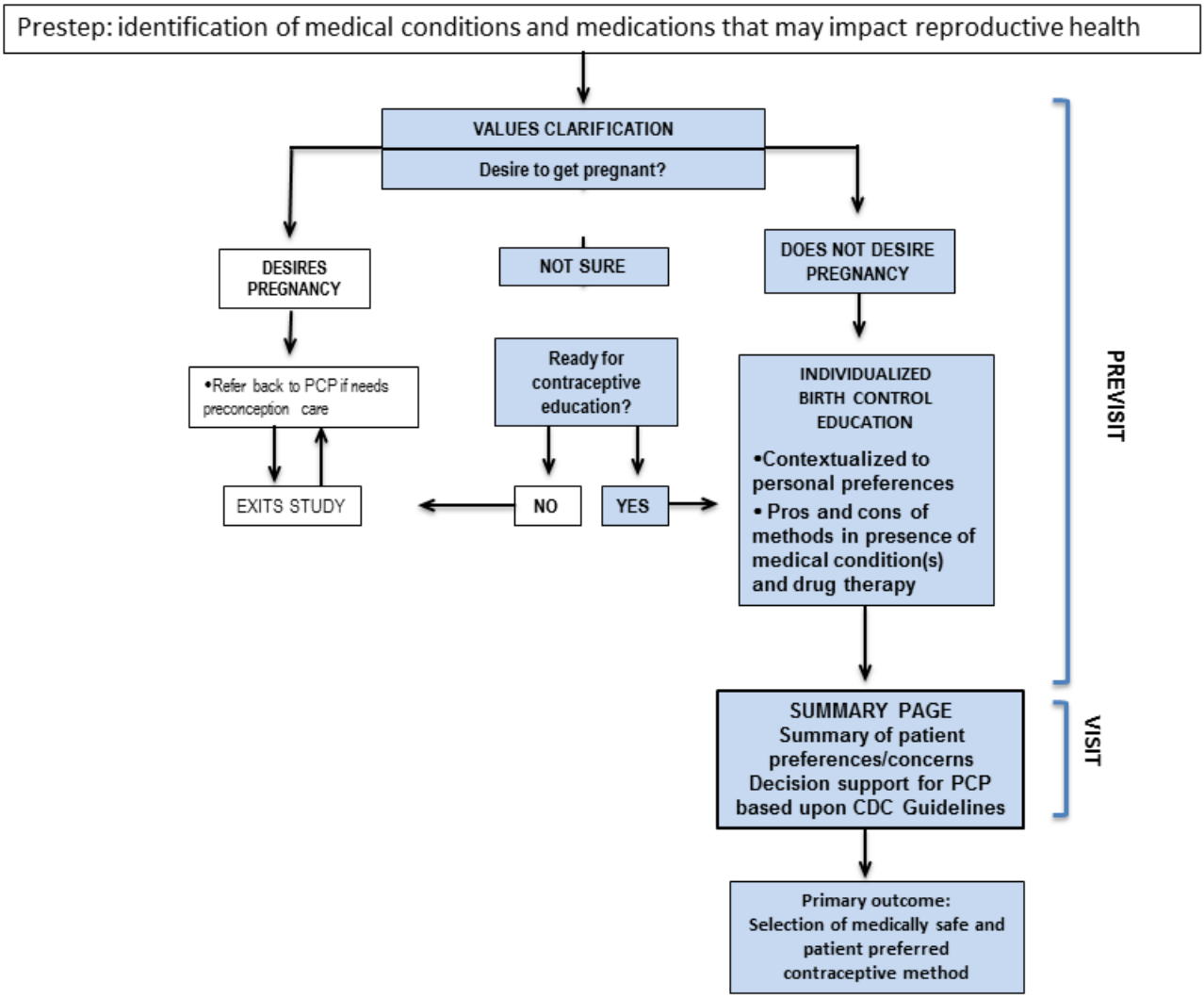
Context Assessment Frameworks to Guide Implementation (Practice and Provider Level)

Dehlendorf and colleagues recently described the development and testing of a tablet-based contraceptive decision aid that underwent rigorous cognitive testing [70] among patients in a safety net clinic. Our adaptation of this decision aid model will be sensitized by the application of our data to selected constructs from the CFIR, a typology of 5 major domains and associated constructs to assess context [59]. We chose CFIR because it identifies constructs at the practice and provider level that are universally relevant to successful implementation of a new intervention in clinical practice and can be tailored to the context of contraception. Furthermore, we anticipate that the use of CFIR will facilitate the collection of qualitative and quantitative data in a harmonized and efficient manner. Because the proposed intervention integrates clinical decision support for individual health providers, we also adapted constructs from the Theoretical Domains Framework to systematically identify determinants of clinical behavior change among PCPs [71]. We created a mixed methods theory-data matrix (see Multimedia Appendices 2-4), CSIR constructs and definitions by Damschroder et al [59]) to summarize how qualitative data (derived from practice observation, artifacts, and interviews) and quantitative data (derived from surveys) map to CFIR and Theoretical Domains Framework constructs (see Multimedia Appendices 2-4).

Conceptual Model to Guide Development of the Decision Tool (Patient-Level)

In a systematic review, Wyatt and colleagues identified 32 unique characteristics among 19 decision aids and classified them into 4 overarching categories: method effect, mechanistic, social/normative, and practical [72]. Among these attributes, studies have shown that women prioritize knowledge regarding mechanism of action [44], contraceptive effectiveness, safety, and side effects [73]. Using the tablet-based decision aid described by Dehlendorf as the prototype model [70], we will customize the above high-priority attributes for this patient population. Using a drop-down menu function, women will first provide their basic health history, including age, smoking status, medical conditions, and medications. We will then elicit patient preferences, guided by a conceptual model that incorporates a synthesis of constructs from reproductive justice theory, behavioral health theories, and evidence-based counseling techniques such as motivational interviewing and values clarification (Figure 2). One of the central tenets of reproductive justice is that people should be equally afforded the right to have a child and parent as well as the right to not have a child [74]. In accordance with this principle, we assert that a patient-centered contraceptive tool must be designed to prevent unconscious or conscious reproductive coercion, particularly toward individuals from marginalized communities. This concern is based upon the disturbing legacy of compulsory sterilization programs that targeted women of color, poor women, women with disabilities, and immigrant women in multiple US states throughout the twentieth century [75] and even as recently as 2010 in California [76]. Therefore, the model explicitly avoids presumptions about the patient's feelings regarding pregnancy and childbearing and starts with a values clarification [77] question by asking the patient about her current feelings regarding pregnancy and parenting.

Figure 2. Conceptual model to guide design of decision tool. PCP: primary care provider; CDC: Centers for Disease Control and Prevention.



Adapting a principle from the transtheoretical model [78], the patient will receive recommendations that are "matched" to her current pregnancy desires. If she does not want to get pregnant *and* indicates she is ready for contraceptive education, she will proceed through a responsive algorithm based upon her personal preferences, concerns, and prior contraceptive experiences. Constructs from the health beliefs model [79] will be operationalized to provide her information regarding the potential impact of her chronic condition on her reproductive health and vice versa, as well as individualized pros and cons of different contraceptive methods. The decision tool will summarize her preferences for methods, concerns she may want to discuss with her PCP, and embed clinical decision support for the PCP based upon the US MEC Guidelines (eg, patient has severe diabetes and should not use estrogen). This information will be made available in paper or electronic form to serve as a template for provider-patient discussion during the office visit.

If the patient indicates she desires pregnancy, she is advised to return to her PCP for preconception counseling and exits the study at this time. If the patient expresses ambivalence regarding pregnancy, the decision aid assesses if she is ready for contraceptive education, and if so, she proceeds through the contraceptive algorithm as outlined above.

Data Collection

Trained research assistants (RA) will spend 2 to 3 days at each clinical site to collect practice-specific data using a Practice Environment Template (PET), a semistructured checklist adapted from prior work by Crabtree and colleagues [80] and Jaén and colleagues [81]. The PET cues the RA to record observations of routine office activities, with a focus on clinical flow and processes relevant to contraceptive services. These data will provide a more complete and nuanced description of "what is happening on ground" and identify data that participants may not report on surveys or during interviews. The designated practice liaison will complete the Practice Information Form, a 29-item survey, also modified from prior work [80,81], that consists of multiple choice and open response items regarding practice demographics, pay structure, preventive and reproductive health services offered, and contraceptive methods offered.

All participants (staff, PCPs, and patients) will fill out a written or electronic (via Qualtrics, Provo, UT) quantitative survey before the face-to-face in-depth interview. There are 3 surveys:

(1) a 34-item Patient Survey, (2) a 19-item Provider Survey (for PCPs), and (3) a 13-item Staff Survey (for practice members other than PCPs). Participants will be interviewed in a quiet, private space designated by each practice. Interviews are audiotaped with the participants' permission and informed consent. We will conduct "member checking" with participants who agree to be contacted after the interview. This qualitative technique, also referred to as respondent validation, helps improve the accuracy, credibility, and transferability of research findings as well as empower participants to verify or modify the final interpretations of the data [61]. Member-checking should be undertaken with caution to minimize the risk of participant discomfort and ensure anonymity [82]. Therefore, we will share general themes and aggregated group data rather than specific quotes from individuals. All participants who complete an in-depth interview will receive a US $30 gift card as a token of appreciation for their time.

Data Analysis

All interview audiotapes will be transcribed verbatim. Qualitative analysis is an iterative process during which investigators go through cycles of reading, summarizing, and re-reading data [83,84]. The qualitative team is composed of 4 individuals from different professional backgrounds and research disciplines, including family medicine, dentistry, epidemiology, and health behavior. Though all team members identify as female, they vary in age, sexual orientation, religious background, and race/ethnicity. The interview transcripts will be uploaded and organized using MAXQDA software (VERBI GmbH, Berlin, Germany Version 12.3.1). We will conduct analysis through a series of iterative steps adapted from techniques described by Marshall and Rossman [85]. First, each team member will review several transcripts independently and code the content of each transcript. Because our research design is driven by predetermined theoretical constructs and research aims, our initial coding will be done with a theory-generated code template [86]. In vivo coding will also occur as new themes emerge from the interviews [85]. The team members will discuss, compare, and reconcile differences in coding and create a consensus code template, which will then be used to code the remainder of transcripts. Analysis of semistructured observations and practice artifacts proceeds in similar manner as described for interview transcripts. Themes and patterns will be identified and synthesized, using the preidentified theoretical constructs as a guide (Multimedia Appendices 2-4), as well as new codes and themes as they emerge. To increase the trustworthiness of our qualitative findings, we will triangulate our qualitative findings on multiple levels [54]: (1) methodological triangulation, by comparing and integrating with quantitative survey data, (2) data triangulation, by comparing and contrasting data obtained via interviews, surveys, observations, and artifacts, and (3) theoretical triangulation, by gathering multiple perspectives of the same phenomenon (patient-, provider-, practice-level perspectives). Data collection continues until saturation is reached, or until we no longer identify new or disconfirming or confirming data [84] with respect to the original research aim. Quantitative survey data will be summarized with simple descriptive statistics (frequencies, means, and SDs). We will conduct bivariate analyses with Fisher exact test to explore the following relationships: (1) demographic traits of providers and their contraceptive recommendations and practices, (2) practice attributes and providers' contraceptive recommendations and practices, (3) the presence of different chronic conditions and current pregnancy desires among women, and (4) the presence of different chronic conditions and current contraceptive use among women. As described by Fetters [60], we will merge the quantitative and qualitative strands of data by identifying content from both datasets to compare, contrast, and synthesize. A final interpretation will summarize to what extent and how the results from the qualitative and quantitative data contribute to the identification of patient-, provider-, and practice-level factors that will then shape the design and implementation of the decision tool.

Results

Enrollment of patients and providers in community-based primary care practices in Michigan is underway. Upon completion of this first study phase, the findings will be used to inform design of the contraceptive decision tool for testing in a future randomized controlled trial. The results of this study will be published in a peer-reviewed journal and presented at scientific conferences.

Discussion

The study design and proposed intervention have several strengths. First, we are collecting multilevel qualitative and quantitative data to gain a comprehensive and deep understanding of the experiences of and interactions among patients, providers, and staff. Constructs from implementation science theory and behavioral health theories drive data collection and analysis. To organize this large volume of data, we employ a rigorous mixed methods design and data integration procedures. A potential weakness of this study is that practices are limited to Michigan, which has a lower prevalence of ethnic and racial minorities than more populous states. However, we will recruit practices that have greater representation of underrepresented groups to mitigate this concern. We also anticipate challenges associated with practice-based research, including efficient recruitment and coordination of research practices with multiple practices outside our institution. The support of a locally based and established state-wide primary care network and previously established relationships between our institution and community partners will be critical to these processes.

This protocol describes the first phase of a multiphase design and implementation of a theory-driven intervention that incorporates customized decision tool attributes and embeds targeted US MEC recommendations to meet the contraceptive needs of women with chronic medical conditions in primary care settings. The study findings will provide critical knowledge regarding the feasibility and best approaches to implement the intervention in real-world primary care settings with the goal of promoting shared decision-making and evidence-based guidelines.

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Authors' Contributions

JW, LD, MF, BZF, BC, SH, and JC contributed to key aspects of the study design, theoretical framework, or conceptual model. JW, MK, ST, and JF developed the survey instruments. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Qualitative sampling matrix.

[PDF File (Adobe PDF File), 23KB - resprot_v7i4e107_app1.pdf]

Multimedia Appendix 2

Mixed methods theory data matrix: mapping data to Consolidated Framework for Implementation Research (CFIR) inner setting constructs.

[PDF File (Adobe PDF File), 40KB - resprot_v7i4e107_app2.pdf]

Multimedia Appendix 3

Mixed methods theory data matrix: mapping data to Consolidated Framework for Implementation Research (CFIR) outer setting and intervention constructs.

[PDF File (Adobe PDF File), 53KB - resprot_v7i4e107_app3.pdf]

Multimedia Appendix 4

Mixed methods theory data matrix: mapping data to Theoretical Domains Framework (TDR) constructs.

[PDF File (Adobe PDF File), 27KB - resprot_v7i4e107_app4.pdf]

References

1. Office of Disease Prevention Health Promotion. 2014. Healthy people 2020 leading health indicators: progress update URL: https://www.healthypeople.gov/2020/leading-health-indicators/Healthy-People-2020-Leading-Health-Indicators%3A-Progress-Update [accessed 2017-12-10] [WebCite Cache ID 6vNE3cYaR]
2. Finer LB, Zolna MR. Shifts in intended and unintended pregnancies in the United States, 2001-2008. Am J Public Health 2014 Feb;104(Suppl 1):S43-S48. [doi: 10.2105/AJPH.2013.301416] [Medline: 24354819]
3. Cheng D, Schwarz EB, Douglas E, Horon I. Unintended pregnancy and associated maternal preconception, prenatal and postpartum behaviors. Contraception 2009 Mar;79(3):194-198. [doi: 10.1016/j.contraception.2008.09.009] [Medline: 19185672]
4. D'Angelo DV, Gilbert BC, Rochat RW, Santelli JS, Herold JM. Differences between mistimed and unwanted pregnancies among women who have live births. Perspect Sex Reprod Health 2004;36(5):192-197. [doi: 10.1363/psrh.36.192.04] [Medline: 15519961]
5. Sonfield A, Kost K, Gold RB, Finer LB. The public costs of births resulting from unintended pregnancies: national and state-level estimates. Perspect Sex Reprod Health 2011 Jun;43(2):94-102. [doi: 10.1363/4309411] [Medline: 21651708]
6. Gavin L, Moskosky S, Carter M, Curtis K, Glass E, Godfrey E, Centers for Disease Control and Prevention (CDC). Providing quality family planning services: recommendations of CDC and the U.S. Office of Population Affairs. MMWR Recomm Rep 2014 Apr 25;63(RR-04):1-54 [FREE Full text] [Medline: 24759690]

7. Gavin L, Frederiksen B, Robbins C, Pazol K, Moskosky S. New clinical performance measures for contraceptive care: their importance to healthcare quality. Contraception 2017 Sep;96(3):149-157. [doi: 10.1016/j.contraception.2017.05.013] [Medline: 28596123]
8. Boghossian NS, Yeung E, Albert PS, Mendola P, Laughon SK, Hinkle SN, et al. Changes in diabetes status between pregnancies and impact on subsequent newborn outcomes. Am J Obstet Gynecol 2014 May;210(5):431.e1-431.14 [FREE Full text] [doi: 10.1016/j.ajog.2013.12.026] [Medline: 24361790]
9. Kiely M, El-Mohandes AA, Gantz MG, Chowdhury D, Thornberry JS, El-Khorazaty MN. Understanding the association of biomedical, psychosocial and behavioral risks with adverse pregnancy outcomes among African-Americans in Washington, DC. Matern Child Health J 2011 Dec;15(Suppl 1):S85-S95 [FREE Full text] [doi: 10.1007/s10995-011-0856-z] [Medline: 21785892]
10. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. Thorax 2006 Feb;61(2):169-176 [FREE Full text] [doi: 10.1136/thx.2005.049718] [Medline: 16443708]
11. Alves E, Azevedo A, Rodrigues T, Santos AC, Barros H. Impact of risk factors on hypertensive disorders in pregnancy, in primiparae and multiparae. Ann Hum Biol 2013;40(5):377-384. [doi: 10.3109/03014460.2013.793390] [Medline: 23682598]
12. Berg CJ, Harper MA, Atkinson SM, Bell EA, Brown HL, Hage ML, et al. Preventability of pregnancy-related deaths: results of a state-wide review. Obstet Gynecol 2005 Dec;106(6):1228-1234. [doi: 10.1097/01.AOG.0000187894.71913.e8] [Medline: 16319245]
13. Berg CJ, Mackay AP, Qin C, Callaghan WM. Overview of maternal morbidity during hospitalization for labor and delivery in the United States: 1993-1997 and 2001-2005. Obstet Gynecol 2009 May;113(5):1075-1081. [doi: 10.1097/AOG.0b013e3181a09fc0] [Medline: 19384123]
14. Hayes DK, Fan AZ, Smith RA, Bombard JM. Trends in selected chronic conditions and behavioral risk factors among women of reproductive age, behavioral risk factor surveillance system, 2001-2009. Prev Chronic Dis 2011 Nov;8(6):A120 [FREE Full text] [Medline: 22005613]
15. Farr SL, Hayes DK, Bitsko RH, Bansil P, Dietz PM. Depression, diabetes, and chronic disease risk factors among US women of reproductive age. Prev Chronic Dis 2011 Nov;8(6):A119 [FREE Full text] [Medline: 22005612]
16. Ward BW, Schiller JS. Prevalence of multiple chronic conditions among US adults: estimates from the National Health Interview Survey, 2010. Prev Chronic Dis 2013 Apr 25;10:E65 [FREE Full text] [doi: 10.5888/pcd10.120203] [Medline: 23618545]
17. Chor J, Rankin K, Harwood B, Handler A. Unintended pregnancy and postpartum contraceptive use in women with and without chronic medical disease who experienced a live birth. Contraception 2011 Jul;84(1):57-63. [doi: 10.1016/j.contraception.2010.11.018] [Medline: 21664511]
18. Gawron LM, Gawron AJ, Kasper A, Hammond C, Keefer L. Contraceptive method selection by women with inflammatory bowel diseases: a cross-sectional survey. Contraception 2014 May;89(5):419-425 [FREE Full text] [doi: 10.1016/j.contraception.2013.12.016] [Medline: 24486008]
19. Maslow BL, Morse CB, Schanne A, Loren A, Domchek SM, Gracia CR. Contraceptive use and the role of contraceptive counseling in reproductive-aged women with cancer. Contraception 2014 Jul;90(1):79-85. [doi: 10.1016/j.contraception.2014.03.002] [Medline: 24792148]
20. Schwarz EB, Postlethwaite D, Hung Y, Lantzman E, Armstrong MA, Horberg MA. Provision of contraceptive services to women with diabetes mellitus. J Gen Intern Med 2012 Feb;27(2):196-201 [FREE Full text] [doi: 10.1007/s11606-011-1875-6] [Medline: 21922154]
21. Schwarz EB, Braughton MY, Riedel JC, Cohen S, Logan J, Howell M, et al. Postpartum care and contraception provided to women with gestational and preconception diabetes in California's Medicaid program. Contraception 2017 Aug 24;96(6):432-438. [doi: 10.1016/j.contraception.2017.08.006] [Medline: 28844877]
22. Schwarz EB, Maselli J, Norton M, Gonzales R. Prescription of teratogenic medications in United States ambulatory practices. Am J Med 2005 Nov;118(11):1240-1249. [doi: 10.1016/j.amjmed.2005.02.029] [Medline: 16271908]
23. Eisenberg DL, Stika C, Desai A, Baker D, Yost KJ. Providing contraception for women taking potentially teratogenic medications: a survey of internal medicine physicians' knowledge, attitudes and barriers. J Gen Intern Med 2010 Apr;25(4):291-297 [FREE Full text] [doi: 10.1007/s11606-009-1215-2] [Medline: 20087677]
24. Centers for Disease Control. National Ambulatory Medical Care Survey: 2010 Summary Tables URL: https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2010_namcs_web_tables.pdf [accessed 2018-01-30] [WebCite Cache ID 6vN6DhF0J]
25. Ornstein SM, Jenkins RG, Litvin CB, Wessell AM, Nietert PJ. Preventive services delivery in patients with chronic illnesses: parallel opportunities rather than competing obligations. Ann Fam Med 2013;11(4):344-349 [FREE Full text] [doi: 10.1370/afm.1502] [Medline: 23835820]
26. Akers AY, Gold MA, Borrero S, Santucci A, Schwarz EB. Providers' perspectives on challenges to contraceptive counseling in primary care settings. J Womens Health (Larchmt) 2010 Jun;19(6):1163-1170 [FREE Full text] [doi: 10.1089/jwh.2009.1735] [Medline: 20420508]
27. Dehlendorf C, Levy K, Ruskin R, Steinauer J. Health care providers' knowledge about contraceptive evidence: a barrier to quality family planning care? Contraception 2010 Apr;81(4):292-298 [FREE Full text] [doi: 10.1016/j.contraception.2009.11.006] [Medline: 20227544]

28. Russo JA, Chen BA, Creinin MD. Primary care physician familiarity with U.S. medical eligibility for contraceptive use. Fam Med 2015 Jan;47(1):15-21 [FREE Full text] [Medline: 25646873]
29. Curtis KM, Tepper NK, Marchbanks PA. Putting risk into perspective: the US medical eligibility criteria for contraceptive use. Rev Endocr Metab Disord 2011 Jun;12(2):119-125. [doi: 10.1007/s11154-011-9177-1] [Medline: 21541854]
30. American College of Obstetricians and Gynecologists. Committee opinion no. 505: understanding and using the U.S. Medical Eligibility Criteria For Contraceptive Use, 2010. Obstet Gynecol 2011 Sep;118(3):754-760. [doi: 10.1097/AOG.0b013e3182310cd3] [Medline: 21860318]
31. Biggs MA, Harper CC, Malvin J, Brindis CD. Factors influencing the provision of long-acting reversible contraception in California. Obstet Gynecol 2014 Mar;123(3):593-602. [doi: 10.1097/AOG.0000000000000137] [Medline: 24499746]
32. Harper CC, Henderson JT, Raine TR, Goodman S, Darney PD, Thompson KM, et al. Evidence-based IUD practice: family physicians and obstetrician-gynecologists. Fam Med 2012 Oct;44(9):637-645 [FREE Full text] [Medline: 23027156]
33. Rubin SE, Fletcher J, Stein T, Segall-Gutierrez P, Gold M. Determinants of intrauterine contraception provision among US family physicians: a national survey of knowledge, attitudes and practice. Contraception 2011 May;83(5):472-478. [doi: 10.1016/j.contraception.2010.10.003] [Medline: 21477692]
34. Wu JP, Gundersen DA, Pickle S. Are the contraceptive recommendations of family medicine educators evidence-based? A CERA survey. Fam Med 2016 Dec;48(5):345-352 [FREE Full text] [Medline: 27159092]
35. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 121: Long-acting reversible contraception: implants and intrauterine devices. Obstet Gynecol 2011 Jul;118(1):184-196. [doi: 10.1097/AOG.0b013e318227f05e] [Medline: 21691183]
36. Nelson AL. Intrauterine device practice guidelines: medical conditions. Contraception 1998 Sep;58(3 Suppl):59S-63S; quiz 72S. [Medline: 9807694]
37. Suri V, Aggarwal N, Kaur R, Chaudhary N, Ray P, Grover A. Safety of intrauterine contraceptive device (copper T 200 B) in women with cardiac disease. Contraception 2008 Oct;78(4):315-318. [doi: 10.1016/j.contraception.2008.05.006] [Medline: 18847580]
38. Bitzer J, Cupanik V, Fait T, Gemzell-Danielsson K, Grob P, Oddens BJ, et al. Factors influencing women's selection of combined hormonal contraceptive methods after counselling in 11 countries: results from a subanalysis of the CHOICE study. Eur J Contracept Reprod Health Care 2013 Oct;18(5):372-380. [doi: 10.3109/13625187.2013.819077] [Medline: 23941311]
39. Harper CC, Brown BA, Foster-Rosales A, Raine TR. Hormonal contraceptive method choice among young, low-income women: how important is the provider? Patient Educ Couns 2010 Dec;81(3):349-354 [FREE Full text] [doi: 10.1016/j.pec.2010.08.010] [Medline: 20837389]
40. Rosenberg MJ, Waugh MS, Burnhill MS. Compliance, counseling and satisfaction with oral contraceptives: a prospective evaluation. Fam Plann Perspect 1998;30(2):89-92, 104 [FREE Full text] [Medline: 9561874]
41. Dehlendorf C, Levy K, Kelley A, Grumbach K, Steinauer J. Women's preferences for contraceptive counseling and decision making. Contraception 2013 Aug;88(2):250-256 [FREE Full text] [doi: 10.1016/j.contraception.2012.10.012] [Medline: 23177265]
42. Langston AM, Rosario L, Westhoff CL. Structured contraceptive counseling--a randomized controlled trial. Patient Educ Couns 2010 Dec;81(3):362-367. [doi: 10.1016/j.pec.2010.08.006] [Medline: 20869187]
43. Melo J, Peters M, Teal S, Guiahi M. Adolescent and young women's contraceptive decision-making processes: choosing “The Best Method for Her”. J Pediatr Adolesc Gynecol 2015 Aug;28(4):224-228. [doi: 10.1016/j.jpag.2014.08.001] [Medline: 26049939]
44. Donnelly KZ, Foster TC, Thompson R. What matters most? The content and concordance of patients' and providers' information priorities for contraceptive decision making. Contraception 2014 Sep;90(3):280-287. [doi: 10.1016/j.contraception.2014.04.012] [Medline: 24863169]
45. George TP, DeCristofaro C, Dumas BP, Murphy PF. Shared decision aids: increasing patient acceptance of long-acting reversible contraception. Healthcare (Basel) 2015 Apr 10;3(2):205-218 [FREE Full text] [doi: 10.3390/healthcare3020205] [Medline: 27417757]
46. Marshall C, Nuru-Jeter A, Guendelman S, Mauldon J, Raine-Bennett T. Patient perceptions of a decision support tool to assist with young women's contraceptive choice. Patient Educ Couns 2017 Feb;100(2):343-348. [doi: 10.1016/j.pec.2016.08.022] [Medline: 27578270]
47. French RS, Wellings K, Cowan FM. How can we help people to choose a method of contraception? The case for contraceptive decision aids. J Fam Plann Reprod Health Care 2009 Oct;35(4):219-220 [FREE Full text] [doi: 10.1783/147118909789587169] [Medline: 19849914]
48. Alston C, Berger Z, Brownlee S, Elwyn G, Fowler FJ, Hall LK, et al. Washington, DC: Discussion Paper, Institute of Medicine Shared decision-making strategies for best care: Patient decision aids URL: https://nam.edu/wp-content/uploads/2015/06/SDMforBestCare2.pdf [accessed 2017-11-30] [WebCite Cache ID 6vMq1bi0M]
49. Dehlendorf C, Grumbach K, Schmittdiel JA, Steinauer J. Shared decision making in contraceptive counseling. Contraception 2017 May;95(5):452-455. [doi: 10.1016/j.contraception.2016.12.010] [Medline: 28069491]

50. Kim YM, Kols A, Martin A, Silva D, Rinehart W, Prammawat S, et al. Promoting informed choice: evaluating a decision-making tool for family planning clients and providers in Mexico. Int Fam Plan Perspect 2005 Dec;31(4):162-171 [FREE Full text] [doi: 10.1363/ifpp.31.162.05] [Medline: 16439343]
51. Chewning B, Mosena P, Wilson D, Erdman H, Potthoff S, Murphy A, et al. Evaluation of a computerized contraceptive decision aid for adolescent patients. Patient Educ Couns 1999 Nov;38(3):227-239. [Medline: 10865688]
52. Garbers S, Meserve A, Kottke M, Hatcher R, Ventura A, Chiasson MA. Randomized controlled trial of a computer-based module to improve contraceptive method choice. Contraception 2012 Oct;86(4):383-390. [doi: 10.1016/j.contraception.2012.01.013] [Medline: 22402258]
53. Marshall C, Nuru-Jeter A, Guendelman S, Mauldon J, Raine-Bennett T. Patient perceptions of a decision support tool to assist with young women's contraceptive choice. Patient Educ Couns 2017 Feb;100(2):343-348. [doi: 10.1016/j.pec.2016.08.022] [Medline: 27578270]
54. Dehlendorf C, Fitzpatrick J, Steinauer J, Swiader L, Grumbach K, Hall C, et al. Development and field testing of a decision support tool to facilitate shared decision making in contraceptive counseling. Patient Educ Couns 2017 Jul;100(7):1374-1381. [doi: 10.1016/j.pec.2017.02.009] [Medline: 28237522]
55. Crabtree BF, Miller WL. Using codes and code manuals. In: Doing Qualitative Research. Thousand Oaks, California: Sage Publications; 1999:163-178.
56. Fetters MD, Freshwaters D. The 1+ 1= 3 Integration Challenge. J Mix Methods Res 2015;9(2):115-117. [doi: 10.1177/1558689815581222]
57. Creswell J, Plano Clark VL. Designing and Conducting Mixed Methods Research. Thousand Oaks, CA: Sage Publications, Inc; 2011.
58. Nilsen P. Making sense of implementation theories, models and frameworks. Implement Sci 2015 Apr 21;10:53 [FREE Full text] [doi: 10.1186/s13012-015-0242-0] [Medline: 25895742]
59. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009;4:50 [FREE Full text] [doi: 10.1186/1748-5908-4-50] [Medline: 19664226]
60. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs-principles and practices. Health Serv Res 2013 Dec;48(6 Pt 2):2134-2156 [FREE Full text] [doi: 10.1111/1475-6773.12117] [Medline: 24279835]
61. Onwuegbuzie AJ, Leech NL. Validity and qualitative research: An oxymoron? Qual Quant 2007;41:233-249 [FREE Full text]
62. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. Adm Policy Ment Health 2015 Sep;42(5):533-544 [FREE Full text] [doi: 10.1007/s10488-013-0528-y] [Medline: 24193818]
63. Chen M, Culwell K. The Global Library of Women's Medicine. Contraception for women with medical problems URL: https://www.glowm.com/section_view/heading/Contraception%20for%20Women%20With%20Medical%20Problems/item/381 [accessed 2017-12-15] [WebCite Cache ID 6vjd2ru6x]
64. Borrero S, Schwarz EB, Creinin M, Ibrahim S. The impact of race and ethnicity on receipt of family planning services in the United States. J Womens Health (Larchmt) 2009;18(1):91-96 [FREE Full text] [doi: 10.1089/jwh.2008.0976] [Medline: 19072728]
65. Agency for Healthcare Research and Quality. Practice-Based Research Networks URL: https://pbrn.ahrq.gov [accessed 2017-12-01] [WebCite Cache ID 6vNCZs8sg]
66. Creswell JW. Sampling and integration issues. In: A Concise Introduction to Mixed Methods Research. Thousand Oaks, California: Sage Publications; 2015:105-120.
67. U.S. Department of Health and Human Services. Washington, D.C; 2015. Multiple chronic conditions: a strategic framework. Optimum health quality of life for individuals with multiple chronic conditions URL: https://www.hhs.gov/sites/default/files/ash/initiatives/mcc/mcc_framework.pdf [accessed 2017-10-17] [WebCite Cache ID 6vT2cLfJt]
68. Ornstein SM, Nietert PJ, Jenkins RG, Litvin CB. The prevalence of chronic diseases and multimorbidity in primary care practice: a PPRNet report. J Am Board Fam Med 2013;26(5):518-524 [FREE Full text] [doi: 10.3122/jabfm.2013.05.130012] [Medline: 24004703]
69. Centers for Disease Control and Prevention. United States Medical Eligibility Criteria (US MEC) for Contraceptive Use 2016 URL: https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html [WebCite Cache ID 6vjiJYRej]
70. Dehlendorf C, Fitzpatrick J, Steinauer J, Swiader L, Grumbach K, Hall C, et al. Development and field testing of a decision support tool to facilitate shared decision making in contraceptive counseling. Patient Educ Couns 2017 Jul;100(7):1374-1381. [doi: 10.1016/j.pec.2017.02.009] [Medline: 28237522]
71. Atkins L, Francis J, Islam R, O'Connor D, Patey A, Ivers N, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci 2017 Jun 21;12(1):77 [FREE Full text] [doi: 10.1186/s13012-017-0605-9] [Medline: 28637486]
72. Wyatt KD, Anderson RT, Creedon D, Montori VM, Bachman J, Erwin P, et al. Women's values in contraceptive choice: a systematic review of relevant attributes included in decision aids. BMC Womens Health 2014 Feb 13;14(1):28 [FREE Full text] [doi: 10.1186/1472-6874-14-28] [Medline: 24524562]

73. Madden T, Secura GM, Nease RF, Politi MC, Peipert JF. The role of contraceptive attributes in women's contraceptive decision making. Am J Obstet Gynecol 2015 Jul;213(1):46.e1-46.e6 [FREE Full text] [doi: 10.1016/j.ajog.2015.01.051] [Medline: 25644443]
74. Ross L. Understanding reproductive justice: Transforming the pro-choice movement. 2006;36:14-19 [FREE Full text] [doi: 10.2307/20838711]
75. Stern AM. Eugenics, sterilization, and historical memory in the United States. Hist Cienc Saude Manguinhos 2016 Dec;23Suppl 1(Suppl 1):195-212 [FREE Full text] [doi: 10.1590/S0104-59702016000500011] [Medline: 28198932]
76. Stern AM. Sterilized in the name of public health: race, immigration, and reproductive control in modern California. Am J Public Health 2005 Jul;95(7):1128-1138. [doi: 10.2105/AJPH.2004.041608] [Medline: 15983269]
77. Witteman HO, Scherer LD, Gavaruzzi T, Pieterse AH, Fuhrel-Forbis A, Chipenda DS, et al. Design features of explicit values clarification methods: a systematic review. Med Decis Making 2016 May;36(4):453-471. [doi: 10.1177/0272989X15626397] [Medline: 26826032]
78. Prochaska JO. Decision making in the transtheoretical model of behavior change. Med Decis Making 2008;28(6):845-849. [doi: 10.1177/0272989X08327068] [Medline: 19015286]
79. Hall KS. The Health Belief Model can guide modern contraceptive behavior research and practice. J Midwifery Womens Health 2012;57(1):74-81 [FREE Full text] [doi: 10.1111/j.1542-2011.2011.00110.x] [Medline: 22251916]
80. Crabtree BF, Miller WL, Stange KC. Understanding practice from the ground up. J Fam Pract 2001 Oct;50(10):881-887. [Medline: 11674891]
81. Jaén CR, Crabtree BF, Palmer RF, Ferrer RL, Nutting PA, Miller WL, et al. Methods for evaluating practice change toward a patient-centered medical home. Ann Fam Med 2010;8 Suppl 1:S9-20; S92 [FREE Full text] [doi: 10.1370/afm.1108] [Medline: 20530398]
82. Goldblatt H, Karnieli-Miller O, Neumann M. Sharing qualitative research findings with participants: study experiences of methodological and ethical dilemmas. Patient Educ Couns 2011 Mar;82(3):389-395. [doi: 10.1016/j.pec.2010.12.016] [Medline: 21257280]
83. Borkan J. Immersion/Crystallization. In: Crabtree BF, Miller WL, editors. Doing Qualitative Research. 2 edition. Thousand Oaks, CA: Sage Publications; 2009:179-194.
84. Creswell J, Clark V. Analyzing and interpreting data in mixed methods research. In: Designing and Conducting Mixed Methods Research. Thousand Oaks, CA: Sage Publications; 2011:203-250.
85. Marshall C, Rossman G. Managing, analyzing, and interpreting data. In: Designing Qualitative Research. Thousand Oaks, California: Sage Publications; 2016.
86. Crabtree BF, Miller WL. Using codes and code manuals: a template organizing style of interpretation. In: Crabtree BF, Miller WL, editors. Doing Qualitative Research. 2 edition. Thousand Oaks, CA: Sage Publications; 1999.

Abbreviations

CDC: Centers for Disease Control and Prevention
CFIR: Consolidated Framework for Implementation Research
LARC: long-acting reversible contraceptives
PCP: primary care provider
PET: Practice Environment Template
US MEC: United States Medical Eligibility Criteria

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Protocol

Effects of Dietary Inorganic Nitrate Supplementation on Exercise Performance in Patients With Heart Failure: Protocol for a Randomized, Placebo-Controlled, Cross-Over Trial

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Abstract

Background: Chronic heart failure is characterized by an inability of the heart to pump enough blood to meet the demands of the body, resulting in the hallmark symptom of exercise intolerance. Chronic underperfusion of the peripheral tissues and impaired nitric oxide bioavailability have been implicated as contributors to the decrease in exercise capacity in these patients. nitric oxide bioavailability has been identified as an important mediator of exercise tolerance in healthy individuals, but there are limited studies examining the effects in patients with chronic heart failure.

Objective: The proposed trial is designed to determine the effects of chronic inorganic nitrate supplementation on exercise tolerance in both patients with heart failure preserved ejection fraction (HFpEF) and heart failure reduced ejection fraction (HFrEF) and to determine whether there are any differential responses between the 2 cohorts. A secondary objective is to provide mechanistic insights into the 2 heart failure groups' exercise responses to the nitrate supplementation.

Methods: Patients with chronic heart failure (15=HFpEF and 15=HFrEF) aged 40 to 85 years will be recruited. Following an initial screen cardiopulmonary exercise test, participants will be randomly allocated in a double-blind fashion to consume either a nitrate-rich beetroot juice (16 mmol nitrate/day) or a nitrate-depleted placebo (for 5 days). Participants will continue daily dosing until the completion of the 4 testing visits (maximal cardiopulmonary exercise test, submaximal exercise test with echocardiography, vascular function assessment, and vastus lateralis muscle biopsy). There will then be a 2-week washout period after which the participants will cross over to the other treatment and complete the same 4 testing visits.

Results: This study is funded by National Heart Foundation of Australia and Victoria University. Enrolment has commenced and the data collection is expected to be completed in mid 2018. The initial results are expected to be submitted for publication by the end of 2018.

Conclusions: If inorganic nitrate supplementation can improve exercise tolerance in patients with chronic heart failure, it has the potential to aid in further refining the treatment of patients in this population.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12615000906550; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=368912 (Archived by WebCite at http://www.webcitation.org/6xymLMiFK)

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KEYWORDS

cardiovascular disease; nitric oxide; exercise tolerance

Introduction

Background

Chronic heart failure (CHF) is a condition characterized by the inability of the heart to pump sufficient blood to meet the metabolic demands of the body. Affecting over 23 million people worldwide, this disease is the leading cause for hospital admission in both Europe and the United States [1]. CHF is a multifarious syndrome that presents with different physiological impairments depending on age, medical history, pathology, and left ventricular ejection fraction status [2]. Although the etiology of CHF may vary, patients are all plagued by the hallmark symptoms of exercise intolerance (low aerobic capacity), dyspnea, and fatigue [3].

Exercise intolerance, defined by a reduced peak oxygen uptake (VO_{2peak}), independently predicts morbidity and mortality and directly contributes to a reduced quality of life in patients with CHF [4-6]. In comparison with healthy controls, patients with CHF have significantly lower VO_{2peak} (~13.5ml/kg/min vs ~23.8ml/kg/min), with accompanying reductions in cardiac output (CO) by 52-53% during maximal exercise [7-9]. Although it was historically assumed that this inability to augment CO during exercise was the primary contributor to exercise intolerance, more recent investigations suggest that resulting under-perfusion of the peripheral muscular tissues may have a more detrimental impact [3,10].

Following acute heart failure, there is an increased activation of the sympathetic nervous system (SNS), which leads to vasoconstriction of arteries supplying blood to the peripheral tissues to defend central blood pressure and vital organ perfusion [10]. Although this SNS response is critical initially, continued overactivation results in chronic underperfusion of the skeletal muscle tissues, thereby contributing to capillary density rarefaction and a preferential loss of type-I oxidative fibers, and thus shifting these patients to a more glycolytic phenotype [11-14]. In the heart and skeletal muscles, there are significant abnormalities in the mitochondrial function, leading to decreases in oxidative phosphorylation [15]. Within the vasculature, a reduction in nitric oxide (NO) bioavailability is also highly prevalent in CHF and has been correlated with both the severity of CHF and the patients' functional capacity [16]. NO is a key regulator of blood flow and as large and small vessel vasodilation is a crucial contributor to exercise capacity, the inability of patients with CHF to up-regulate NO could be a limiting factor in their exercise tolerance [3,17]. This knowledge has brought about a fundamental shift in the treatment focus for CHF, whereby interventions are now targeting improvements within the peripheral tissue function to restore exercise tolerance.

One emerging therapeutic approach is supplementing with dietary inorganic nitrate (found in kale, green leafy vegetables, or beetroot juice [BTR]) to increase circulating NO bioavailability [18]. This occurs via a 2-step process, whereby nitrate is swallowed and absorbed via the gut and released into circulation. Approximately 25% of nitrate becomes highly concentrated in the salivary glands, which is then secreted and subsequently reduced via oral commensal bacteria to nitrite, which is then swallowed and absorbed into the circulation [19]. The circulating nitrite in the plasma may act as a relatively protected NO species that can be reduced to NO in low-oxygen environments (such as in tissues with low partial pressure of oxygen or during exercise).

Studies in healthy populations have demonstrated a myriad of benefits in exercise performance following nitrate supplementation, including increases in time to exhaustion, oxygen consumption efficiency (during submaximal exercise), total power output, and decreased systemic blood pressure [20-27]. Inorganic nitrate supplementation has even greater potential efficacy in clinical populations as supplementation may be an effective way of assisting in the targeted redistribution of blood flow in the underperfused peripheral tissues [18]. However, in contrast to the numerous studies in healthy populations, there are relatively few studies to date that have examined the effects of inorganic nitrate supplementation on exercise capacity in clinical patients, and only 4 have been on the CHF population [28-31]. A further limitation in our current understanding of inorganic nitrate supplementation in patients with CHF is the lack of substantial evidence in each of the 2 individual classifications of CHF, with a large proportion of the publications focusing only on one classification.

Currently, there are 2 classifications for patients with heart failure differentiated by whether the patient has a preserved ejection fraction (HFpEF, also known as diastolic dysfunction) or a reduced ejection fraction (HFrEF, also known as systolic dysfunction). HFrEF often results from an acute ischemic event that causes tissue death, leaving the cardiac muscle less able to contract adequately. In these patients, the ejection fraction is reduced because of left ventricular chamber dilation [32,33]. Patients with HFrEF have a lower CO both at rest and during exercise as compared with HFpEF patients and healthy controls [8]. HFpEF typically has a slower onset and these patients are more likely to be older, female, and suffer from a myriad of other comorbidities. Although they also have significant left ventricular remodeling, in HFpEF, the chamber size remains unchanged, but there are increases in the wall thickness and the ratio of ventricular mass to chamber volume. These maladaptations lead to significant elevations in LV filling pressures, which is known to cause exertional dyspnea and further contribute to exercise intolerance [34]. Additionally, the impaired arterial hemodynamic profile of these patients (increased arterial stiffness, reduced exercise induced vasodilation) creates a unique model for which a vasodilatory intervention, such as inorganic nitrate supplementation, could be very effective [35,36].

In CHF, the HFpEF cohort has been the most studied. Zamani et al provided acute supplementation of inorganic nitrate in the

form of beetroot juice (12.9 mmol nitrate) to 17 HFpEF patients and saw improvements in total time to exhaustion (TTE) and VO_{2peak} during a maximal exercise test [29]. The performance benefits were accompanied by an increase in CO, although this was secondary to a decrease in systemic vascular resistance [29]. Following chronic inorganic nitrate dosing, Eggebeen et al found that 6.1 mmol nitrate/day for 7 days (in the form of beetroot juice) led to a 24% increase in TTE during an exercise bout of cycling at 75% of each individual's maximum power output [28]. Similarly, Zamani et al identified significant increases in TTE following a 2-week potassium nitrate dosing regimen (6 mmol/day for 1 week, increasing to 18 mmol/day for the second week) [37]. These studies lend support to inorganic nitrate supplementation's potential efficacy for improving exercise tolerance in patients with HFpEF; however, the small sample sizes and limited mechanistic data leave plenty of scope for future studies.

In comparison with the positive results seen in HFpEF cohorts, data for HFrEF remains limited. A recent study by Hirai et al supplemented HFrEF patients with 12.9 mmol nitrate/day in the form of beetroot juice for 9 days and reported no changes in any of the parameters examined, including exercise performance, central hemodynamics, and blood pressure [31]. The authors suggest that the negative findings could be because HFrEF patients have relatively normal oxygen extraction rates within the peripheral tissues. Although Hirai et al is the only human study examining the effects of inorganic nitrate supplementation on exercise capacity in patients with HFrEF, Coggan et al conducted a study examining the effects of nitrate supplementation on isokinetic knee extensor power [30]. This study showed a 13% increase in the maximal power output following a single dose of inorganic nitrate (11.2 mmol). The authors suggested that the substantial improvement (they note that it is much larger than the 6% increase observed in healthy controls) was due to NO's known effect of increasing the activation of cyclic guanosine monophosphate. As this activation is known to lead to increases in maximal power output, particularly in type II fibers, it lends further support to nitrate's efficacy in CHF (where patients are known to be more type II-fiber dominant). In further support of these findings, 2 separate CHF rat model studies, 1 using an acute dose (5 mg/kg sodium nitrite) and 1 using a chronic dose (1 mmol nitrate/kg/day for 5 days), demonstrated significant increases in blood flow and vascular conductance in skeletal muscle [38,39]. The acute sodium nitrite infusion also showed a preferential increase in blood flow, specifically in the muscles of the rats with a higher percentage of both type IIb + IId/x fast-twitch fibers [38]. This further illustrates the potential efficacy of nitrate supplementation within the HFrEF population. Thus, despite the lack of positive findings in the study by Hirai et al, there remains a lot of promise in the use of nitrate supplementation in patients with HFrEF.

Overall, the area of inorganic nitrate supplementation in patients with CHF is relatively new. The current studies have small sample sizes (3 of the 5 human studies had ≤12 participants) that lack diversity in gender (Hirai et al only had male participants) and testing modalities (all exercise studies used cycle ergometry). Moreover, no study to date has sought to examine and compare the effects of nitrate supplementation in HFrEF and HFpEF patients within the same testing protocol. The development of research trials recruiting both HFrEF and HFpEF patients is critical to advancing our understanding of how to best clinically target and treat the mechanistic differences between these 2 distinct classes of CHF.

Objective

The primary aim of this study is to test the hypothesis that 5 days of inorganic nitrate supplementation (16 mmol/day) will improve exercise tolerance (VO_{2peak} and TTE) in both HFpEF and HFrEF patients. We further hypothesize that patients with HFpEF will have larger improvements in exercise tolerance than patients with HFrEF because of greater impairments in their peripheral muscular tissues. The secondary aim of the project is to identify the mechanistic contributors to exercise tolerance in both heart failure classifications via examining the following outcome measures:

1. Gastrocnemius tissue oxygenation at rest and during submaximal and maximal exercise via near-infrared spectroscopy (NIRS)
2. Vastus lateralis muscle tissue composition and function (angiogenesis, capillaries per unit area and per muscle fiber, mitochondrial function, and muscle fiber composition)
3. Vascular function via brachial artery flow-mediated dilation, lower-limb blood flow via plethysmography, and pulse wave velocity (PWV) and reflection.

Methods

Study Design and Participants

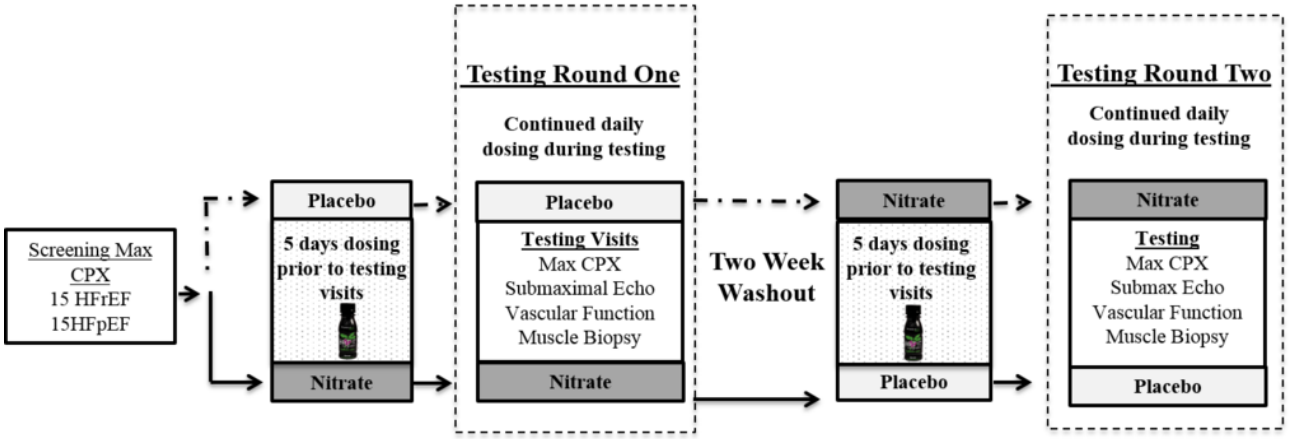
This is a randomized, double-blind, placebo-controlled, crossover study (see Figure 1). Following a screening visit, participants will be randomized to consume either nitrate-rich beetroot juice or a nitrate-depleted placebo for 5 days. Following this 5-day loading, the participants will continue daily dosing until the completion of the 4 testing visits (maximal cardiopulmonary exercise test (CPX), submaximal exercise test with echocardiography, vascular function assessment, and vastus lateralis muscle biopsy). Due to the need for adequate rest days between exercise visits, it could take up to 2 weeks in total to complete all testing visits within each round. However, both the dosing days and testing order will be matched within each participant between the 2 rounds of supplementation. Participants will then have a 2-week washout period before completing the second round of the study.

Recruitment Strategies and Eligibility

We aim to recruit 15 patients with HFrEF and 15 patients with HFpEF. A total sample of 30 is a realistic number of patients that can be recruited within the time frame of the study (18 months) and is similar to other successful studies in this field [29,40].

Recruitment will be open to individuals between the ages of 40 and 85 years who have diagnosed stable CHF with either HFrEF ≤40% or HFpEF ≥50% with no major changes in medications for at least 3 months (see Textboxes 1 and 2).

Figure 1. Max CPX: maximal cardiopulmonary exercise test; submaximal echo: submaximal exercise test with echocardiograph imaging; vascular testing: resting measures of blood flow and arterial function; and muscle biopsy: vastus lateralis muscle biopsy.



Textbox 1. Inclusion criteria.

1. Aged between 40 and 85 years
2. Diagnosed stable chronic heart failure (CHF) with either reduced ejection fraction (HFrEF) ≤40% or preserved ejection fraction (HFpEF) ≥50%
3. New York Heart Association class II-III
4. On stable medications for at least 3 months
5. Peak VO_2 <85% of age-predicted max

Additional criteria for HFpEF recruitment

1. Evidence of abnormal diastolic filling pressure (eg, abnormal E/e′, abnormal deceleration time, dilated left atrial volume, or elevated brain natriuretic peptide [if available]) [41]
2. Signs and symptoms of heart failure, plus definite episodes of decompensated heart failure (adjudicated via Boston Criteria)

Textbox 2. Exclusion criteria.

1. A major cardiovascular event within the previous 6 weeks or a planned hospitalization within the next 2 months
2. Patients with an ejection fraction between 41 and 49
3. Uncontrolled diabetes (>9% HbA1C [glycated hemoglobin])—Can delay start of testing by 3 months until levels are controlled and stable
4. Foot ulcers/advanced neuropathy or other musculoskeletal condition that could limit exercise performance
5. Abnormal response to CPX
6. Allergy to beets or proton pump inhibitors
7. Refusal or inability to abstain from the use of proton pump inhibitors for 24 hours before testing

Potential participants will be identified through medical chart reviews and will be contacted in person during a hospital or clinic visit. They will be given the contact information for the trial recruitment coordinator and instructed to contact the team if they wish to learn more about the study. At all stages, potential participants will be reminded that their participation in the study is voluntary and that their decision to participate or not will in no way affect their usual care.

Screening Visit

Patients who wish to participate in the study will be asked to sign an informed consent. They will then complete a screening maximal CPX that will be supervised by a medical practitioner. Although the primary purpose of CPX is to screen for adverse events or contraindications to participation in the study, it will also serve as a familiarization visit for the participants. This CPX employs a 2-step protocol that includes 6 min of low-intensity walking at 1.4 km/hour at a 4% grade. Following this, the speed and/or incline will be increased in an individualized manner as the participants' capabilities allow until maximal exertion is achieved. The test will only be stopped if the medical practitioner deems it unsafe to continue or the patient requests to stop. The max CPX protocol will be kept constant between visits for each individual subject. Similar protocols have been previously used in this population as the 2-step protocol allows for collection of both submaximal and maximal measures of aerobic capacity and function within 1 exercise bout [42-44].

Supplementation

Following successful completion of the screening CPX, participants who meet the inclusion criteria will be randomly allocated in a double-blind fashion to determine the order of treatment (beetroot juice or placebo). A technical staff member of Victoria University, external to the project, will color code the beetroot juice bottles and provide a randomization sheet to the research team that has the conditions removed and replaced with colors.

Participants will consume three 70-ml bottles of beetroot juice (BEET IT shot, James White Drinks, Ipswich, UK) per day of either a nitrate-rich beetroot juice (16 mmol of nitrate/day total) or a nitrate-depleted placebo for 5 days before they commence testing. They will then continuously dose until they complete all 4 testing visits. There will be a 2-week washout period between the 2 rounds. As the half-life of nitrate is 5-8 hours, a 2-week washout period should be sufficient to minimize any possible residual effect of nitrate [45]. The order of testing visits will be kept consistent for each participant between the beetroot juice and placebo testing rounds. On testing days, patients will consume the first bottle of either beetroot juice or placebo 2.5 to 3 hours prior, as plasma nitrite concentration peaks within 2.5 to 3 hours postingestion [23,24]. To assess supplementation compliance, participants will maintain a dosing log and return all bottle caps to the research team.

The cumulative body of literature identifies that decreases in the oxygen cost of exercise and increases in power output and time to exhaustion were seen in studies using a minimum dose of 5.2 mmol nitrate for 6 days [22,25-27]. A longer dosing protocol (15 days) demonstrated that improvements in steady-state VO_2 seen at day 5 were maintained but not increased at day 15 [46]. A previous clinical trial has demonstrated that an 18.1 mmol nitrate/day dose was feasible and safe for patients with peripheral arterial disease, whereas doses as high as 12.9 mmol nitrate/day have been used in the CHF population [40,47,48]. Thus, the dosing amount (16 mmol nitrate) and duration (minimum of 5 days before first testing session) for this study were selected to maximize the potential effects of the nitrate supplementation.

Quality of Life and Health Status Questionnaires

In addition to the physiological measures attained, participants will be asked to complete a series of questionnaires through the study, including the Minnesota Living with Heart Failure Questionnaire (MLHFQ) to determine how their CHF has affected their life during the last month; the Subjective Exercise Experience Scale (SEES) to assess the effect of an acute exercise bout on positive well-being, psychological distress, and fatigue; and finally, they will complete a Physical Activity Questionnaire (PAQ) to confirm their current level of physical activity [49,50].

Participants will be asked to complete MLHFQ and PAQ a total of 2 times, once before commencing each testing round to ensure there is no change in how their CHF affects their daily life and how much they are exercising. MLHFQ has been previously validated for the use of the resulting physical, emotional, and total scores in patients with CHF [50]. Participants will be asked to complete SEES after every exercise test for the duration of the study, including the screening CPX. This 12-question scale was developed and validated as a 3-factor measure (positive well-being, psychological distress, and fatigue) of psychological response to exercise and has been previously validated [51].

Maximal Cardiopulmonary Exercise Test Testing Visit

Participants will complete a 2-phase treadmill test identical to the screening CPX but with the addition of blood draws at rest and 10 min into recovery (to allow for postexercise blood volume stabilization) to quantify both resting plasma nitrate/nitrite as well as postexercise nitrate/nitrite changes.

Upon arrival for the testing visit, a catheter will be inserted into the antecubital vein of the participant to allow for repeated blood sampling. At this visit, 30 ml of blood will be collected in total. Following the resting blood draw, participants will be fitted with a 12-lead electrocardiograph to monitor their heart rhythms throughout the maximal test. Additionally, a near-infrared spectrometry (NIRS, PortaMon, Artinis Medical Systems B.V., The Netherlands) device will be placed on the skin above the gastrocnemius muscle of the participant. The NIRS system is noninvasive and provides an assessment of tissue oxygenation via the transmission of specific wavelengths of light (850 nm and 764 nm) that are absorbed by oxy- and deoxyhemoglobin, respectively [52]. A detection probe within the device measures the intensity of the received and transmitted light, which is communicated to a laptop via Bluetooth, and the corresponding software calculates the relative concentrations (and relative change) of oxygenated and deoxygenated hemoglobin within the muscle tissue. The device will be placed on the widest part of the medial head of the gastrocnemius, which is located by having the participant perform a short series of calf raises. A measuring tape will be used to identify the vertical point on the calf corresponding to the widest girth. A skinfold measurement will be taken at the selected site to ensure that the adipose tissue is less than 1.5 cm (typically the calf has less than 1 cm) [53]. The site will then be prepped with alcohol wipes (and shaving if appropriate), and the device will be affixed with micropore tape. Once the device is placed, vertical measurements are then taken from the top of the device to the bottom of the medial malleolus for reproducibility purposes on future tests. To ensure no light enters the NIRS device, a black plastic will be wrapped over the device and taped into place.

Additionally, a PhysioFlow (Physio Flow; Manatec Biomedical; Macheren, France) device will be used to estimate CO and the systemic vascular resistance index both at rest and during exercise. The device is a noninvasive hemodynamic monitor that provides real-time calculations of CO and various other parameters based on the morphological analysis of the bioelectrical impedance waveform. This device has been previously validated for measures of CO in healthy populations, but the studies in clinical populations thus far have been limited [54-57].

After 10 min of resting data collection, participants will be asked to complete a 2-step maximal treadmill CPX (as in the screening visit). Upon completion, the participant will be seated for recovery and at 10-min postcompletion will have a final 5 ml of blood drawn. Additionally, to allow for comparisons of the NIRS results to be made between subjects, a postexercise

physiological calibration will be used to convert the relative concentration values to a normalized scale. For this, an occlusion cuff will be applied to the NIRS leg just above the knee, and the patients will undergo 5 min of ischemia. The baseline value for the scale will be the plateau of the oxygenated hemoglobin signal, whereas the signal response to postcuff release will provide a functional maximum for the normalized scale. All values obtained during the testing will then be expressed as a percentage value within these ranges [58].

Vascular Function Visit

Patients will be asked to fast overnight and to abstain from exercise for the 24 hours prior and to avoid caffeine and smoking for the 3 hours before testing. They will also be asked to hold their morning medications until immediately post-testing. All vascular testing will occur following a minimum of 10 min, with the participant in the supine position.

Brachial artery flow-mediated dilation (FMD) will be obtained using a high-resolution Terason ultrasound (LifeHealthcare, New South Whales, Australia) to capture images of the brachial artery. This method has been previously used in clinical populations and has been shown to be reliable [40,59,60]. In brief, FMD will be assessed at baseline, following 5 min of forearm occlusion, and 2 min following occlusion cuff release (reactive hyperemia). These data points will be used to calculate the percentage of change in brachial artery diameter following reactive hyperemia.

Lower limb blood flow will be assessed via venous occlusion strain gauge plethysmography both at rest and during reactive hyperemia following 5 min of occlusion via Hokanson A16 (DE Hokanson, Bellevue, WA), as was previously described [61,62]. Participants will remain in a supine position with their legs elevated (to facilitate venous emptying) for the duration of the test. A cuff will be placed on the upper thigh of the nonbiopsy leg (so as not to put pressure on the biopsy site) to act both as a venous and arterial occlusion cuff while a mercury strain gauge (sized at ~4 cm less than calf width) is affixed around the largest part of the gastrocnemius. For resting measures, the thigh cuff will be inflated to 50 mmHg for 4 to 6 cycles of inflation and deflation to obtain resting blood flow measures. Resting blood flow will be recorded as the average of 3 measurements. Peak hyperemic blood flow will be determined following an ischemic occlusion (pressure set to 30 mmHg above systolic pressure) of the thigh for a period of 5 min. Postocclusion blood flow measurements were obtained every few seconds following cuff release, with the peak value being recorded as the highest value achieved.

Vascular stiffness will be assessed by PWV and pulse wave reflection using applanation tonometry via a SphygmoCor XCEL system (AtCor Medical, New South Whales, Australia. The SphygmoCor is a noninvasive diagnostic system that has been used to provide assessments of both the central blood pressure and PWV of clinical patients [63]. For the measurement of pulse wave analysis (PWA), a SphygmoCor arm cuff is placed on the upper arm, aligning the designated markings with the brachial artery. The system then measures pulsations recorded at the brachial artery to produce central aortic pressure waveforms and predict the following: central systolic pressure, central pulse pressure, augmentation pressure, and augmentation index. PWV is measured via a simultaneous comparison of the carotid and femoral arterial pulses. A thigh cuff will be placed around the participant's upper thigh, which acts to measure the femoral pulse via pulsations, while simultaneously a tonometer will be used to assess the carotid pulse. Higher pulse wave velocities from the carotid to femoral arteries indicate higher aortic stiffness.

Submaximal Echocardiograph Visit

For this visit, participants will again be asked to refrain from exercise and alcohol for the 24 hours before testing and to abstain from caffeine and smoking for the 3 hours before testing. They will be instructed to follow their normal dietary routine and take their medications. For this visit, participants will complete a series of 3 discontinuous stages (5-min rest in between each stage) of exercise on an echo-compatible recumbent cycle ergometer (Vivid 7 echocardiographic machine, GE, Milwaukee, Wisconsin). At present, the most common measure to assess the heart function during exercise is to have the participant exercise and then capture images immediately after exercise completion. The design of this cycle places the participant in an ideal position to capture echocardiograph images during exercise, allowing for more accurate assessment of cardiac function during exercise. Three independent workloads will be chosen based on participant capacity (Stage 1: 5-20 watts, Stage 2: 15-40 watts, and Stage 3: 30-60 watts). During the exercise test, participants will be fitted with the NIRS device, PhysioFlow, and electrocardiogram, similar to the one used during the max CPX. The echocardiograph will provide measures of CO, stroke volume (SV), mean arterial pressure (MAP), cardiac power output, left-ventricular end-systolic elastance, arterial elastance, preload recruitable stroke work, long-axis contraction and relaxation, mitral flow propagation velocity, and tricuspid incompetence. All echocardiograph assessments will be taken by the same tester to control for intertester variability.

Vastus Lateralis Muscle Biopsy Visit

The biopsy will be performed in a similar fashion to previous studies by our group on a separate day with at least 48 hours recovery between other testing visits [64,65]. In brief, the participant will be placed in a supine position. Following an injection of local anesthetic into the skin and fascia (1% Xylocaine), a small incision will be made at the level of the left vastus lateralis. A muscle sample will be taken (~150-300 mg wet weight) using a Bergström biopsy needle with manual suction applied [66]. Once obtained, muscle samples will be processed; cleaned of excess blood, fat, and connective tissue; and split into 3 portions. One portion (10-20 mg) will be immediately immersed in a 5-ml tube containing ~3 ml of biopsy-preserving solution kept on ice and used for in situ measurements of mitochondrial respiration. The second portion (around 20 mg) will be imbedded with Tissue-Tek for the immunohistochemistry analysis. The samples will be immediately frozen in liquid nitrogen and stored at −80°C for subsequent analyses.

Ethical Considerations

This study has been approved by the Melbourne Health [HREC/15/MH/166] and Victoria University Ethics Committees. The trial has been registered in the Australian New Zealand Clinical Trials Registry [ACTRN12615000906550].

Outcome Measurements

The primary outcome measure will be exercise tolerance [VO_{2peak} and TTE] during the 2-step CPX test. Secondary outcomes will include measures at rest and during exercise for cardiac function (CO, SV, MAP), as well as peripheral tissue function (lower limb blood flow, endothelial function, PWA, PWV, mitochondrial function). In addition, measures of plasma nitrate and nitrite will be recorded for nitrate-nitrite conversion rate calculations.

Complications and Adverse Events

Although complications and adverse events associated with the intervention are unlikely, participants will be asked to self-report any symptoms or adverse events they experience. The only previously documented side effects are beeturia (red urine) and red stools [23,67]. Any adverse events noted by the researchers or participants will be reported in the final manuscript.

Statistical Analysis

The primary endpoint of this pilot study is exercise capacity (VO_{2peak} and TTE) during the maximal CPX in both the HFpEF and HFrEF cohorts. A repeated-measures *t* test will be conducted to determine the changes in exercise capacity variables in the 2 groups combined. This will be followed by a repeated measure analysis of variance to determine the time×group effect in HFpEF and HFrEF patients. Similar analyses will be performed on the secondary endpoints/variables listed in the Specific Aims. Post hoc comparisons of change scores for relevant variables between HFpEF and HFrEF will be performed. Additional pairwise tests as well as linear regressions between the placebo and beetroot juice conditions will be used to determine what physiological factors (mitochondrial efficiency, endothelial function, tissue perfusion, leg blood flow, CO) contribute to any potential changes in exercise tolerance in HFpEF versus HFrEF.

Results

Data collection from this paper is currently underway. Predicted completion of the recruitment phase is mid-2018.

Discussion

Principal Findings

Heart failure is a chronic, progressive condition that has deleterious effects on both the central and peripheral function of the body, resulting in the hallmark symptom of exercise intolerance. This decrease in aerobic capacity is linked with lower rates of survival, a higher burden of disability, and increased rates of hospitalization for patients with CHF and is a prime target for rehabilitative interventions [4,68]. Thus, interventions that can acutely improve the tolerability of exercise for these patients could represent a crucial step forward for treatment.

The proposed project will be the first to comprehensively compare the central and peripheral function at rest and during exercise in both HFpEF and HFrEF patients on and off nitrate supplementation. This study will also be the first study in CHF that assesses the effects of nitrate supplementation within the skeletal muscle tissue (mitochondrial function, capillary density, and muscle fiber composition). Results from previous trials (in healthy individuals) have indicated the potential beneficial impact of nitrate supplementation on mitochondrial function, but this mechanistic change has yet to be demonstrated in CHF patients [21].

Limitations

The sample size for this study, although larger than some comparable trials, is still quite small. However, the crossover design helps to reduce the potential variability and improve the possibility of detecting differences between both the placebo and beetroot juice groups and the HFpEF and HFrEF groups. The high chronic dose was chosen to maximize the potential benefits of the supplementation, but the authors note that the amount is much higher than what would be consumed naturally in the diet. Finally, although every effort will be made to keep the supplementation days consistent before each testing visit between the placebo and beetroot juice rounds, because of patient and medical team availability, it is not possible to fully control this aspect. The 5-day loading period before any testing should help to standardize the dosing days. However, we will report any difference in dosing days between the 2 treatment arms.

Conclusions

Our understanding of the potential effects of nitrate supplementation in patients with CHF is still in its infancy. Although the initial studies show promise, the studies have been small and limited in scope to just 1 classification of CHF. This is the first study to directly compare the effects of inorganic nitrate supplementation on patients with HFrEF and HFpEF following an identical protocol to tease out any changes (and/or differences in changes) in peripheral and central factors. This is a critical step in advancing our current knowledge of CHF as a disease as well as the efficacy of nitrate supplementation. Given the relationship between exercise capacity and mortality and morbidity, if inorganic nitrate supplementation can improve exercise tolerance in patients with CHF, it has the potential to aid in further refining the treatment of patients in this population.

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Conflicts of Interest

None declared.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation 2010 Feb 23;121(7):948-954 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.109.192666] [Medline: 20177011]
2. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011 Jan;8(1):30-41 [FREE Full text] [doi: 10.1038/nrcardio.2010.165] [Medline: 21060326]
3. Piña IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, American Heart Association Committee on exercise, rehabilitation, and prevention. Exercise and heart failure: a statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation 2003 Mar 04;107(8):1210-1225 [FREE Full text] [Medline: 12615804]
4. Cicoira M, Davos CH, Francis DP, Doehner W, Zanolla L, Franceschini L, et al. Prediction of mortality in chronic heart failure from peak oxygen consumption adjusted for either body weight or lean tissue. J Card Fail 2004 Oct;10(5):421-426. [Medline: 15470653]
5. Francis DP, Shamim W, Davies LC, Piepoli MF, Ponikowski P, Anker SD, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2)slope and peak VO(2). Eur Heart J 2000 Jan;21(2):154-161. [doi: 10.1053/euhj.1999.1863] [Medline: 10637089]
6. Jeng C, Yang M, Chen P, Ho C. The influence of exercise tolerance on quality of life among patients with heart failure. Qual Life Res 2004 Jun;13(5):925-932. [doi: 10.1023/B:QURE.0000025604.15624.82] [Medline: 15233506]
7. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW. Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. J Am Coll Cardiol 2011 Jul 12;58(3):265-274 [FREE Full text] [doi: 10.1016/j.jacc.2011.02.055] [Medline: 21737017]
8. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB, et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. Circ Heart Fail 2015 Mar;8(2):286-294 [FREE Full text] [doi: 10.1161/CIRCHEARTFAILURE.114.001825] [Medline: 25344549]
9. Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. Muscle blood flow is reduced with maintenance of arterial perfusion pressure. Circulation 1989 Oct;80(4):769-781. [Medline: 2791242]
10. Nilsson K, Duscha B, Hranitzky P, Kraus W. Chronic heart failure and exercise intolerance: the hemodynamic paradox. Curr Cardiol Rev 2008 May;4(2):92-100 [FREE Full text] [doi: 10.2174/157340308784245757] [Medline: 19936283]
11. Duscha BD, Kraus WE, Keteyian SJ, Sullivan MJ, Green HJ, Schachat FH, et al. Capillary density of skeletal muscle: a contributing mechanism for exercise intolerance in class II-III chronic heart failure independent of other peripheral alterations. J Am Coll Cardiol 1999 Jun;33(7):1956-1963 [FREE Full text] [Medline: 10362199]
12. Sullivan MJ, Green HJ, Cobb FR. Altered skeletal muscle metabolic response to exercise in chronic heart failure. Relation to skeletal muscle aerobic enzyme activity. Circulation 1991 Oct;84(4):1597-1607. [Medline: 1914100]
13. Sullivan MJ, Green HJ, Cobb FR. Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. Circulation 1990 Feb;81(2):518-527. [Medline: 2297859]
14. Williams AD, Selig S, Hare DL, Hayes A, Krum H, Patterson J, et al. Reduced exercise tolerance in CHF may be related to factors other than impaired skeletal muscle oxidative capacity. J Card Fail 2004 Apr;10(2):141-148. [Medline: 15101026]
15. Rosca MG, Hoppel CL. Mitochondria in heart failure. Cardiovasc Res 2010 Oct 01;88(1):40-50 [FREE Full text] [doi: 10.1093/cvr/cvq240] [Medline: 20668004]
16. Meyer B, Mörtl D, Strecker K, Hülsmann M, Kulemann V, Neunteufl T, et al. Flow-mediated vasodilation predicts outcome in patients with chronic heart failure: comparison with B-type natriuretic peptide. J Am Coll Cardiol 2005 Sep 20;46(6):1011-1018 [FREE Full text] [doi: 10.1016/j.jacc.2005.04.060] [Medline: 16168284]
17. Katz SD, Yuen J, Bijou R, LeJemtel TH. Training improves endothelium-dependent vasodilation in resistance vessels of patients with heart failure. J Appl Physiol (1985) 1997 May;82(5):1488-1492. [doi: 10.1152/jappl.1997.82.5.1488] [Medline: 9134897]
18. Lundberg JO, Weitzberg E, Gladwin MT. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. Nat Rev Drug Discov 2008 Feb;7(2):156-167. [doi: 10.1038/nrd2466] [Medline: 18167491]
19. Spiegelhalder B, Eisenbrand G, Preussmann R. Influence of dietary nitrate on nitrite content of human saliva: possible relevance to in vivo formation of N-nitroso compounds. Food Cosmet Toxicol 1976 Dec;14(6):545-548. [Medline: 1017769]
20. Larsen FJ, Weitzberg E, Lundberg JO, Ekblom B. Dietary nitrate reduces maximal oxygen consumption while maintaining work performance in maximal exercise. Free Radic Biol Med 2010 Jan 15;48(2):342-347. [doi: 10.1016/j.freeradbiomed.2009.11.006] [Medline: 19913611]

21. Larsen FJ, Schiffer TA, Borniquel S, Sahlin K, Ekblom B, Lundberg JO, et al. Dietary inorganic nitrate improves mitochondrial efficiency in humans. Cell Metab 2011 Feb 02;13(2):149-159 [FREE Full text] [doi: 10.1016/j.cmet.2011.01.004] [Medline: 21284982]
22. Lansley KE, Winyard PG, Fulford J, Vanhatalo A, Bailey SJ, Blackwell JR, et al. Dietary nitrate supplementation reduces the O2 cost of walking and running: a placebo-controlled study. J Appl Physiol (1985) 2011 Mar;110(3):591-600 [FREE Full text] [doi: 10.1152/japplphysiol.01070.2010] [Medline: 21071588]
23. Webb AJ, Patel N, Loukogeorgakis S, Okorie M, Aboud Z, Misra S, et al. Acute blood pressure lowering, vasoprotective, and antiplatelet properties of dietary nitrate via bioconversion to nitrite. Hypertension 2008 Mar;51(3):784-790 [FREE Full text] [doi: 10.1161/HYPERTENSIONAHA.107.103523] [Medline: 18250365]
24. Kapil V, Milsom AB, Okorie M, Maleki-Toyserkani S, Akram F, Rehman F, et al. Inorganic nitrate supplementation lowers blood pressure in humans: role for nitrite-derived NO. Hypertension 2010 Aug;56(2):274-281 [FREE Full text] [doi: 10.1161/HYPERTENSIONAHA.110.153536] [Medline: 20585108]
25. Bailey SJ, Winyard P, Vanhatalo A, Blackwell JR, Dimenna FJ, Wilkerson DP, et al. Dietary nitrate supplementation reduces the O2 cost of low-intensity exercise and enhances tolerance to high-intensity exercise in humans. J Appl Physiol (1985) 2009 Oct;107(4):1144-1155 [FREE Full text] [doi: 10.1152/japplphysiol.00722.2009] [Medline: 19661447]
26. Pinna M, Roberto S, Milia R, Marongiu E, Olla S, Loi A, et al. Effect of beetroot juice supplementation on aerobic response during swimming. Nutrients 2014 Jan 29;6(2):605-615 [FREE Full text] [doi: 10.3390/nu6020605] [Medline: 24481133]
27. Cermak NM, Gibala MJ, van Loon LJ. Nitrate supplementation's improvement of 10-km time-trial performance in trained cyclists. Int J Sport Nutr Exerc Metab 2012 Feb;22(1):64-71. [Medline: 22248502]
28. Eggebeen J, Kim-Shapiro DB, Haykowsky M, Morgan TM, Basu S, Brubaker P, et al. One week of daily dosing with beetroot juice improves submaximal endurance and blood pressure in older patients with heart failure and preserved ejection fraction. JACC Heart Fail 2016 Jun;4(6):428-437. [doi: 10.1016/j.jchf.2015.12.013] [Medline: 26874390]
29. Zamani P, Rawat D, Shiva-Kumar P, Geraci S, Bhuva R, Konda P, et al. Effect of inorganic nitrate on exercise capacity in heart failure with preserved ejection fraction. Circulation 2015 Jan 27;131(4):371-80; discussion 380 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.114.012957] [Medline: 25533966]
30. Coggan AR, Leibowitz JL, Spearie CA, Kadkhodayan A, Thomas DP, Ramamurthy S, et al. Acute dietary nitrate intake improves muscle contractile function in patients with heart failure: a double-blind, placebo-controlled, randomized trial. Circ Heart Fail 2015 Sep;8(5):914-920 [FREE Full text] [doi: 10.1161/CIRCHEARTFAILURE.115.002141] [Medline: 26179185]
31. Hirai DM, Zelt JT, Jones JH, Castanhas LG, Bentley RF, Earle W, et al. Dietary nitrate supplementation and exercise tolerance in patients with heart failure with reduced ejection fraction. Am J Physiol Regul Integr Comp Physiol 2017 Jan 01;312(1):R13-R22. [doi: 10.1152/ajpregu.00263.2016] [Medline: 27784687]
32. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. J Am Med Assoc 2002 Nov 06;288(17):2144-2150. [Medline: 12413374]
33. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation 2011 May 10;123(18):2006-13; discussion 2014 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.110.954388] [Medline: 21555723]
34. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010 Sep;3(5):588-595 [FREE Full text] [doi: 10.1161/CIRCHEARTFAILURE.109.930701] [Medline: 20543134]
35. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 2006 Nov 14;114(20):2138-2147 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.106.632745] [Medline: 17088459]
36. Weber T, Wassertheurer S, O'Rourke MF, Haiden A, Zweiker R, Rammer M, et al. Pulsatile hemodynamics in patients with exertional dyspnea: potentially of value in the diagnostic evaluation of suspected heart failure with preserved ejection fraction. J Am Coll Cardiol 2013 May 07;61(18):1874-1883 [FREE Full text] [doi: 10.1016/j.jacc.2013.02.013] [Medline: 23500307]
37. Zamani P, Tan V, Soto-Calderon H, Beraun M, Brandimarto JA, Trieu L, et al. Pharmacokinetics and pharmacodynamics of inorganic nitrate in heart failure with preserved ejection fraction. Circ Res 2017 Mar 31;120(7):1151-1161. [doi: 10.1161/CIRCRESAHA.116.309832] [Medline: 27927683]
38. Glean AA, Ferguson SK, Holdsworth CT, Colburn TD, Wright JL, Fees AJ, et al. Effects of nitrite infusion on skeletal muscle vascular control during exercise in rats with chronic heart failure. Am J Physiol Heart Circ Physiol 2015 Oct;309(8):H1354-H1360 [FREE Full text] [doi: 10.1152/ajpheart.00421.2015] [Medline: 26371165]
39. Ferguson S, Holdsworth C, Colburn T, Wright JL, Craig JC, Fees A, et al. Dietary nitrate supplementation: impact on skeletal muscle vascular control in exercising rats with chronic heart failure. J Appl Physiol (1985) 2016 Sep 01;121(3):661-669 [FREE Full text] [doi: 10.1152/japplphysiol.00014.2016] [Medline: 27445296]

40. Kenjale AA, Ham KL, Stabler T, Robbins JL, Johnson JL, Vanbruggen M, et al. Dietary nitrate supplementation enhances exercise performance in peripheral arterial disease. J Appl Physiol (1985) 2011 Jun;110(6):1582-1591 [FREE Full text] [doi: 10.1152/japplphysiol.00071.2011] [Medline: 21454745]
41. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007 Oct;28(20):2539-2550. [doi: 10.1093/eurheartj/ehm037] [Medline: 17428822]
42. Brunner-La Rocca HP, Weilenmann D, Follath F, Schlumpf M, Rickli H, Schalcher C, et al. Oxygen uptake kinetics during low level exercise in patients with heart failure: relation to neurohormones, peak oxygen consumption, and clinical findings. Heart 1999 Feb;81(2):121-127 [FREE Full text] [Medline: 9922345]
43. Brunner-La Rocca HP, Weilenmann D, Schalcher C, Schlumpf M, Follath F, Candinas R, et al. Prognostic significance of oxygen uptake kinetics during low level exercise in patients with heart failure. Am J Cardiol 1999 Sep 15;84(6):741-4, A9. [Medline: 10498150]
44. Schalcher C, Rickli H, Brehm M, Weilenmann D, Oechslin E, Kiowski W, et al. Prolonged oxygen uptake kinetics during low-intensity exercise are related to poor prognosis in patients with mild-to-moderate congestive heart failure. Chest 2003 Aug;124(2):580-586. [Medline: 12907546]
45. Jungersten L, Edlund A, Petersson AS, Wennmalm A. Plasma nitrate as an index of nitric oxide formation in man: analyses of kinetics and confounding factors. Clin Physiol 1996 Jul;16(4):369-379. [Medline: 8842573]
46. Vanhatalo A, Bailey SJ, Blackwell JR, DiMenna FJ, Pavey TG, Wilkerson DP, et al. Acute and chronic effects of dietary nitrate supplementation on blood pressure and the physiological responses to moderate-intensity and incremental exercise. Am J Physiol Regul Integr Comp Physiol 2010 Oct;299(4):R1121-R1131. [doi: 10.1152/ajpregu.00206.2010] [Medline: 20702806]
47. Shaltout HA, Eggebeen J, Marsh AP, Brubaker PH, Laurienti PJ, Burdette JH, et al. Effects of supervised exercise and dietary nitrate in older adults with controlled hypertension and/or heart failure with preserved ejection fraction. Nitric Oxide 2017 Sep 30;69:78-90. [doi: 10.1016/j.niox.2017.05.005] [Medline: 28549665]
48. Hirai DM, Zelt JT, Jones JH, Castanhas LG, Bentley RF, Earle W, et al. Dietary nitrate supplementation and exercise tolerance in patients with heart failure with reduced ejection fraction. Am J Physiol Regul Integr Comp Physiol 2017 Jan 01;312(1):R13-R22. [doi: 10.1152/ajpregu.00263.2016] [Medline: 27784687]
49. Naveiro-Rilo JC, Diez-Juárez DM, Romero BA, Rebollo-Gutiérrez F, Rodríguez-Martínez A, Rodríguez-García MA. Validation of the Minnesota living with heart failure questionnaire in primary care. Rev Esp Cardiol 2010 Dec;63(12):1419-1427 [FREE Full text] [Medline: 21144402]
50. Bilbao A, Escobar A, García-Perez L, Navarro G, Quirós R. The Minnesota living with heart failure questionnaire: comparison of different factor structures. Health Qual Life Outcomes 2016 Feb 17;14:23 [FREE Full text] [doi: 10.1186/s12955-016-0425-7] [Medline: 26887590]
51. MeAuley E, Courneya K. The Subjective Exercise Experiences Scale (SEES): development and preliminary validation. J Sport Exercise Psy 1994 Jun;16(2):163-177. [doi: 10.1123/jsep.16.2.163]
52. Kennedy MD, Haykowsky MJ, Boliek CA, Esch BT, Scott JM, Warburton DE. Regional muscle oxygenation differences in vastus lateralis during different modes of incremental exercise. Dyn Med 2006 Jul 03;5:8 [FREE Full text] [doi: 10.1186/1476-5918-5-8] [Medline: 16817964]
53. Leahy S, Toomey C, McCreesh K, O'Neill C, Jakeman P. Ultrasound measurement of subcutaneous adipose tissue thickness accurately predicts total and segmental body fat of young adults. Ultrasound Med Biol 2012 Jan;38(1):28-34. [doi: 10.1016/j.ultrasmedbio.2011.10.011] [Medline: 22104525]
54. Kemps HM, Thijssen EJ, Schep G, Sleutjes BT, De Vries WR, Hoogeveen AR, et al. Evaluation of two methods for continuous cardiac output assessment during exercise in chronic heart failure patients. J Appl Physiol (1985) 2008 Dec;105(6):1822-1829. [doi: 10.1152/japplphysiol.90430.2008] [Medline: 18948448]
55. Charloux A, Lonsdorfer-Wolf E, Richard R, Lampert E, Oswald-Mammosser M, Mettauer B, et al. A new impedance cardiograph device for the non-invasive evaluation of cardiac output at rest and during exercise: comparison with the "direct" Fick method. Eur J Appl Physiol 2000 Jul;82(4):313-320. [doi: 10.1007/s004210000226] [Medline: 10958374]
56. Richard R, Lonsdorfer-Wolf E, Charloux A, Doutreleau S, Buchheit M, Oswald-Mammosser M, et al. Non-invasive cardiac output evaluation during a maximal progressive exercise test, using a new impedance cardiograph device. Eur J Appl Physiol 2001 Aug;85(3-4):202-207. [doi: 10.1007/s004210100458] [Medline: 11560071]
57. Tonelli A, Alnuaimat H, Li N, Carrie R, Mubarak KK. Value of impedance cardiography in patients studied for pulmonary hypertension. Lung 2011 Oct;189(5):369-375. [doi: 10.1007/s00408-011-9299-y] [Medline: 21604215]
58. Kounalakis SN, Koskolou MD, Geladas ND. Oxygen saturation in the triceps brachii muscle during an arm Wingate test: the role of training and power output. Res Sports Med 2009;17(3):171-181. [doi: 10.1080/15438620903120421] [Medline: 19731177]
59. Welsch MA, Allen JD, Geaghan JP. Stability and reproducibility of brachial artery flow-mediated dilation. Med Sci Sports Exerc 2002 Jun;34(6):960-965. [Medline: 12048322]

60. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, International Brachial Artery Reactivity Task Force. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002 Jan 16;39(2):257-265 [FREE Full text] [Medline: 11788217]
61. Robbins JL, Jones WS, Duscha BD, Allen JD, Kraus WE, Regensteiner JG, et al. Relationship between leg muscle capillary density and peak hyperemic blood flow with endurance capacity in peripheral artery disease. J Appl Physiol (1985) 2011 Jul;111(1):81-86 [FREE Full text] [doi: 10.1152/japplphysiol.00141.2011] [Medline: 21512146]
62. Hellige G, Ensink FB, Baller D, Prennschütz-Schützenau H, Sigmund-Duchanova H, Zipfel J. Measurement of arterial and venous reactivity by an advanced strain gauge plethysmograph. Angiology 1979 Aug;30(8):539-548. [doi: 10.1177/000331977903000804] [Medline: 464342]
63. Wohlfahrt P, Melenovsky V, Redfield MM, Olson TP, Lin G, Abdelmoneim SS, et al. Aortic waveform analysis to individualize treatment in heart failure. Circ Heart Fail 2017 Feb;10(2) [FREE Full text] [doi: 10.1161/CIRCHEARTFAILURE.116.003516] [Medline: 28159826]
64. Levinger I, Howlett KF, Peake J, Garnham A, Hare DL, Jerums G, et al. Akt, AS160, metabolic risk factors and aerobic fitness in middle-aged women. Exerc Immunol Rev 2010;16:98-104 [FREE Full text] [Medline: 20839494]
65. Levinger I, Levinger P, Trenerry MK, Feller JA, Bartlett JR, Bergman N, et al. Increased inflammatory cytokine expression in the vastus lateralis of patients with knee osteoarthritis. Arthritis Rheum 2011 May;63(5):1343-1348 [FREE Full text] [doi: 10.1002/art.30287] [Medline: 21538317]
66. Bergstrom J. Percutaneous needle biopsy of skeletal muscle in physiological and clinical research. Scand J Clin Lab Invest 1975 Nov;35(7):609-616. [Medline: 1108172]
67. Bailey SJ, Fulford J, Vanhatalo A, Winyard PG, Blackwell JR, DiMenna FJ, et al. Dietary nitrate supplementation enhances muscle contractile efficiency during knee-extensor exercise in humans. J Appl Physiol (1985) 2010 Jul;109(1):135-148. [doi: 10.1152/japplphysiol.00046.2010] [Medline: 20466802]
68. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds Jr LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991 Mar;83(3):778-786. [Medline: 1999029]

Abbreviations

CHF: chronic heart failure
CO: cardiac output
CPX: cardiopulmonary exercise test
FMD: flow-mediated dilation
HFpEF: heart failure preserved ejection fraction
HFrEF: heart failure reduced ejection fraction
MAP: mean arterial pressure
MLHFQ: Minnesota Living With Heart Failure Questionnaire
NIRS: near-infrared spectroscopy
NO: nitric oxide
PAQ: Physical Activity Questionnaire
PWA: pulse wave analysis
PWV: pulse wave velocity
SEES: Subjective Exercise Experience Scale
SNS: sympathetic nervous system
SV: stroke volume
TTE: time to exhaustion
VO2peak: peak oxygen consumption

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Protocol

Safer Prescribing and Care for the Elderly (SPACE): Protocol of a Cluster Randomized Controlled Trial in Primary Care

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Abstract

Background: High-risk prescribing, adverse drug events, and avoidable adverse drug event hospitalizations are common. The single greatest risk factor for high-risk prescribing and adverse drug events is the number of medications a person is taking. More people are living longer and taking more medications for multiple long-term conditions. Most on-going prescribing occurs in primary care. The most effective, cost-effective, and practical approach to safer prescribing in primary care is not yet known.

Objective: To test the effect of the Safer Prescribing And Care for the Elderly (SPACE) intervention on high-risk prescribing of nonsteroidal anti-inflammatory and antiplatelet medicines, and related adverse drug event hospitalizations.

Methods: This is a protocol of a cluster randomized controlled trial. The clusters will be primary care practices. Data collection and analysis will be at the level of patient.

Results: Recruitment started in 2018. Six-month data collection will be in 2018.

Conclusions: This study addresses an important translational gap, testing an intervention designed to prompt medicines review and support safer prescribing in routine primary care practice.

Trial Registration: Australian New Zealand Clinical Trials Registry: ACTRN12618000034235 http://www.ANZCTR.org.au/ACTRN12618000034235.aspx (Archived with Webcite at http://www.webcitation.org/6yj9RImDf)

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KEYWORDS

general practice; safety; prescriptions; multimorbidity; polypharmacy; adverse drug events

Introduction

Avoidable Adverse Drug Events

Adverse drug events (ADEs) and avoidable ADE hospital admissions are common, costing health systems billions of dollars every year [1-7]. Internationally, approximately 7% of hospital admissions result from drug-related problems, of which 59% are considered avoidable through safer prescribing [3,4,8]. Most drug-related admissions are caused by commonly prescribed drugs, notably nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelet medications, and anticoagulants, which together account for one-third of ADE admissions [3,4,9].

High-risk Prescribing

High-risk prescribing is prescribing that places patients at increased risk of ADEs. The single greatest predictor of ADEs and high-risk prescribing is the number of medications a person is taking [10]. With demographic ageing, there are increasing numbers of older people prescribed multiple medications for

multiple co-existing medical conditions [11]. In New Zealand, approximately 10% of people aged 65 years and older are taking ten or more regular medications, and high-risk prescribing is common, often involving NSAIDs [12-14]. The individual circumstances of a patient may justify high-risk prescribing, but to minimize harm it is necessary that medications are regularly reviewed and stopped or started as appropriate [15].

Most on-going medications are prescribed in primary care. Despite strong evidence to guide safe prescribing, a gap remains between existing evidence and current prescribing practice. Translating research evidence into practice is difficult. There are many barriers to regular medication review in everyday practice [16]. The large variation in prescribing between practices and regions in New Zealand suggests room for improvement [13,17,18].

Safer Prescribing

In New Zealand primary care, most quality improvement processes are delivered through Primary Health Organisations (PHOs), professional groupings of practices for administrative and quality improvement purposes [19]. The most effective, cost-effective, and practical approach to safer prescribing in everyday practice is not yet known [20,21]. There is evidence to suggest education programmes can improve prescribing but education alone is not enough to induce lasting change [13,22]. Complex interventions as part of ongoing quality improvement programs show the most promise, in particular interventions combining audit and feedback, education, incentive for participation, and patient engagement [20,23-26]. The Australian Veterans' Medicines Advice and Therapeutics Education Service (MATES) quality improvement program in primary care has shown promising results in the Australian Veterans population, especially when delivering a focused message targeting single medications and less so when delivering a combination of messages targeting general topics such as interactions and potentially inappropriate medications in older people with polypharmacy [24]. The MATES programme is based on sound theoretical underpinnings and delivers 4 interventions per year. The MATES intervention uses practice prescribing audits, patient-specific feedback, education to doctors, and a practice mail-out to selected at-risk patients to encourage their engagement.

The Safer Prescribing and Care for the Elderly (SPACE) Intervention

Adapted from the Australian Veterans' MATES programme, we developed the Safer Prescribing and Care for the Elderly (SPACE) intervention to prompt medication reviews and support safer prescribing in the New Zealand primary care context. We recently piloted the SPACE intervention in two New Zealand primary care practices in preparation for this proposed randomized trial, focusing on the topic of NSAIDs and antiplatelet prescribing. This topic was chosen because these drugs are commonly prescribed and are associated with serious ADEs including bleeding and renal impairment. The SPACE intervention was found to be feasible to implement using existing primary care structures and both acceptable and useful to patients, doctors, and the PHO clinical advisory pharmacists [27]. In the pilot study, we developed practice audit queries to identify patients with high-risk prescribing of NSAIDs and/or antiplatelet medications; integrated the SPACE intervention into practice management software; developed processes to collect, encrypt, and link study data; and derived information for calculating sample sizes for the randomized trial.

Objectives

We will assess whether the SPACE intervention can reduce the rate of high-risk prescribing of NSAIDs and/or antiplatelet medications and related ADE hospitalizations over 12 months using existing PHO infrastructure and systems in New Zealand primary care.

Trial Design

We will conduct a cluster randomized control trial. The clusters will be primary care practices. Data collection and analysis will be at the level of patient.

Methods

Setting

The study will be conducted in primary care practices in Auckland and Northland, New Zealand.

Eligibility Criteria

Primary care practices will be eligible to participate if:

1. The practice is based in the Auckland or Northland region of New Zealand and has not recently participated in a similar NSAID audit exercise or taken part in the pilot for the SPACE trial
2. The practice uses electronic practice management software compatible with our data collection systems
3. The practice has fewer than 15,000 enrolled patients
4. All physicians in the practice consent to participate

The study will target all physicians working in participating practices since patients can receive a prescription from any physician in a practice.

Patient inclusion criteria:

1. Patients of any age ("vulnerable patients") will be included in the study if, at baseline, they fulfil one or more of the following inclusion criteria as listed in Table 1 that puts them at increased risk of an ADE related to NSAIDs and/or antiplatelet medications.
2. Participants are "vulnerable patients" at baseline; that is, those patients at increased risk of gastrointestinal, renal or cardiac adverse events related to NSAIDs and/or antiplatelet medications (Table 1).

Table 1. Categories of vulnerable patients and high-risk prescribing of NSAIDs and antiplatelet medications [23]. ADE: adverse drug event.

Type of adverse drug event	Risk factor making patients vulnerable (at increased risk of ADE)	High-risk prescribing
Gastrointestinal	Prior peptic ulcer	In patient with prior peptic ulcer, NSAID or aspirin without gastro-protection
	75 years and older	In patient 75 years and older, NSAID without gastro-protection
	65 years and older prescribed aspirin	In patient 65 years and older taking aspirin, NSAID without gastro-protection
		In patient 65 years and older taking aspirin, clopidogrel without gastro-protection
	Prescribed oral anticoagulant	In patient taking an oral anticoagulant, NSAID without gastro-protection
		In patient taking an oral anticoagulant, aspirin or clopidogrel without gastro-protection
Renal	Prescribed both renin-angiotensin system blocker and diuretic	In patient taking both renin-angiotensin system blocker and diuretic, NSAID
	Chronic kidney disease (Estimated Glomerular Filtration Rate[eGFR] <60)	In patient with chronic kidney disease (eGFR <60), NSAID
Cardiac	Heart failure	In patient with history of heart failure, NSAID

All data collected on patients is anonymized prior to leaving the practice using a unique identifier (National Health Index number) to enable linking of clinical data over time and linking to hospitalization data.

Intervention

The SPACE intervention is designed to prompt medication reviews and support safer prescribing decisions in primary care practice. The intervention comprises a practice audit to identify for each doctor a list of their patients with high-risk prescribing for the chosen topic; an outreach visit from a clinical advisory pharmacist to physicians to provide education about the prescribing topic and to go through with each physician their list of patients identified as having high-risk prescribing; a tick-box for physicians to indicate the action they will take in response to the feedback for each patient ("review medications + patient mail-out," "review medications + no mail-out," or "no action"); and a mail-out from the practice to patients selected by physicians with information about their medications and a letter encouraging them to discuss their medications when they are at the practice next seeing their physician [27]. All prescribing decisions are made as usual by the doctor in discussion with the patient. The individual circumstances of the patient may justify high-risk prescribing and, after review, the prescribing may or may not be changed. The prescribing topic for the trial is the prescribing of NSAIDs and antiplatelet medications.

Control practices will deliver care as usual. If the SPACE intervention is shown to be effective, we aim to deliver the intervention to control practices after 12 months.

All practices and doctors will participate as usual in PHO quality improvement initiatives and medical education activities. See Figure 1 for the flow of practices through the study.

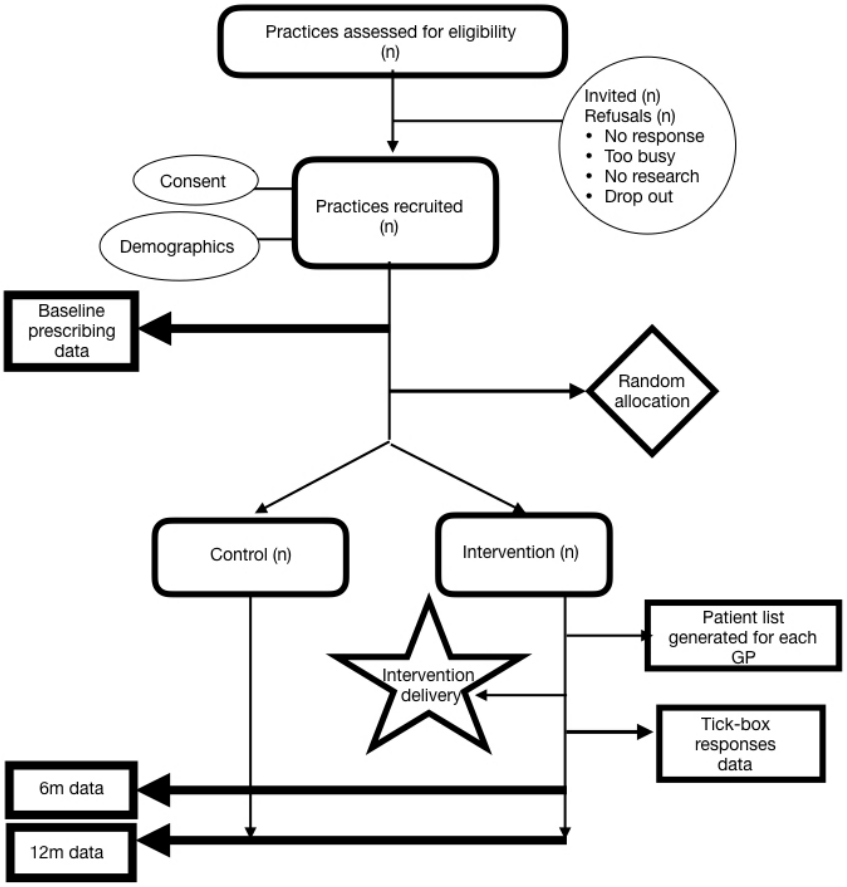
Outcome Measures

Assessment time-points will be baseline, 6 months, and 12 months. The outcomes of interest are the difference between intervention and control groups at 6 months controlling for baseline, and the difference between intervention and control groups at 12 months.

The primary outcome measure is:

The difference in proportion of the participants (those vulnerable at baseline) receiving high-risk prescribing of NSAID and/or antiplatelet medications between the control and intervention groups at 6 months. That is, the proportion of "vulnerable-at-baseline patients" (with gastro-intestinal, renal, or cardiac risk factors) receiving high-risk prescribing of NSAID and/or antiplatelet medications at 6 months according to the definitions listed in Table 1. Whether difference in proportion between the two groups is sustained at 12 months will also be examined. Participants will be considered to have high-risk prescribing at each time-point if they fulfil any of the high-risk prescribing criteria set out in Table 1 in the 14 weeks leading up to each time-point.

Figure 1. Flow of practices through the randomized control trial.



Secondary outcome measures include:

1. The difference in proportion of study participants at increased risk of gastrointestinal ADEs according to the definitions listed in Table 1 receiving gastrointestinal high-risk prescribing of NSAID and/or antiplatelet medications between the control and intervention groups at 6 months.
2. The difference in proportion of study participants at increased risk of renal ADEs according to the definitions listed in Table 1 receiving renal high-risk prescribing of NSAID medications between the control and intervention groups at 6 months.
3. The difference in proportion of study participants at increased risk of cardiac ADEs according to the definitions listed in Table 1 receiving cardiac high-risk prescribing of NSAID medications between the control and intervention groups at 6 months.
4. The difference in proportion of study participants (vulnerable patients), and those with high risk prescribing, admitted for related adverse drug events (gastrointestinal ulcer or bleeding, acute kidney injury, and heart failure) between the control and intervention groups during the 12 months after baseline for the intervention. Hospitalization data will be linked to primary care patient data by encrypted National Health Index.
5. The difference in proportion of vulnerable patients in the practice overall receiving high-risk prescribing of NSAIDs and/or antiplatelet medications between the control and intervention groups at 6 months. This will include newcomers to the practice and practice patients who were not vulnerable at baseline but were at 6 months and/or 12 months.

Whether difference in proportion between the 2 groups is sustained at 12 months will also be examined for secondary outcomes 1, 2, 3, and 5 months.

These outcomes have been used in similar trials previously [23]. Data will also be collected to enable a subsequent cost-effectiveness evaluation of the intervention from a societal and health funder perspective. The cost-effectiveness of the intervention will be measured as the cost per reduction in high-risk prescribing and cost per reduction in hospitalizations from the health funder (District Health Board) perspective. The data collected will include the cost of delivering the intervention (including pharmacist and doctor time for the feedback outreach session, travel time and costs for the outreach visit, audit time and cost); cost of medications; cost of hospitalizations.

Sample Size

The sample size calculation for this study is based on previous trials demonstrating a clinically relevant 25-45% relative risk reduction in the proportion of high-risk prescribing, [23,25] one trial of which also demonstrated how such reduction (3.7% to 2.2%) in high-risk prescribing can translate to significant reductions in hospitalizations due to bleeding complications [23]. Based on the local pilot data, we estimated an average of 200 “vulnerable patients” per practice and an 8% high-risk prescribing rate [28]. We estimated an intracluster correlation

coefficient of 4.68 x 10^{-7} for the primary outcome based on a cluster randomized trial examining similar outcome of NSAIDs prescribed to patients with a history of peptic ulcer and not prescribed gastro-protection [25]. Assuming approximately 12% of patients would be lost to follow-up over the 12 month study period, data from 8000 patients from 40 practices (20 practices in each group) with an average of 200 vulnerable patients per practice would be required to detect a statistically significant difference of 6% in the intervention group and 8% in the control group of high-risk prescribing at 12 months (*P*=.90, alpha=.05).

Recruitment

Practices will be purposively sampled and recruited, aiming to include both medium sized (3000-7999 enrolled patients) and smaller practices (0-2999 enrolled patients) in the Auckland and Northland regions. Practices and physicians will be invited by a colleague using a comprehensive list of practices. Consent for participation will be at the practice and physician level. Written informed consent will be obtained from all participating physicians. Participants, 'vulnerable patients', will be identified using a standard query applied to the practice enrolled population. Consent will not be sought from individual patients because outcomes data are collected in routine patient care and will be anonymised prior to extraction for analysis and linking.

Assignment of Interventions: Randomization

Practices will be randomized 1:1 to intervention or control. Randomization will be stratified by practice location (Auckland vs Northland) and practice size (medium [3000-7999 enrolled patients] and smaller practices [0-2999 enrolled patients]). Block randomization will be carried out using randomly varying block sizes of 2, 4, and 6. Random sequence generation and allocation of randomization will be undertaken by a statistician not involved in recruitment or baseline data extraction.

Analyses

Analyses will be performed according to the intention-to-treat principle, with the use of mixed-effect models to account for clustering in the data. The primary and secondary outcomes will be analyzed using generalized linear mixed effect model, GLIMMIX, with the individual as the unit of analysis and the practice included as the random effect to control for the effects of clustering. GLIMMIX with Group x Time interaction will be used to assess the overall difference between intervention and control. The model will adjust for the stratification factors including practice location (Northland or Auckland) and practice size. Baseline covariates including (age, sex, and baseline number of long-term medications) will be adjusted if appropriate.

Ethics

Study approved by the University of Auckland Human Participants Ethics Committee: Ref 020092, expires 9 Oct 2020.

Results

Recruitment will start in 2018. The SPACE trial will run for 2 years from recruitment to analyses and dissemination.

Discussion

Most ongoing prescribing occurs in primary care. The prevalence of high-risk prescribing and avoidable ADE admissions, and the unnecessary cost imposed on an already stretched health system, justify greater efforts to improve the safety of prescribing in primary care. The ageing population, with more people living longer and taking more medications for more chronic conditions, means the problems of high-risk polypharmacy and avoidable ADE hospital admissions will continue to increase unless we can improve the safety of prescribing in primary care. The most effective and cost-effective intervention to support safer prescribing in everyday primary care practice is not yet known.

Intervention Design

The SPACE intervention is based on sound theoretical underpinnings, is acceptable and useful in the New Zealand primary care context, and identifies and reaches patients with high-risk prescribing who are at increased risk of ADEs. The intervention builds on existing primary care infrastructure and uses existing primary care staff to deliver a safety improvement intervention. The intervention combines audit and feedback with mail-out to motivate patient engagement. It is amenable to repeat use, and could be used in an on-going quality improvement program to target different high-risk prescribing topics.

Practical Applications From Study Results

If shown to be effective and cost-effective, the SPACE intervention could be rolled out nationally and used regularly by PHOs to support safer prescribing in practices and minimize avoidable ADE hospital admissions in the short-to-medium term. Since the SPACE intervention is designed to support behavior change, it could be applied to other evidence-based topics, including other prescribing topics and test ordering and monitoring.

Study Design

Interventions that have been shown to improve practice have been published [23,25]. However, most previous trials of primary care interventions in this area have involved time-series or noncontrolled trials [20,22,24]. The SPACE trial uses a cluster randomized controlled trial design to provide robust evidence to assess whether such an intervention can change prescribing and improve clinical outcomes.

Outcome Measures

Since the SPACE intervention is designed to prompt medication reviews and support safer prescribing, the primary outcome measure is designed to reflect a change in prescribing behavior (a reduction in the rate of high-risk prescribing in patients vulnerable at baseline). Since the ultimate aim is to change prescribing behavior overall and improve patient outcomes, we will also measure the rate of high-risk prescribing overall and related ADE hospital admissions.

Anticipated Challenges

There is a risk of contamination between intervention and control practices and between intervention practices and those waiting for the intervention; doctors might change their prescribing behavior if they are alerted to the study prescribing topic. However, rolling delivery of the intervention is the only practical and feasible way to progress this study, given the educational outreach visit component of the intervention and the limitations of our study team. We are also limited to using small to medium sized practices (fewer than 8000 enrolled patients), since all doctors in participating practices must receive one-on-one feedback from the clinical advisory pharmacist at an outreach visit.

Conclusions

This study addresses an important translational gap, testing an economically sustainable intervention designed to support safer prescribing in routine practice. The new knowledge generated will help to address the most important threat to patient safety in primary care: high-risk prescribing and adverse drug events.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Reviewers' feedback on funding application for study.

[PDF File (Adobe PDF File), 246KB - resprot_v7i4e109_app1.pdf]

References

1. Taché SV, Sönnichsen A, Ashcroft D. Prevalence of adverse drug events in ambulatory care: a systematic review. Ann Pharmacother 2011 Jul;45(7-8):977-989. [doi: 10.1345/aph.1P627] [Medline: 21693697]
2. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med 2011 Nov 24;365(21):2002-2012. [doi: 10.1056/NEJMsa1103053] [Medline: 22111719]
3. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004 Jul 03;329(7456):15-19 [FREE Full text] [doi: 10.1136/bmj.329.7456.15] [Medline: 15231615]
4. Howard RL, Avery AJ, Slavenburg S, Royal S, Pipe G, Lucassen P, et al. Which drugs cause preventable admissions to hospital? A systematic review. Br J Clin Pharmacol 2007 Feb;63(2):136-147 [FREE Full text] [doi: 10.1111/j.1365-2125.2006.02698.x] [Medline: 16803468]
5. Meier F, Maas R, Sonst A, Patapovas A, Müller F, Plank-Kiegele B, et al. Adverse drug events in patients admitted to an emergency department: an analysis of direct costs. Pharmacoepidemiol Drug Saf 2015 Feb;24(2):176-186. [doi: 10.1002/pds.3663] [Medline: 24934134]
6. Guthrie B, McCowan C, Davey P, Simpson C, Dreischulte T, Barnett K. High risk prescribing in primary care patients particularly vulnerable to adverse drug events: cross sectional population database analysis in Scottish general practice. BMJ 2011 Jun 21;342(jun21 1):d3514-d3514. [doi: 10.1136/bmj.d3514]
7. Gyllensten H, Rehnberg C, Jönsson AK, Petzold M, Carlsten A, Andersson SK. Cost of illness of patient-reported adverse drug events: a population-based cross-sectional survey. BMJ Open 2013 Jun 20;3(6):a [FREE Full text] [doi: 10.1136/bmjopen-2013-002574] [Medline: 23794552]
8. Thomsen LA, Winterstein AG, Søndergaard B, Haugbølle LS, Melander A. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. Ann Pharmacother 2007 Sep;41(9):1411-1426. [doi: 10.1345/aph.1H658] [Medline: 17666582]
9. Ministry of Health. 2016. Pharmaceutical collection URL: https://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/pharmaceutical-collection [accessed 2018-04-16] [WebCite Cache ID 6yjRWJEXb]
10. Fried T, O'Leary J, Towle V, Goldstein M, Trentalange M, Martin D. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J Am Geriatr Soc 2014 Dec;62(12):2261-2272 [FREE Full text] [doi: 10.1111/jgs.13153] [Medline: 25516023]
11. Charlesworth C, Smit E, Lee D, Alramadhan F, Odden M. Polypharmacy Among Adults Aged 65 Years and Older in the United States: 1988-2010. J Gerontol A Biol Sci Med Sci 2015 Aug;70(8):989-995 [FREE Full text] [doi: 10.1093/gerona/glv013] [Medline: 25733718]
12. Nishtala P, Salahudeen M. Temporal Trends in Polypharmacy and Hyperpolypharmacy in Older New Zealanders over a 9-Year Period: 2005–2013. Gerontology 2015;61(3):195-202. [doi: 10.1159/000368191] [Medline: 25428287]

13. Love T, Ehrenberg N. Variation and improving services: case studies and key questions. Wellington: Health Quality and Safety Commission; 2014. URL: http://www.hqsc.govt.nz/assets/Health-Quality-Evaluation/PR/Variation-case-studies-and-key-questions-May-2014.pdf [accessed 2018-04-16] [WebCite Cache ID 6yjRJgCS3]
14. Narayan S, Nishtala P. Prevalence of potentially inappropriate medicine use in older New Zealanders: a population-level study using the updated 2012 Beers criteria. J Eval Clin Pract 2015 Aug;21(4):633-641. [doi: 10.1111/jep.12355] [Medline: 25940302]
15. Scott I, Hilmer S, Reeve E, Potter K, Le CD, Rigby D, et al. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med 2015 May;175(5):827-834. [doi: 10.1001/jamainternmed.2015.0324] [Medline: 25798731]
16. Wallis K, Andrews A, Henderson M. Swimming Against the Tide: Primary Care Physicians' Views on Deprescribing in Everyday Practice. Ann Fam Med 2017 Jul;15(4):341-346 [FREE Full text] [doi: 10.1370/afm.2094] [Medline: 28694270]
17. Health Quality & Safety Commission New Zealand. 2015. Atlas of healthcare variation: Polypharmacy in older people URL: https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/polypharmacy/ [accessed 2018-04-16] [WebCite Cache ID 6yjR9svcl]
18. Tomlin A, Gillies T, Tilyard M, Dovey S. Variation in the pharmaceutical costs of New Zealand general practices: a national database linkage study. J Public Health (Oxf) 2016 Mar;38(1):138-146. [doi: 10.1093/pubmed/fdu116] [Medline: 25599688]
19. Ministry of Health. NZ health system: Primary Health Organisations 2017 URL: https://www.health.govt.nz/new-zealand-health-system/key-health-sector-organisations-and-people/primary-health-organisations [accessed 2018-04-16] [WebCite Cache ID 6yjQxrd9w]
20. Patterson S, Cadogan C, Kerse N, Cardwell C, Bradley M, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev 2014 Oct 07;10(10):CD008165. [doi: 10.1002/14651858.CD008165.pub3] [Medline: 25288041]
21. Duerden M, Avery T, Payne R. Polypharmacy and medicines optimisation: making it safe and sound. London, UK: King's Fund; 2013. URL: https://www.kingsfund.org.uk/sites/default/files/field/field_publication_file/polypharmacy-and-medicines-optimisation-kingsfund-nov13.pdf [accessed 2018-04-16] [WebCite Cache ID 6yjRlEmkN]
22. Richards D, Toop L, Graham P. Do clinical practice education groups result in sustained change in GP prescribing? Family Practice 2003 Apr 01;20(2):199-206. [doi: 10.1093/fampra/20.2.199]
23. Dreischulte T, Donnan P, Grant A, Hapca A, McCowan C, Guthrie B. Safer Prescribing--A Trial of Education, Informatics, and Financial Incentives. N Engl J Med 2016 Mar 17;374(11):1053-1064. [doi: 10.1056/NEJMsa1508955] [Medline: 26981935]
24. Roughead EE, Kalisch ELM, Ramsay EN, Pratt NL, Barratt JD, LeBlanc VT, et al. Bridging evidence-practice gaps: improving use of medicines in elderly Australian veterans. BMC Health Serv Res 2013 Dec 12;13:514 [FREE Full text] [doi: 10.1186/1472-6963-13-514] [Medline: 24330781]
25. Avery A, Rodgers S, Cantrill J, Armstrong S, Cresswell K, Eden M, et al. A pharmacist-led information technology intervention for medication errors (PINCER): a multicentre, cluster randomised, controlled trial and cost-effectiveness analysis. The Lancet 2012 Apr;379(9823):1310-1319. [doi: 10.1016/S0140-6736(11)61817-5]
26. Mugunthan K, McGuire T, Glasziou P. Minimal interventions to decrease long-term use of benzodiazepines in primary care: a systematic review and meta-analysis. Br J Gen Pract 2011 Sep;61(590):e573-e578 [FREE Full text] [doi: 10.3399/bjgp11X593857] [Medline: 22152740]
27. Wallis K, Tuckey R. Safer Prescribing and Care for the Elderly (SPACE): feasibility of audit and feedback plus practice mail-out to patients with high-risk prescribing. J Prim Health Care 2017 Jun;9(2):145-152. [doi: 10.1071/HC17018] [Medline: 29530226]
28. Wallis K, Elley C, Moyes S, Kerse N. Safer Prescribing And Care for the Elderly (SPACE): Pilot Study in General Practice. British Journal of General Practice Open 2018 (forthcoming).

Abbreviations

ADE: adverse drug event
eGFR: estimated glomerular filtration rate
GLIMMIX: generalized linear mixed effect model
MATES: Australian Veterans' Medicines Advice and Therapeutics Education Service
NSAID: nonsteroidal anti-inflammatory drug
PHO: Primary Health Organisation
SPACE: Safer Prescribing and Care for the Elderly

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Protocol

Combined Topical Growth Factor and Protease Inhibitor in Chronic Wound Healing: Protocol for a Randomized Controlled Proof-of-Concept Study

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Abstract

Background: Leg ulcers due to venous disease are chronic wounds that can take 6 or more months to heal. Growth factors have been used to try and improve this healing; however, many such studies have failed, and that is thought to be due to enzymes in the wound that degrade the growth factors and prevent them from working.

Objective: This is a proof-of-concept study that will evaluate the treatment of chronic leg ulcers with topically applied growth factors that are combined with a therapy to prevent their inactivation in the wound. This combined therapy has the potential to speed up the healing of these wounds and thereby improve the quality of life of patients and reduce the costs to the health system.

Methods: This will be a double-blind, placebo-controlled, randomized controlled proof-of-concept study comparing growth factor with protease inhibitor wound dressings to growth factors with standard wound dressings.

Results: The project was funded by the Canadian Institutes for Health Research and enrollment is expected to be initiated in 2018. It is expected that results will be available in 2021.

Conclusions: It is expected that the results of this trial will inform as to whether modifying the wound environment through the use of protease inhibitors increases the effectiveness of topically applied growth factors in the healing of chronic wounds.

Trial Registration: ClinicalTrials.gov NCT02845466; https://clinicaltrials.gov/ct2/show/NCT02845466 (Archived by WebCite at http://www.webcitation.org/6yOPhSBUA)

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KEYWORDS

leg ulcers; growth factors; protease inhibitors

Introduction

Chronic Wounds

Chronic wounds are prevalent across the Canadian health care continuum [1] and have a significant financial and social burden on the health care systems, patients, and their families [1-4]. Chronic wounds are defined as wounds that are poorly healing and persisting for 3 months or more [1]. Clinical subtypes of chronic wounds include the following: (1) venous leg ulcers (VLUs), (2) arterial ulcers, (3) diabetic foot ulcers (DFUs), and (4) pressure ulcers. VLUs and DFUs are the most prevalent chronic wounds and have high rates of recurrence ranging from 16% at 1 year to 60% at 5 years for VLU [5,6] and greater than 50% after 3 years for DFU [2]. The cost attributed to chronic wound management in Canada is considerable [7] with more than Can $1 million per year estimated for each Canadian hospital to treat just pressure ulcers and surgical wound infections [8]. The total annual cost associated with DFU-related care was $547 million CAD, or $21,371 CAD annual cost per prevalent case in 2011 [3]. It is imperative that new cost-effective treatments that significantly increase healing rates

and reduce amputation and hospital admission rates are required. Cost-effective wound management is a key priority for Canadian health care organizations [9-11].

Venous Leg Ulcers

Lower limb ulcers occur in 1% to 2% of adults, with 70% of leg ulcers being of venous etiology [12]. The point prevalence in the population over 70 years of age is approximately 1% [13]. The majority of VLUs are long-standing; 60% of ulcer patients in the community experience ulcers that remain unhealed for more than 26 weeks, and 23% for more than 2 years [14]. In their Canadian Bandaging Trial, Harrison and colleagues identified that most patients were over 65 years in age and over two-thirds had experienced leg ulcers for many months. Half of the affected population had a leg ulcer history spanning from 5 to 10 years and one-third exceeding 10 years [15]. Some ulcers require skin grafting to achieve healing. The delayed healing of leg ulcers and the high costs associated with outpatient, inpatient, and community care represent a significant economic burden to the health care system, estimated to be in the order of 1% of total health care budget in Western societies [16]. Current clinical treatment guidelines for venous ulcers involve the use of compression bandaging to counter the effects of venous hypertension and dressings to promote an optimum wound-healing environment. Despite treatment with compression, healing times are still long, with only 45% of ulcers healing in 13 weeks [17]. There is a need for cost-effective therapies that improve these ulcer-healing rates.

Diabetic Foot Ulcers

Diabetes is one of the most burdensome chronic diseases in Canada with an estimated 7% of the population living with diabetes [17]. Over their lifetime, 15% to 25% of people with diabetes will develop a DFU [18], and 12% of those patients will require lower extremity amputation due to the progression of their chronic DFU [19]. The current standard for treating DFUs is pressure off-loading in addition to treatments for wound infection, maintaining adequate blood supply, local wound care, and control of the diabetes. There is a need for cost-effective therapies that improve ulcer-healing rates and prevent amputations.

Impaired Healing in Chronic Wounds

Wound healing is a complex process that has 4 phases [20]. The initial hemostatic phase occurs immediately after the injury, and during this phase, growth factors released from platelets that bind to the wound site initiate the wound-healing process. Growth factors are soluble signaling proteins that instruct cells during cell development and influence the process of wound healing [21]. The second phase is the inflammatory phase during which white cells migrate to the wound and release additional growth factors as well as remove foreign material. The third phase is the proliferative phase, which involves formation of granulation tissue, wound matrix formation, and epithelialization. The final phase is remodeling, which is an ongoing phase during which excessive material is removed and collagen synthesis and breakdown occur as the wound is remodeled. The last 3 phases overlap over time.

Chronic wounds are typically characterized by an ongoing and excessive inflammatory phase while proliferative phase is trying to occur at the same time [22]. This profound inflammatory phase is thought to play a key role in delaying healing. During this phase, there is evidence of elevated levels of inflammatory cytokines [23-25], elevated levels of proteases including matrix metalloproteases (MMPs) and elastase [22,26-28], impaired function of cellular components including fibroblasts and epithelial cells [29-31], and reduced levels of growth factors [22,32,33]. Contaminating bacteria also affect the inflammatory phase [34-36]. In chronic wounds, impaired healing is considered to be caused by a number of factors that are a result of this prolonged inflammatory phase: (1) degradation of extracellular matrix (ECM) proteins that form the new healed tissue, (2) degradation of healing regulators including peptide growth factors and endogenous protease inhibitors [22,27,28,37], and (3) impaired responses of the cellular components within the wounds [30,31,38].

Increased Protease Activity in Wounds and Wound Fluid

The levels of a number of proteases and their inhibitors have been measured in different chronic wound types. These have assessed levels of proteases within chronic wound fluid (CWF), have compared levels between acute and chronic wounds, and have compared levels between nonhealing and healing chronic wounds. Results indicate that CWF has consistently elevated levels of MMPs (MMP-1,-2,-8,-9,-13) and neutrophil elastase compared with acute wound fluid [22,26,28]. Studies have demonstrated a reduction in MMPs during healing phases of VLUs and DFUs and reduced levels of tissue inhibitors of metalloproteinases (TIMPs) in nonhealing or reduced MMP/TIMP ratios during healing [23,37]. Although the levels vary between individuals, these studies indicate an association between lower levels of MMPs and healing of VLUs and DFUs.

In addition, the elevated levels of proteases within CWF are inhibitory to the healing process within chronic wounds by degrading ECM proteins and regulators of the healing process. Therefore, reduction of protease levels in CWF has the potential to improve the healing process in these wounds.

Reduction in Protease Activity

A number of potential agents have been identified to reduce or modulate MMP activities and to control the proteolytic environment in the chronic wound. These include the antibiotic doxycycline [39], the wound dressing Promogran (Systagenix) [40], and nanocrystalline silver [41]. Promogran is a protease-modulating matrix wound dressing composed of 55% collagen and 44% oxidized regenerated cellulose in an absorbent open-pored, sterile, freeze-dried matrix. Once the matrix comes in contact with the wound exudate, it absorbs the fluid and forms a soft gel. The gel physically binds to and inactivates the damaging proteases (MMPs) and elastase and also binds to growth factors, protecting them and preventing them from being degraded [42]. The growth factors are then released back into the wound in an active form [40]. One small clinical study has shown a decrease in protease activity in CWF samples taken from patients with chronic venous ulcers treated with Promogran [43]. This study demonstrated a significant reduction of elastase

and MMP-9 activity after 5 days of treatment with Promogran. Accelerated healing in both VLUs and DFUs has been observed in clinical trials with Promogran alone [44-46].

A small observational study of 15 patients indicated that Promogran, in combination with Regranex, had a stimulating effect on DFUs, with rapid wound area reduction [47]. Moreover, a small randomized prospective clinical study showed that the combination of Promogran and autologous growth factors from platelets was significantly better than the Promogran or autologous growth factors from platelets alone in DFUs [48]. Larger analyses do not show a significant benefit from applying topical autologous growth factors from platelets to wounds [49]. It is possible that the protease inhibition enabled the effect that was observed in this study.

Enhancing Delayed Healing

Wound repair is controlled by a number of growth factors that include platelet-derived growth factor (PDGF), keratinocyte growth factor, transforming growth factor β, and a number of other growth factors. The increasing understanding of the role of growth factors, including PDGF and transforming growth factor-β, in wound repair has resulted in their clinical application for the treatment of chronic wounds. Over the past decade, there have been an increasing number of randomized controlled trials using PDGF in the format of becaplermin gel (Regranex). Becaplermin (recombinant human PDGF-BB, rhPDGF-BB) is a homodimer produced by recombinant DNA (deoxyribonucleic acid) technology utilizing the insertion of the gene for the B chain of PDGF into the yeast *Saccharomyces cerevisiae*. The biological activity of rhPDGF-BB is similar to the naturally occurring PDGF and includes formation of granulation tissue at the wound site and stimulation of the wound-healing processes [50].

There have been a number of trials for the treatment of nonhealing DFUs demonstrating statistically significant effects in phase 2, phase 3, and phase 4 clinical trials [51,52]. These trials have demonstrated the efficacy of rhPDGF-BB gel at 30 g/g and 100 g/g when used in conjunction with optimal wound care. Patients treated with rhPDGF-BB gel had a significant increase in complete healing compared with patients given placebo gel (50% vs 36% at dose of 100 g/g) and a decrease in the time to complete healing by 30% (14 weeks vs 20 weeks) [53]. It was concluded that rhPDGF-BB gel used in conjunction with optimal wound care is effective and well tolerated in patients with full-thickness DFUs. A systematic review and meta-analysis has concluded that rhPDGF-BB gel improves the healing of DFUs [54].

In other types of chronic wounds such as pressure ulcers, studies using rhPDGF-BB gel showed promising results [55,56]. In patients with chronic venous ulcers, 2 small randomized, placebo-controlled trials have evaluated the application of rhPDGF-BB gel (100 mg/g). In both studies, a greater percentage of patients treated with rhPDGF-BB gel achieved complete healing compared with patients in the placebo-treated group, but this was not statistically significant [57].

There is an ongoing safety review and warning from the US Food and Drug Administration regarding the amount of rhPDGF-BB gel that can be used. In a retrospective study of patients treated with rhPDGF-BB gel, the incidence rate for all cancers was 10.2 per 1000 compared with 9.2 per 1000 in matched controls [58]. An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of rhPDGF-gel in a postmarketing retrospective cohort study. A warning is now included in the product label, indicating the increased rate of mortality secondary to malignancy in patients who use 3 or more tubes of rhPDGF-BB gel [58].

Double-blind, placebo-controlled trials of other growth factors in venous ulcers—epidermal growth factor (EGF) [59], human growth factor [60], granulocyte-macrophage colony-stimulating factor (GMCSF) [61], and transforming growth factor-beta2) [62]—have not demonstrated significant improvements in ulcer healing.

Lack of Response of Wounds to Topical Growth Factors

This lack of response may be due to a number of factors including the following: degraded ECM; inefficient presentation of growth factors to the cell surface receptors in ways that do not reflect normal in vivo cell surface receptor activation; use of single growth factors instead of more physiologic combinations of growth factors; delivery of free growth factors instead of growth factors bound to or associated with appropriate ECM proteins; and the rapid loss of growth factors from the wound site, possibly due to diffusion or degradation. There is some evidence of mild to complete degradation in venous ulcer wound fluid of proteins such as vitronectin [63] and EGF [64]; therefore, the lack of response to individual topical growth factors for VLUs may be due to the breakdown of the growth factors by proteases in the chronic wound environment [65]. The lack of response of VLU to topical growth factors may be reversed by reducing the protease activity in CWF, and it is postulated that the response of DFU to topical growth factors will be enhanced by reducing protease activity.

Point-of-Care Testing for Protease Level

A novel point-of-care testing tool, WOUNDCHEK Protease Status (WOUNDCHEK Laboratories), has been developed to determine whether wounds have an increased total protease activity. This test indicates that the total protease activity is either elevated or not elevated based on a predetermined level. It does not give a quantitative measure of total or individual protease levels. If the predetermined levels are meaningful, the test may help to guide the usage of topical agents including growth factors and protease inhibitors. There are 2 registered, ongoing, and unpublished noncomparative studies of the WOUNDCHEK Protease Status test that started recruiting in March 2012, with estimated completions in March 2013 [66], although the results are not as yet available. The studies are designed to enter 250 patients—one study for VLU and another for DFU. Each study aims to determine whether wounds with elevated total protease levels treated with protease modulating therapies have improved clinical healing trajectories at 4 weeks, which are indicative of healing outcomes at 12 weeks. There is a need for randomized controlled trials to determine whether the use of protease inhibitors guided by WOUNDCHEK Protease Status test is accurate and sensitive as compared with

using a laboratory protease level assay. If WOUNDCHEK Protease Status test demonstrates clinical utility, it could be used in routine real-time wound management practice.

Recent work in the principal investigator's laboratory has identified a potential biomarker that with a single test can determine the state of healing of a wound. In this study, GMCSF levels in CWF were elevated in nonhealing compared with healing wounds with apparent separation between the 2 groups. Overall, 90% of nonhealing wounds had a level above an observed threshold. This biomarker test, in combination with a point-of-care protease test such as WOUNDCHEK Protease Status, would provide tools for the clinician to make informed decisions on the use of topical protease inhibitors and growth factors in real time. This would represent a major advance in current wound management and be a completely novel paradigm of therapy for VLU and DFU.

Novel Approach to Improving Healing

The novel concept of this study is to translate the different elements of research on topical growth factors, protease inhibitors, and point-of-care testing in VLU and DFU into a paradigm of treatment that combines topical growth factors and protease inhibition. This may enable topical growth factors to be effective where they have not been previously in VLU and may enhance the benefit that has been shown in DFU. This model is based on modifying CWF to have more of the characteristics of acute wound fluid. A proof-of-concept study is needed to evaluate whether the use of topical protease inhibitors in both VLUs and DFUs inhibits protease activity and protects topically applied growth factors from degradation and whether this can be monitored by existing or future potential point-of-care tests.

Hypothesis

A protease inhibitor in combination with PDGF will reduce protease levels and prevent growth factor degradation in chronic VLUs and DFUs as compared with a placebo.

Primary Aim

The primary aim of this study was to determine whether the topical application of a protease inhibitor in combination with a topical growth factor prevents the degradation of applied growth factors in chronic VLUs and DFUs.

Secondary Aims

The secondary aims were as follows:

1. To determine whether the topical application of a protease inhibitor in combination with a topical growth factor reduces protease levels in chronic VLUs and DFUs
2. To determine whether the topical application of a protease inhibitor increases the levels of endogenous growth factors in chronic VLUs and DFUs
3. To determine whether there is an increase in healing rates at 4 weeks for both chronic VLUs and chronic DFUs treated with a protease inhibitor dressing in combination with topical PDGF as compared with a placebo
4. To determine the validity of the WOUNDCHEK Protease Status point-of-care test using the gold standard wound fluid assay of total protease
5. To determine whether the changes in protease and growth factor levels are associated with changes in the potential biomarker of wound healing, GMCSF
6. To pilot a cost diary for a possible subsequent phase 3 randomized controlled trial whereby cost-effectiveness will be evaluated

Methods

Trial Design

This is a proof-of-concept study that is a double-blind, randomized controlled trial. This trial has received provisional approval from the Hamilton Integrated Research Ethics Board, project number 2067.

Planned Interventions

Participants will be randomized to receive a protease inhibitor or a placebo for 4 weeks of the study, in combination with a topical growth factor. All participants will receive just the topical growth factor for 2 weeks to obtain baseline data on growth factor and protease levels in the wound fluid.

The interventions patients will receive are as follows:

1. All participants will have Regranex gel (Smith & Nephew) containing a recombinant human PDGF for topical administration, applied to their leg or foot ulcers on a weekly basis for 6 weeks. Regranex is a nonsterile, sodium carboxymethylcellulose-based topical gel. Each gram of Regranex gel contains 100 g of rhPDGF-BB. This is applied by measuring a length of gel from a 15 g tube and is applied at a rate of 0.25 cm length of gel per cm^2 of ulcer area. A maximum of 2 tubes will be used for each patient, and each patient will have his or her own treatment tubes to ensure that the limit of 2 tubes is not exceeded.
2. Participants randomized to receive the protease inhibitor will receive Promogran (Johnson & Johnson) cut to the size of the ulcer and applied over the rhPDGF-BB.
3. Participants in the placebo arm will receive Aquacel (ConvaTec) dressing applied in a similar manner to the Promogran. This dressing is very similar in appearance to Promogran and has no active protease inhibition function.
4. VLU participants will have an absorbent pad and a 4-layer compression bandage system (Profore, Smith & Nephew) applied over the dressings.
5. Diabetic foot ulcer participants will have an absorbent pad fixed with tape applied over the dressings.

Randomization Method

Randomization will occur after the first week in which the participant's compliance with optimal standard therapy is assessed. If the participant is not compliant at this point, he or she will not be randomized into the study. The research coordinator will randomly assign eligible participants using a computer-generated randomization tool. Following eligibility screening by the research coordinator, the system will generate a unique number. The research coordinator then telephones the treatment nursing staff and reports the number. In turn, treatment research nurses refer to a manual of unique numbers generated by an independent biostatistician before study activation to

determine the study intervention allocated to the randomized patient. The randomization schedule will be stratified by wound type (VLU or DFU) in variable blocks of 4 and 6. Randomized patients will receive all treatments during the study period according to the intervention they were allocated. The patients, study investigators, research coordinator, laboratory technologists, and assessing research nurses will be blinded to the treatment allocation. Only the treating team members are not blinded.

Protecting Against Bias

The researchers assessing the protease, growth factor, and biomarker levels in the wound fluid will be blinded to the treatment group, as will the researcher who performs the measurements on the wounds. A dressing similar in appearance to Promogran will be used in the control group so that the participants will also be blinded.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows:

- Men and women aged ≥18 years
- Ulcer size 1-64 cm^2
- Ulcer extends through both the epidermis and dermis, with no exposed tendon or bone
- Ulcer duration >3 months and <12 months
- Ulcer located between and including the knee and ankle
- For VLUs—venous refilling time <25 s on photoplethysmography or abnormal venous insufficiency duplex scan
- For DFUs—confirmed type 1 or type 2 diabetes mellitus with a hemoglobin A1C <12%
- Wounds that have not been treated with Promogran in the previous 4 weeks
- Patients able to give informed consent

Exclusion criteria were as follows:

- Ankle-brachial index <0.8
- Ulcer with local or systemic signs of infection
- Patients who have been previously treated with rhPDGF-BB gel
- Patients receiving corticosteroids or immune suppressants
- History of autoimmune disease
- Uncontrolled diabetes (baseline hemoglobin A1C >12%)
- Severe rheumatoid arthritis
- Uncontrolled congestive heart failure
- Malnutrition (albumin <2.5 g/dL)
- Unable to adhere to the protocol
- Known sensitivities to the wound dressings used in the trial
- History of any previous malignancy
- Pregnant or lactating woman

Treatment Period

Participants will be in the study for a total of 7 weeks. During the first week, participants will not receive the study treatment. During this week, the participants with VLUs will have a standardized bandaging regimen applied and the DFU participants will have their pressure off-loading optimized. Once they have demonstrated tolerance and compliance for wearing these bandaging, they will continue for 6 weeks of study treatment.

Frequency and Duration of Follow-Up

Patients will be followed up 3 times in a week by a research clinical nurse for the treatment and by a blinded research nurse for outcome measurements (Table 1). The first visit could take up to 1.5 hours as wound fluid collection can be slow. The second visit would be scheduled within a 24-hour period and could take up to 1.5 hours for wound fluid collection. This visit would include the application of the protease inhibitor but not the growth factor. The third visit would require 45 min and it is not measurement visit. Table 1 contains the treatments and measurements at each visit for the each of the treatment weeks. There will be one final visit at the end of the last week of treatment.

At the first follow-up visit each week, the following will be performed:

1. The wound dressing will be taken down and the wound cleansed.
2. The surface area of the wound will be traced and the area will be measured using the Visitrak device (Smith & Nephew).
3. A photograph of the wound will be taken using a standardized protocol.
4. The amount of rhPDGF-BB to be applied for that week will be calculated based on the ulcer size.
5. A swab of the fluid on the surface of the wound will be taken using the WOUNDCHEK system to assess for elevated protease activity.
6. A sample of wound fluid will be collected using a standardized methodology.
7. The rhPDGF-BB will be applied to the wounds.
8. The protease inhibitor dressing or the placebo will be applied.
9. The secondary dressings will be applied.

At the second follow-up visit each week, the following will be performed:

1. Wound fluid will be collected.
2. No measurements will be done; wound photography will be taken.
3. The rhPDGF-BB will be applied to the wounds.
4. The protease inhibitor dressing or the placebo will be applied.
5. The secondary dressings will be applied.

At the third follow-up visit in the same week, the following will be performed:

1. No measurements, wound photography or fluid collection.
2. The rhPDGF-BB will be applied to the wounds.
3. The protease inhibitor dressing or the placebo will be applied.
4. Secondary dressings will be applied.

Table 1. Treatments and measurements at each study visit.

Day	Growth factor application	Protease inhibitor application	Wound fluid collection	Point of Careswab for total protease activity (WOUNDCHEK)
1	x	x	x	x
2	x	x	x	x
5	x	x		x

Outcome Measures

Primary outcome:

- The difference in levels of nondegraded PDGF in CWF from the treatment and placebo treatment groups

Secondary outcomes:

- The difference in levels of total protease and individual proteases in CWF from the treatment and placebo treatment groups as determined by enzyme-linked immunosorbent assay (ELISA) assay
- The difference in levels of endogenous growth factors in CWF from the treatment and placebo treatment groups as determined by ELISA assay
- Percentage reduction in size of ulcers after 1 month of therapy and the proportion of VLU and DFU that are in a healing trajectory. In VLU, a wound area reduction of 40% within 4 weeks is predictive of healing at 12 weeks [67], and in DFUs, a wound area reduction of greater than 50% in 4 weeks is predictive of healing at 12 weeks [68]
- The presence of elevated total protease activity using WOUNDCHEK and the change with time
- The presence of a healing or nonhealing status as measured by GMCSF levels in CWF and the change with time as measured by ELISA assay
- The completeness, ease of use, literacy, and timeliness of completing the pilot cost diary from a societal perspective. Both medical staff and participants will complete cost diaries

Measurement of Outcomes at Follow-Up Visits

At the first follow-up visit each week, the following will be performed:

1. The surface area of the wound will be traced and the area will be measured using the Visitrak device (Smith & Nephew).
2. A photograph of the wound will be taken using a standardized protocol.
3. A swab of the fluid on the surface of the wound will be taken using the WOUNDCHEK system to assess for elevated protease activity. The swabs will be stored for subsequent analysis of actual protease levels.
4. A sample of wound fluid will be collected from the chronic wounds by covering the wound with a transparent occlusive dressing (Opsite, Smith & Nephew, Hull, UK) for approximately 1 hour. Fluid that has accumulated will then be aspirated and stored at −80°C. The wound fluid samples will be aliquoted into 20 ul samples and will be stored at −80°C. At the completion of the study, the samples will be analyzed using Quantibody analysis to measure the levels of proteases and nondegraded growth factors in the wound fluid, and a Western blot will be performed to assess rhPDGF-BB degradation. All of these samples will be assayed at the end of the study.

At the second visit in the same week, the following will be performed:

1. A sample of wound fluid will be collected.
2. A swab of the fluid on the surface of the wound will be taken using the WOUNDCHEK system to assess for elevated protease activity.

At the third follow-up visit in the same week, the following will be performed:

1. Swab of the fluid on the surface of the wound will be taken using the WOUNDCHEK system to assess for elevated protease activity.
2. The cost diary for that week will be completed.

Health Services Issues

As this is a proof-of-concept study of the biochemical efficacy of the therapy, no health service evaluations will be undertaken; however, a cost diary from a societal perspective will be validated in preparation for a future study.

Sample Size

One small study has assessed the levels of proteases in CWF from VLU after the application of Promogran [43]. In that study, the reduction in elastase after 5 days was approximately 80%, and the reduction in MMP-9 was approximately 45%. There are no data on the degradation of rhPDGF-BB that is applied topically to VLU or DFU. For the sample size analysis, a modest reduction in protease levels of 25% was estimated. Due to the variability of factors, an SD of 35% of the value for the control levels was used. Using a power of 80% and a 5% level of significance, the calculated sample size was 31 in each group. Due to possible nonadherence with the study and collection of samples, the number of participants to be recruited is 40 in each group.

Planned Recruitment Rate

Patients will be approached and recruited by the research coordinator after being identified in the clinic by the participating physicians. The study will be conducted over 3 years. The first 3 months requires study preparation including intensive protocol training to ensure reliability. A number of protocols such as wound fluid collection are not typical wound care procedures. On the basis of previous studies from this laboratory, recruitment will need 2 years, given the average of 3.5 participants recruited per month. The last 3 months will

include conducting the assay analysis and data analysis and disseminating the results.

Compliance

On the basis of previous studies from this laboratory, compliance is a risk, given the complexity of the participants' chronic wound, comorbidities, and tolerance for either compression bandaging or pressure off-loading. Compliance will be assessed on the participants' second visit by noting if they are wearing their prescribed compression bandaging or pressure off-loading device. If they are not complying with standard therapy, the participants will not enter the treatment segment of the study. The need to attend the study clinic 3 times a week for 6 weeks is demanding and risks noncompliance; however, these visits replace the need for the participants to attend their regular clinic to have their dressings changed.

Likely Rate of Loss to Follow-Up

An allowance has been made for just over 20% loss of participants to follow-up. To assist participants in attending the visits, reimbursement of costs for travel and parking will be offered in the form of gift certificates. The average of these would be Can $40.00.

Number of Centers

A total of 2 sites within the same health region are required to meet the recruitment targets.

Data Analysis

Data analysis will be performed on the outcome measures as follows:

1. The trial will meet Consolidated Standards of Reporting trials (CONSORT) requirements for reporting of randomized controlled trials. Baseline characteristics of patients in the 2 treatment groups will be reported using frequency distributions and descriptive statistics including measures of central tendency and dispersion.
2. The changes in levels of nondegraded PDGF in CWF from the treatment and placebo treatment groups will be analyzed using repeated measures analysis of variance (ANOVA), using the wound type and treatment group as covariates.
3. The changes in levels of proteases and endogenous growth factors in CWF from the treatment and placebo treatment groups will be analyzed using repeated measures ANOVA, with the wound type and treatment group as covariates.
4. The percentage change in wound area after 4 weeks in the study will be assessed on an intention-to-treat basis using Student *t* test. On the basis of the percentage reduction in size at 4 weeks, the ulcers will be categorized as predicted to heal or not heal at 12 weeks. These healing predictions for the Promogran and placebo groups will be assessed by chi-squared analysis.
5. The change in total protease status after application of the Promogran or the placebo will be assessed by chi-squared analysis.
6. The change in healing status as determined by GMCSF biomarker after application of the Promogran or the placebo will be assessed by chi-squared analysis. Healing analysis will be performed on an intention-to-treat basis.
7. All analysis will be completed using SPSS version 22 (IBM Corporation, Armonk, New York).

Frequency of Analyses

All statistical analyses will be performed only at the completion of the study and after final data checking is completed.

Planned Subgroup Analyses

If the initial analysis demonstrates a difference between VLU and DFU responses to protease inhibitor application, subgroup analyses of these 2 groups will be performed.

Previous Pilot Testing

There is one small study that has demonstrated reduction in elastase and MMP-9 levels in CWF from VLU with the application of Promogran [43]. There is one study that has demonstrated degradation of EGF by CWF, but none that has demonstrated degradation of PDGF in VLU or DFU [26].

Trial Management

The study will employ a research coordinator 2 days per week to manage data handling, randomization, and other aspects of the study. A total of 2 clinical research nurses will be employed to perform the dressings and application of the study treatments.

The principal applicant will oversee, in conjunction with the research coordinator, the management of the study, the location and facilities for the study, treatment materials and data storage systems, and the analysis of the data from the study.

A study steering committee will be formed from experienced researchers within the Population Health Research Institute in Hamilton. A data and safety monitoring board will be blinded to treatment group. The board will review serious adverse events.

Results

The project was funded by the Canadian Institutes for Health Research and enrollment is expected to be initiated in 2018. It is expected that results will be available in 2021.

Discussion

It is expected that the results of this trial will inform as to whether modifying the wound environment through the use of protease inhibitors increases the effectiveness of topically applied growth factors in the healing of chronic wounds.

Acknowledgments

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Conflicts of Interest

None declared.

References

1. Canada Institute for Health Information. 2013. Compromised Wounds in Canada URL: https://secure.cihi.ca/free_products/AiB_Compromised_Wounds_EN.pdf [accessed 2018-04-02] [WebCite Cache ID 6yOK1ekmz]
2. Boulton A, Vileikyte L, Ragnarsson-Tenvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005;366(9498):1719-1724.
3. Hopkins R, Burke N, Harlock J, Jegathisawaran J, Goeree R. Economice burden of illness associated with diabetic foot ulcers in Canada. BMC Health Services Research 2015;15:1-9.
4. Waters N. The challenges of providing cost-effective quality wound care in Canada. Wound Care Can 2005;3(1):22-26.
5. Gloviczki P, Bergan JJ, Rhodes JM, Canton LG, Harmsen S, Ilstrup DM. Mid-term results of endoscopic perforator vein interruption for chronic venous insufficiency: lessons learned from the North American subfascial endoscopic perforator surgery registry. The North American Study Group. J Vasc Surg 1999 Mar;29(3):489-502 [FREE Full text] [Medline: 10069914]
6. Wounds International. 2013. International Best Practice-Best Practice Guidelines: Wound Management in Diabetic Foot Ulcers URL: http://www.woundsinternational.com/media/best-practices/_/673/files/dfubestpracticeforweb.pdf [accessed 2018-04-02] [WebCite Cache ID 6yOKcxDIc]
7. Posnett J, Gottrup F, Lundgren H, Saal G. The resource impact of wounds on health-care providers in Europe. J Wound Care 2009;18(4):154-161.
8. Hurd T, Posnett J. Point prevalence of wounds in a sample of acute hospitals in Canada. Int Wound J 2009;6(4):287-293. [Medline: 19719525]
9. Council of the Federation of Wound Healing Societies. Canadian Health Human Resources Network. 2012. From Innovation to Action: the First Report of the Health Care Innovation Working Group URL: https://bit.ly/2uQo8Ob [WebCite Cache ID 6ySNUQO5Q]
10. Wound Care Alliance Canada. Scribd. 2012. Wounds National Stakeholder Round-table: Report of the June 27, 2012 meeting URL: https://www.scribd.com/doc/108577300/WOUNDS-National-Stakeholder-Round-Table-Report [accessed 2018-04-02] [WebCite Cache ID 6yOLNBFZJ]
11. Botros M, Woodbury M, Kuhnke J, Despatis M. Saving diabetic limbs in Canada: partnership between the Public Health Agency of Canada and the Canadian Association of Wound Care. Int Wound J 2012;9(3):231-233. [Medline: 22571320]
12. Burrows C, Miller R, Townsend D, Bellefontaine R, MacKean G, Orstead HL, et al. Best practice recommendations for the prevention and treatment of venous leg ulcers update 2006. Wound Care Can 2006;4(1):45-55 [FREE Full text]
13. Baker SR, Stacey MC. Epidemiology of chronic leg ulcers in Australia. Aust N Z J Surg 1994 Apr;64(4):258-261. [Medline: 8147778]
14. Baker SR, Stacey MC, Jopp-McKay AG, Hoskin SE, Thompson PJ. Epidemiology of chronic venous ulcers. Br J Surg 1991 Jul;78(7):864-867. [Medline: 1873720]
15. Lipscombe LL, Hux JE. Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study. Lancet 2007;369(9563):750-756. [Medline: 17336651]
16. Laing W. Chronic Venous Diseases of the Leg. London, UK: Office of Health Economics; 1992.
17. Stacey MC, Jopp-Mckay AG, Rashid P, Hoskin SE, Thompson PJ. The influence of dressings on venous ulcer healing--a randomised trial. Eur J Vasc Endovasc Surg 1997 Feb;13(2):174-179. [Medline: 9091151]
18. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. J Am Med Assoc 2005 Jan 12;293(2):217-228. [doi: 10.1001/jama.293.2.217] [Medline: 15644549]
19. Public Health Agency of Canada. 2011. Diabetes in Canada: facts and figures from a public health perspective URL: http://www.phac-aspc.gc.ca/cd-mc/publications/diabetes-diabete/facts-figures-faits-chiffres-2011/pdf/facts-figures-faits-chiffres-eng.pdf [accessed 2018-04-02] [WebCite Cache ID 6yOLukw2H]
20. Schultz GS, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, et al. Wound bed preparation: a systematic approach to wound management. Wound Repair Regen 2003;11 Suppl 1:S1-28. [Medline: 12654015]
21. Lee K, Silva E, Mooney D. Growth factor delivery-based tissue engineering: general approachs and a review of recent developments. J R Soc Interface 2011;8:152-170.
22. Mast BA, Schultz GS. Interactions of cytokines, growth factors, and proteases in acute and chronic wounds. Wound Repair Regen 1996 Oct;4(4):411-420. [doi: 10.1046/j.1524-475X.1996.40404.x] [Medline: 17309691]
23. Trengove NJ, Bielefeldt-Ohmann H, Stacey MC. Mitogenic activity and cytokine levels in non-healing and healing chronic leg ulcers. Wound Repair Regen 2000;8(1):13-25. [Medline: 10760211]
24. Wallace HJ, Stacey MC. Levels of tumor necrosis factor-alpha (TNF-alpha) and soluble TNF receptors in chronic venous leg ulcers--correlations to healing status. J Invest Dermatol 1998 Mar;110(3):292-296 [FREE Full text] [doi: 10.1046/j.1523-1747.1998.00113.x] [Medline: 9506452]

25. Tarnuzzer RW, Schultz GS. Biochemical analysis of acute and chronic wound environments. Wound Repair Regen 1996;4(3):321-325. [doi: 10.1046/j.1524-475X.1996.40307.x] [Medline: 17177727]
26. Trengove NJ, Stacey MC, MacAuley S, Bennett N, Gibson J, Burslem F, et al. Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. Wound Repair Regen 1999;7(6):442-452. [Medline: 10633003]
27. Lauer G, Sollberg S, Cole M, Flamme I, Stürzebecher J, Mann K, et al. Expression and proteolysis of vascular endothelial growth factor is increased in chronic wounds. J Invest Dermatol 2000 Jul;115(1):12-18 [FREE Full text] [doi: 10.1046/j.1523-1747.2000.00036.x] [Medline: 10886501]
28. Yager DR, Chen SM, Ward SI, Olutoye OO, Diegelmann RF, Kelman CI. Ability of chronic wound fluids to degrade peptide growth factors is associated with increased levels of elastase activity and diminished levels of proteinase inhibitors. Wound Repair Regen 1997;5(1):23-32. [doi: 10.1046/j.1524-475X.1997.50108.x] [Medline: 16984454]
29. Mustoe TA, O'Shaughnessy K, Kloeters O. Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. J Plast Reconstr Surg 2006;117(7 Suppl):35S-41S. [Medline: 16799373]
30. Menke NB, Ward KR, Witten TM, Bonchev DG, Diegelmann RF. Impaired wound healing. Clin Dermatol 2007;25(1):19-25. [doi: 10.1016/j.clindermatol.2006.12.005] [Medline: 17276197]
31. Henderson EA. The potential effect of fibroblast senescence on wound healing and the chronic wound environment. J Wound Care 2006 Jul;15(7):315-318. [doi: 10.12968/jowc.2006.15.7.26932] [Medline: 16869200]
32. Robson MC. The role of growth factors in the healing of chronic wounds. Wound Repair Regen 1997;5(1):12-17. [doi: 10.1046/j.1524-475X.1997.50106.x] [Medline: 16984452]
33. Barrientos S, Brem H, Stojadinovic O, Tomic-Canic M. Clinical application of growth factors and cytokines in wound healing. Wound Repair Regen 2014;22(5):569-578 [FREE Full text] [doi: 10.1111/wrr.12205] [Medline: 24942811]
34. Moor AN, Vachon DJ, Gould LJ. Proteolytic activity in wound fluids and tissues derived from chronic venous leg ulcers. Wound Repair Regen 2009;17(6):832-839. [doi: 10.1111/j.1524-475X.2009.00547.x] [Medline: 19903304]
35. Liu Y, Min D, Bolton T, Nubé V, Twigg SM, Yue DK, et al. Increased matrix metalloproteinase-9 predicts poor wound healing in diabetic foot ulcers. Diabetes Care 2009 Jan;32(1):117-119 [FREE Full text] [doi: 10.2337/dc08-0763] [Medline: 18835949]
36. Xu L, McLennan SV, Lo L, Natfaji A, Bolton T, Liu Y, et al. Bacterial load predicts healing rate in neuropathic diabetic foot ulcers. Diabetes Care 2007 Feb;30(2):378-380. [doi: 10.2337/dc06-1383] [Medline: 17259515]
37. Rayment EA, Upton Z, Shooter GK. Increased matrix metalloproteinase-9 (MMP-9) activity observed in chronic wound fluid is related to the clinical severity of the ulcer. Br J Dermatol 2008 May;158(5):951-961. [doi: 10.1111/j.1365-2133.2008.08462.x] [Medline: 18284390]
38. Mustoe T. Understanding chronic wounds: a unifying hypothesis on their pathogenesis and implications for therapy. Am J Surg 2004;187(5A):65S-70S. [Medline: 15147994]
39. Stechmiller J, Cowan L, Schultz G. The role of doxycycline as a a matrixmetalloproteinase inhibitor for the treatment of chronic wounds. Biol Res Nurs 2010;11(4):226-244. [Medline: 20031955]
40. Cullen B, Smith R, McCulloch E, Silcock D, Morrison L. Mechanism of action of PROMOGRAN, a protease modulating matrix, for the treatment of diabetic foot ulcers. Wound Repair Regen 2002;10(1):16-25. [Medline: 11983003]
41. Widgerow AD. Chronic wound fluid--thinking outside the box. Wound Repair Regen 2011;19(3):287-291. [doi: 10.1111/j.1524-475X.2011.00683.x] [Medline: 21518088]
42. Cullen B, Smith R, McCulloch E, Silcock D, Morrison L. Mechanism of action of PROMOGRAN, a protease modulating matrix, for the treatment of diabetic foot ulcers. Wound Repair Regen 2002;10(1):16-25. [Medline: 11983003]
43. Smeets R, Ulrich D, Unglaub F, Wöltje M, Pallua N. Effect of oxidised regenerated cellulose/collagen matrix on proteases in wound exudate of patients with chronic venous ulceration. Int Wound J 2008 Jun;5(2):195-203. [doi: 10.1111/j.1742-481X.2007.00367.x] [Medline: 18494625]
44. Vin F, Teot L, Meaume S. The healing properties of Promogran in venous leg ulcers. J Wound Care 2002;11(9):335-341. [Medline: 12430368]
45. Veves A, Sheehan P, Pham HT. A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. Arch Surg 2002 Jul;137(7):822-827. [Medline: 12093340]
46. Kakagia DD, Kazakos KJ, Xarchas KC, Karanikas M, Georgiadis GS, Tripsiannis G, et al. Synergistic action of protease-modulating matrix and autologous growth factors in healing of diabetic foot ulcers. A prospective randomized trial. J Diabetes Complications 2007;21(6):387-391. [doi: 10.1016/j.jdiacomp.2007.03.006] [Medline: 17967712]
47. Cullen B, Kemp L, Essler A, Wallenfang-Sohle K, Stadler R. Rebalancing wound biochemistry improves healing: A clinical study examining effect of promogran. Wound Repair Regen 2004;12(2):A4. [doi: 10.1111/j.1067-1927.2004.0abstracth.x]
48. Smeets R, Ulrich D, Unglaub F, Wöltje M, Pallua N. Effect of oxidised regenerated cellulose/collagen matrix on proteases in wound exudate of patients with chronic venous ulceration. Int Wound J 2008 Jun;5(2):195-203. [doi: 10.1111/j.1742-481X.2007.00367.x] [Medline: 18494625]
49. Greer N, Foman N, Dorrian J, Fitzgerald P, MacDonald R, Rutks I, et al. Advanced Wound Care Therapies for Non-Healing Diabetic, Venous, and Arterial Ulcers: A Systematic Review. Washington, DC: Department of Veterans Affairs; 2012.

50. Grotendorst GR, Martin GR, Pencev D, Sodek J, Harvey AK. Stimulation of granulation tissue formation by platelet-derived growth factor in normal and diabetic rats. J Clin Invest 1985 Dec;76(6):2323-2329 [FREE Full text] [doi: 10.1172/JCI112243] [Medline: 3908487]
51. Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. Diabetic Ulcer Study Group. J Vasc Surg 1995 Jan;21(1):71-8; discussion 79 [FREE Full text] [Medline: 7823364]
52. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. Diabetes Care 1998 May;21(5):822-827. [Medline: 9589248]
53. Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. Plast Reconstr Surg 2006;117(Suppl 7):143S-149S; discussion 150S-151S. [Medline: 16799381]
54. Zhao X, Gu H, Xu Z, Zhang Q, Lv X, Zheng X, et al. Efficacy of topical recombinant human platelet-derived growth factor for treatment of diabetic lower-extremity ulcers: Systematic review and meta-analysis. Metabolism 2014 Oct;63(10):1304-1313. [doi: 10.1016/j.metabol.2014.06.005] [Medline: 25060693]
55. Robson MC, Phillips LG, Thomason A, Robson LE, Pierce GF. Platelet-derived growth factor BB for the treatment of chronic pressure ulcers. Lancet 1992 Jan 04;339(8784):23-25. [Medline: 1345953]
56. Rees RS, Robson MC, Smiell JM, Perry BH. Becaplermin gel in the treatment of pressure ulcers: a phase II randomized, double-blind, placebo-controlled study. Wound Repair Regen 1999;7(3):141-147. [Medline: 10417749]
57. Wieman TJ. Efficacy and safety of recombinant human platelet-derived growth factor-BB (Becaplermin) in patients with chronic venous ulcers: A pilot study. Wounds 2003;15(9):257-264 [FREE Full text]
58. Food and Drug Administration. URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProPostma/DrugSafetyInformationforHeathcareProfessionals/ucm072121.htm [accessed 2018-02-28] [WebCite Cache ID 6xZk0qUwO]
59. Falanga V, Eaglstein WH, Bucalo B, Katz MH, Harris B, Carson P. Topical use of human recombinant epidermal growth factor (h-EGF) in venous ulcers. J Dermatol Surg Oncol 1992 Jul;18(7):604-606. [Medline: 1624634]
60. Rasmussen LH, Karlsmark T, Avnstorp C, Peters K, Jorgensen M, Jensen L. Topical human growth hormone treatment of chronic leg ulcers. Phlebology 1991;6(1):23-30. [doi: 10.1177/026835559100600105]
61. Marques da Costa R, Jesus FM, Ancieto C, Mendes M. Double-blind randomized placebo-controlled trial of the use of granulocyte-macrophage colony-stimulating factor in chronic leg ulcers. Am J Surg 1997;173:165-168. [Medline: 9124619]
62. Robson MC, Phillip LG, Cooper DM, Lyle WG, Robson LE, Odom L, et al. Safety and effect of transforming growth factor-beta(2) for treatment of venous stasis ulcers. Wound Repair Regen 1995;3(2):157-167. [doi: 10.1046/j.1524-475X.1995.30207.x] [Medline: 17173644]
63. Grinnell F, Ho C, Wysocki A. Degradation of fibronectin and vitronectin in chronic wound fluid: analysis by cell blotting, immunoblotting, and cell adhesion assays. J Invest Dermatol 1992;98(4):410-416.
64. Trengove NJ, Stacey MC, MacAuley S, Bennett N, Gibson J, Burslem F, et al. Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. Wound Repair Regen 1999;7(6):442-452. [Medline: 10633003]
65. Fu X, Li X, Cheng B, Chen W, Sheng Z. Engineered growth factors and cutaneous wound healing: success and possible questions in the past 10 years. Wound Repair Regen 2005;13(2):122-130. [doi: 10.1111/j.1067-1927.2005.130202.x] [Medline: 15828936]
66. Clinicaltrials.gov. WOUNDCHEK™ Protease Status Point of Care (POC) Diagnostic Test URL: https://clinicaltrials.gov/ct2/show/NCT01537003 [accessed 2017-11-21] [WebCite Cache ID 6v8r4CWzv]
67. Flanagan M. Improving accuracy of wound measurement in clinical practice. Ostomy Wound Manage 2003 Oct;49(10):28-40 [FREE Full text] [Medline: 14652419]
68. Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care 2003 Jun;26(6):1879-1882. [Medline: 12766127]

Abbreviations

ANOVA: analysis of variance
CWF: chronic wound fluid
DFU: diabetic foot ulcer
ECM: extracellular matrix
EGF: epidermal growth factor
ELISA: enzyme-linked immunosorbent assay
GMCSF: granulocyte-macrophage colony-stimulating factor
MMP: matrix metalloprotease
PDGF: platelet-derived growth factor
rhPDGF-BB: recombinant human PDGF-BB

TIMP: tissue inhibitors of metalloproteinase
VLU: venous leg ulcer

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Original Paper

Recruitment of Participants and Delivery of Online Mental Health Resources for Depressed Individuals Using Tumblr: Pilot Randomized Control Trial

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Abstract

Background: Adolescents and young adults frequently post depression symptom references on social media; previous studies show positive associations between depression posts and self-reported depression symptoms. Depression is common among young people and this population often experiences many barriers to mental health care. Thus, social media may be a new resource to identify, recruit, and intervene with young people at risk for depression.

Objective: The purpose of this pilot study was to test a social media intervention on Tumblr. We used social media to identify and recruit participants and to deliver the intervention of online depression resources.

Methods: This randomized pilot intervention identified Tumblr users age 15-23 who posted about depression using the search term "#depress". Eligible participants were recruited via Tumblr messages; consented participants completed depression surveys and were then randomized to an intervention of online mental health resources delivered via a Tumblr message, while control participants did not receive resources. Postintervention online surveys assessed resource access and usefulness and control groups were asked whether they would have liked to receive resources. Analyses included *t* tests.

Results: A total of 25 participants met eligibility criteria. The mean age of the participants was 17.5 (SD 1.9) and 65% were female with average score on the Patient Health Questionnaire-9 of 17.5 (SD 5.9). Among the 11 intervention participants, 36% (4/11) reported accessing intervention resources and 64% (7/11) felt the intervention was acceptable. Among the 14 control participants, only 29% (4/14) of reported that receiving resources online would be acceptable (*P*=.02). Participants suggested anonymity and ease of use as important characteristics in an online depression resource.

Conclusions: The intervention was appropriately targeted to young people at risk for depression, and recruitment via Tumblr was feasible. Most participants in the intervention group felt the social media approach was acceptable, and about a third utilized the online resources. Participants who had not experienced the intervention were less likely to find it acceptable. Future studies should explore this approach in larger samples. Social media may be an appropriate platform for online depression interventions for young people.

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KEYWORDS

adolescents; depression; intervention; social media; tumblr

Introduction

Depression is among the most common illnesses affecting adolescents and young adults but many do not seek clinical care or know about available resources [1-3]. Previous studies have illustrated several barriers to mental health care among young people, including recognition of a problem, access to care, fear of stigma if care is accessed, and identification of young people–specific resources [4-6]. Many of the services offered do not address the needs of young people during the later years of adolescence and young adulthood [4]. Given these barriers to mental health care, innovative solutions are needed. Online approaches may be one such solution.

Due to the continuous rise in social media use among young people, researchers are investigating the impact and influence of online mental health resources [7,8] . The vast majority of young people are online and most of these young people use social media to express themselves and get social support [9-11]. Many social media users report feeling more comfortable self-disclosing information online rather than in person [11]. Previous studies suggest depression symptom disclosures on social media are common and are associated with offline depression symptoms [12,13]. One study found one-third of public college Facebook profiles displayed at least one reference to a depression symptom and 2.5% of Facebook profiles fit the Diagnostic and Statistical Manual (DSM-IV) criteria for a major depressive episode [13]. Thus, it is possible that social media posts could be used to identify young people at risk for depression based on posting references to depression symptoms. In this way, young people could be identified and even provided resources or support online.

There are several ways in which online and social media interventions present opportunities to reach and engage with young people [9,14,15]. Online and social media interventions often cost less and allow researchers to reach a more diverse population [14,15] **.** Reaching young people is a critical challenge as young people are the least likely age group to have a primary care provider and a majority do not seek professional help for mental health problems [2,6,16]. Previous online intervention studies had more participation from underrepresented and underserved individuals compared to traditional intervention methods [14,17]. Online interventions allow individuals to access the intervention anytime without geographical and time barriers. A majority of the successful online intervention studies used structured online programs that included education and coping strategies as their means of intervention [3,8,18-21]. Many young people prefer online intervention options because they offer privacy, anonymity, 24-hour accessibility, and avoid face-to-face interactions [9,22].

While previous online interventions have addressed alcohol use, sexual behaviors, depression, and other mental health disorders, none of those interventions offered online resources for adolescents to use independently and a majority of studies did not use social media for participant identification and recruitment [3,21,23]. The purpose of this study was to determine whether a social media intervention offering resources to young people displaying references to depression appropriately targeted young people with depression and was accessed by, and deemed acceptable by, young people.

Methods

Study Setting

This randomized control pilot intervention occurred from October 2014 to December 2015 on Tumblr [24]. Tumblr is a popular social media site among young people that allows profiles to be created and displayed anonymously [7]. An email address and username is the only information Tumblr requires to create an account. Tumblr users are not required to display identifying information on their profile page. The email address provided to create a profile is not visible to other users. Thus, users can post personal multimedia content labeled with hashtags with fewer restrictions compared to Facebook or Twitter. Similar to Facebook and Twitter, users can repost, like, and comment on other user's posts. A majority of Tumblr blogs are publically available and profiles and posts can be viewed without having a Tumblr profile [25]. The Western Institutional Review Board approved this pilot study.

Participants

The goal for this pilot study was to identify participants who displayed depression symptoms on social media. The target sample size was 45 for this pilot test. Potential participants were identified via a post on Tumblr using the search term #depress to encompass both key words "depression" and "depressed," and search filter of "most recent posts."

A codebook from a previous study was used to determine whether the post displayed a reference to depression [12]. The codebook was created using the DSM-IV diagnostic criteria for a major depressive episode (see Table 1). Examples of posts eligible for participation included: "I feel like I am not good enough for anyone #depress #sad;" "I can't do anything right. Straight A's still isn't good enough for my parents. I'm so exhausted and I am hurting physically and emotionally. #depress #zzz #alone #depression"; and a picture of cuts on an arm with the caption, "they thought I was fine. #alone #depress #tears #die".

After a post was determined to meet the depression codebook criteria, the profile of the individual that created the post was reviewed. Participants whose Tumblr profiles were in English, displayed their profile age as between 15 and 23 years, and displayed one or more depression symptoms consistent with the DSM-IV in their Tumblr post within the last 14 days were considered eligible [13,26].

Individuals with Tumblr profiles who displayed other mental health comorbidities (ie, #bipolar) were excluded. Additional inclusion criteria were the ability to receive private Tumblr messages and presence of timestamps on profile posts.

Table 1. Depression codebook criteria.

Category	Terms or phrases to include	Terms or phrases to exclude
Depressed mood	Sad, empty, crying, tearful, alone, lonely, sad face emoticon	"I had a bad day", "FML"
Decreased interest or pleasure in activities	Not having fun, don't feel like doing anything, giving up	
Increase/decrease in appetite	No appetite, don't feel like eating, can't stop eating, eating everything in sight	"I ate too much at McDonalds this weekend," references to poor eating habits rather than changes in appetite
Sleep problems	Sleeping too much, slept more than 10 hours, fatigue, tired, exhausted	
Psychomotor agitation/retardation	Feeling slow	
Loss of energy	Can't get anything done, no motivation	
Feelings of guilt, worthlessness, negative self-appraisal	Feels guilty or worthless, "I'm so stupid"	
Indecisiveness	Can't decide on something, don't feel like deciding, can't make up mind	
Recurrent thoughts of death or suicidal ideation	Thinking of ways to commit suicide, references to jumping	
Difficulty concentrating	Can't study, can't finish work, can't concentrate	Don't want to concentrate, can't concentrate because of activity (TV, friends, Facebook)

Intervention

The intervention tested in this research protocol was designed to be delivered online and provide online depression resources. A resource sheet was developed in consultation with an adolescent health mental health expert listing mental health resources that were nationally available, free, online, and publicly accessible (Multimedia Appendix 1). Not all of the resources provided were explicitly for young people, however some of the resources had specific pages or topics specifically for young people. Because a majority of young people do not seek help or know how to access mental health resources, the resource sheet offered a variety of depression resources for participants to access [1]. The resources included chat rooms, information-based websites, hotlines, and means to find a mental health professional for depression. A majority of the resources could be accessed 24 hours a day. The resource sheet was delivered using a study team Tumblr profile via a private Tumblr message explaining the study and the research team (Multimedia Appendix 1). Participants were asked to message the research group via Tumblr if they did not wish to be contacted again by the research group.

Procedures

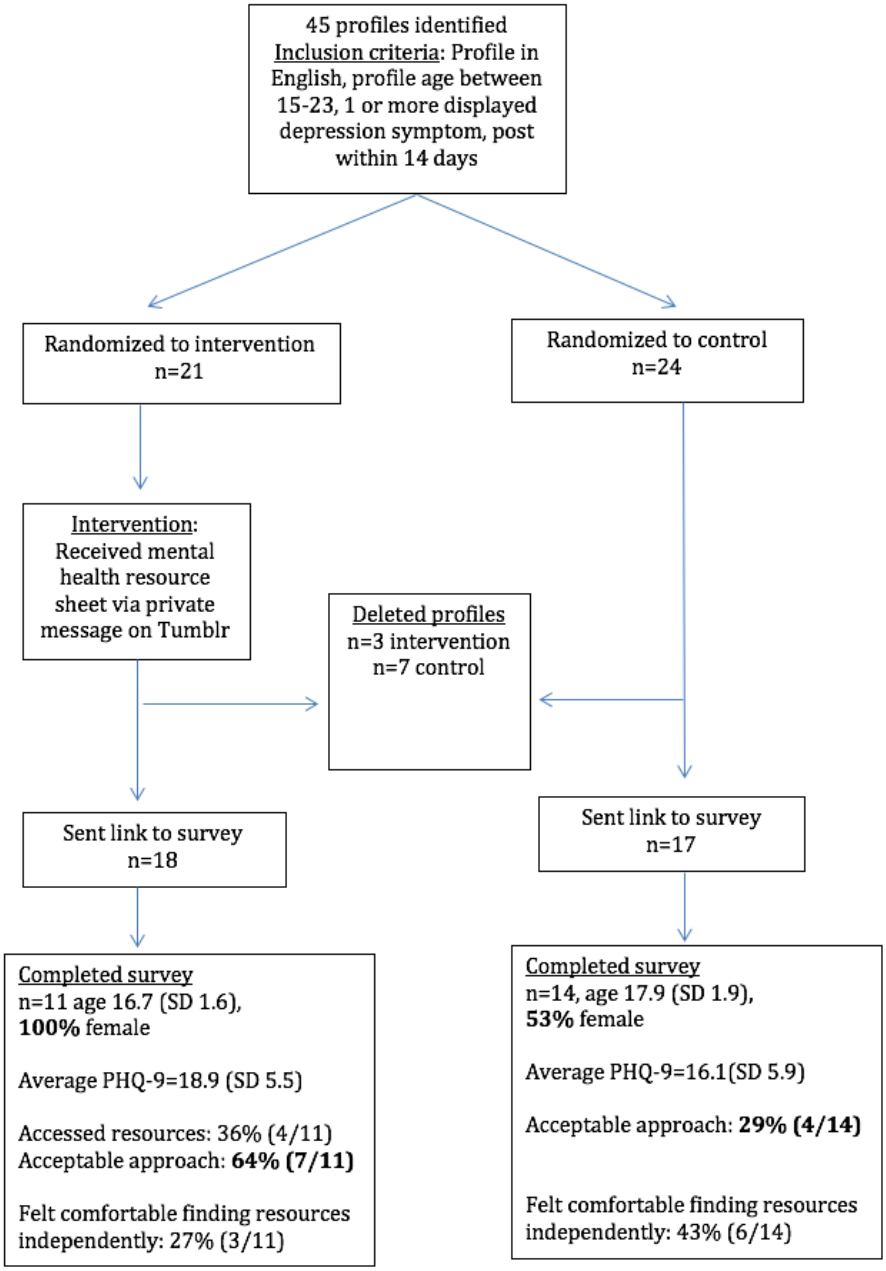
After eligible individuals' Tumblr profiles were identified and randomized, the username, profile URL, post with the depression symptom reference, and hashtags of participants were stored in an excel spreadsheet. Participants were randomized using a randomization website [27]. The numbers 1 through 45 were randomized into intervention and control numbers. Participants were assigned numbers in the order their post appeared on Tumblr. Intervention participants received a resource list as the intervention while the participants in the control group were not initially contacted. One month after the intervention was delivered, a private Tumblr message was sent to both groups that included a link to the secure, anonymous online survey and consent form. Participants were provided information about the research group and how to contact the group, anonymity of the survey, how long the data would be stored, and how to exit the survey. There was one question per page with a maximum of 22 questions depending on how the participant answered specific questions. Participants were not required to provide an answer for any of the questions and were provided a back button to change previous answers. Due to the anonymity of the survey, researchers were not able to identify which participants completed the survey. IP addresses were verified to prevent duplicate entries from the same user. Intervention procedures are described in Figure 1. Participants who completed the survey were provided a $10 gift card.

Variables

Feasibility of Recruitment

In order to assess the feasibility of recruiting teens at risk for depression, our survey included the Patient Health Questionnaire-9 (PHQ-9) [28]. The PHQ-9 is a 9-item measure that assesses DSM-IV criteria for depression within the last two weeks and is commonly used as a clinical screening tool across the United States with the following Likert scaled responses (0=Not at all, 1=Several days, 2=More than half days, and 3=Nearly every day). The scores on the PHQ-9 were computed and categories of depression level were established based on the PHQ-9 scoring guidelines: none to minimal depression (0-4 score), mild depression (5-9 score), moderate depression (10-14 score), moderate to severe depression (15-19 score), and severe depression (20-27 score). We hypothesized that if the average PHQ-9 score was in the range of mild to moderate depression, our search strategy was a feasible method of identifying teens at-risk for depression.

Figure 1. Flowchart of study design. *P* values calculated using an unpaired *t* test. Bolded values indicate significant values. PHQ-9: Patient Health Questionnaire-9.



Access to intervention resources

To assess whether intervention participants accessed resources, we asked the intervention group on the follow-up survey to describe resources the participant accessed or viewed and which ones they found helpful. To understand participants' access to online mental health resources in general, all participants were asked whether they knew of, felt comfortable accessing, or used other online depression resources in the past.

Acceptability of intervention approach

For both groups, the survey assessed acceptability of the approach of sending resources via Tumblr. The control group survey asked if they would have liked to receive depression resources and if the intervention approach would be acceptable.

Participant suggestions

All participants were asked to provide suggestions on key components of online mental health interventions that would support their acceptability.

Analysis

Descriptive data were summarized; group comparisons and comparison of PHQ-9 scores postintervention were both conducted using an unpaired *t* test. There was no blinding for this study.

Results

Participants

Among the 45 participants initially selected, 21 were randomized to the intervention. A total of 10 (3 intervention) participants

deleted their profiles before receiving a survey. There were 25 completed surveys, 65% (16/25) were female and were an average age of 17.5 years (SD 1.9; Figure 1). The average PHQ-9 score was 17.5 (SD 5.4), not differing among groups. None of the participants messaged the researchers to not be contacted again.

Intervention Group

Among intervention participants (n=11), 64% (7/11) of the participants found this intervention method to be an acceptable approach. Roughly one-third (4/11) of participants accessed intervention resources. Of those 4 participants, 100% (4) felt the approach was acceptable and 75% (3/4) answered they would likely use the resources again. The Depression Chat Rooms, IM ALIVE, and National Suicide Hotline were the resources accessed. Only 27% (3/11) felt comfortable finding resources independently. Before receiving the resources, half of the participants that accessed the resources did not know of other online resources for mental health (2/4).

Control Group

Among control group participants (n=14), only 14% (2/14) of the control group would have wanted to receive resources online and 29% (4/14) of control group participants reported they thought the intervention would be an acceptable approach. There was a statistically significant difference between the acceptability of the intervention approach between the intervention and control groups (P=.02). Although 71% (10/14) of control participants had used online resources for mental health, only 43% (6/14) felt comfortable finding resources independently. Common resources accessed by control participants included WedMD, psychcentral, anonymous chat groups and hotlines, and Tumblr.

Participant Suggestions

Overall, participants in both groups felt anonymity, supportiveness, and ease of use as important characteristics in an online depression resource. Participants in the control group found websites with young people going through similar experiences and chat groups to be the most helpful resources. A majority (9/11) of participants in the intervention group were not sure or did not have resources to suggest. The two suggestions were to offer cognitive behavior therapy resources and www.emotionalbaggage.com.

Discussion

Principal Findings

The research protocol tested in this pilot intervention study included an online mental health resource sheet and used Tumblr to identify teens that posted about depression as well as to deliver the resource. We found that the intervention was appropriately targeted to young people at risk for depression and recruitment via Tumblr was feasible.

The young people in this study had an average PHQ-9 score of 17.5, which can be interpreted as moderately severe depression [28]. Thus, identifying participants based on depression posts on Tumblr targeted the appropriate population for this study. Findings are similar to previous work in which depression displays on Facebook were associated with self-reported depression symptoms [13]. Therefore, displayed depression references on Tumblr could be a helpful tool in identifying young people at risk for depression.

Over one-third of participants in the intervention group accessed the online resources provided. The participants that used the resources found the resources to be helpful and stated they would use them in the future. Participants utilized the anonymous chat rooms and hotlines, which were similar to many of the resources accessed independently by the control group. However, it is important to highlight that Tumblr and WebMD, though unverified by a mental health expert, were considered depression resources for some participants in the control group. It is possible that participants in the control group did not find this approach acceptable because they were unaware of different kinds of available online mental health resources and therefore did not think online resources could be helpful.

It is notable that more than half of control participants did not feel comfortable finding online mental health resources independently. However, they suggested and accessed similar online depression resources the intervention group received. A majority of participants in both groups found anonymity, supportiveness, and accessibility to be helpful characteristics in an online mental health resource. These findings are similar to previous online intervention studies for young people [9,22]. Of importance, the intervention resource list encompassed the characteristics mentioned above.

Limitations

There were several limitations to the study. Only one social media site was used and the sample size was small, therefore findings cannot be generalized; however, this study was intended to test a research protocol and determine whether it could be used in future studies. Due to profile deletion and nonresponse to the survey, the intervention group had only female participants. However, males and females are equally likely to post a reference to depression on social media [12,29]. A previous depression intervention study did not find a statistically significant difference in the success of the intervention between males and females [3]. The deletion of several profiles in the course of this study was unexpected, further study could investigate whether other social media sites promote more stable or long-lasting profiles. Due to the anonymity of the surveys and the priority to protect participant identities, researchers had no capacity to follow up if participants answered that they had thoughts self-harm or suicide. The anonymity of the survey also prevented researchers from contacting participants to remind them to take the survey. This could be an explanation for the low percentage of completed surveys.

Future Studies

Findings support future work to test this approach and should consider the following:

- Obtain larger sample sizes with less restrictive inclusion criteria. Many profiles were not able to be included due to the age, language, and privacy restrictions.
- Utilize other social media sites such as Facebook or Twitter to reach a larger population of social media users.

- Follow up with participants for feedback on why they found the intervention and certain resources to be helpful or not helpful and whether this approach was considered intrusive. This would allow a mental health expert to verify a resource list more suitable for young people.

Conclusions

Previous successful online intervention studies have not incorporated social media for the identification and recruitment of participants or to offer mental health resources. Findings support the need for mental health resources targeting the adolescent and young adult population, and this study offers a novel approach for offering these services. Social media is an appropriate platform for mental health interventions for young people because it can reach a diverse population while remaining cost effective. This intervention protocol could be utilized and expanded in future studies to further understand resources utilized by young people and find new approaches to reaching this population.

Acknowledgments

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Conflicts of Interest

None declared.

Editorial Notice

This randomized study was not registered, explained by authors as the study not meeting criteria as Applicable Clinical Trial (ACT) Under 42 CFR 11.22(b). The editor granted an exception from ICMJE rules mandating prospective registration of randomized trials as he considered the study formative. However, readers are advised to carefully assess the validity of any potential explicit or implicit claims related to primary outcomes or effectiveness, as lack of registration does not prevent authors from changing their outcome measures retrospectively.

Multimedia Appendix 1

Resources sent to intervention participants.

[JPG File, 288KB - resprot_v7i4e95_app1.jpg]

Multimedia Appendix 2

CONSORT-EHEALTH checklist (V 1.6.1).

[PDF File (Adobe PDF File), 568KB - resprot_v7i4e95_app2.pdf]

References

1. Kazdin AE. Addressing the treatment gap: A key challenge for extending evidence-based psychosocial interventions. Behav Res Ther 2017 Jan;88:7-18. [doi: 10.1016/j.brat.2016.06.004] [Medline: 28110678]
2. Mojtabai R, Olfson M, Han B. National Trends in the Prevalence and Treatment of Depression in Adolescents and Young Adults. Pediatrics 2016 Dec;138(6) [FREE Full text] [doi: 10.1542/peds.2016-1878] [Medline: 27940701]
3. Moreno MA, Christakis DA, Egan KG, Jelenchick LA, Cox E, Young H, et al. A pilot evaluation of associations between displayed depression references on Facebook and self-reported depression using a clinical scale. J Behav Health Serv Res 2012 Jul;39(3):295-304 [FREE Full text] [doi: 10.1007/s11414-011-9258-7] [Medline: 21863354]
4. Patel V, Flisher AJ, Hetrick S, McGorry P. Mental health of young people: a global public-health challenge. Lancet 2007 Apr 14;369(9569):1302-1313. [doi: 10.1016/S0140-6736(07)60368-7] [Medline: 17434406]
5. Eisenberg D, Downs MF, Golberstein E, Zivin K. Stigma and help seeking for mental health among college students. Med Care Res Rev 2009 Oct;66(5):522-541. [doi: 10.1177/1077558709335173] [Medline: 19454625]
6. Hunt J, Eisenberg D. Mental health problems and help-seeking behavior among college students. J Adolesc Health 2010 Jan;46(1):3-10. [doi: 10.1016/j.jadohealth.2009.08.008] [Medline: 20123251]
7. Lenhart A, Page D. Teens, Social Media & Technology Overview 2015. Washington, DC: Pew Research; 2015. URL: http://assets.pewresearch.org/wp-content/uploads/sites/14/2015/04/PI_TeensandTech_Update2015_0409151.pdf [WebCite Cache ID 6yL42oB9M]
8. Rickwood DJ, Mazzer KR, Telford NR. Social influences on seeking help from mental health services, in-person and online, during adolescence and young adulthood. BMC Psychiatry 2015;15:40 [FREE Full text] [doi: 10.1186/s12888-015-0429-6] [Medline: 25886609]
9. Naslund JA, Aschbrenner KA, McHugo GJ, Unützer J, Marsch LA, Bartels SJ. Exploring opportunities to support mental health care using social media: A survey of social media users with mental illness. Early Interv Psychiatry 2017 Oct 20. [doi: 10.1111/eip.12496] [Medline: 29052947]

10. Perrin A. Social Media Usage. Washington, DC: PEW Research; 2015. URL: http://assets.pewresearch.org/wp-content/uploads/sites/14/2015/10/PI_2015-10-08_Social-Networking-Usage-2005-2015_FINAL.pdf [WebCite Cache ID 6yL4AmW7q]
11. Lachmar EM, Wittenborn AK, Bogen KW, McCauley HL. #MyDepressionLooksLike: Examining Public Discourse About Depression on Twitter. JMIR Ment Health 2017 Oct 18;4(4):e43 [FREE Full text] [doi: 10.2196/mental.8141] [Medline: 29046270]
12. Moreno MA, Jelenchick LA, Egan KG, Cox E, Young H, Gannon KE, et al. Feeling bad on Facebook: depression disclosures by college students on a social networking site. Depress Anxiety 2011 Jun;28(6):447-455 [FREE Full text] [doi: 10.1002/da.20805] [Medline: 21400639]
13. Moreno MA, Christakis DA, Egan KG, Jelenchick LA, Cox E, Young H, et al. A pilot evaluation of associations between displayed depression references on Facebook and self-reported depression using a clinical scale. J Behav Health Serv Res 2012 Jul;39(3):295-304 [FREE Full text] [doi: 10.1007/s11414-011-9258-7] [Medline: 21863354]
14. Rice S, Robinson J, Bendall S, Hetrick S, Cox G, Bailey E, et al. Online and Social Media Suicide Prevention Interventions for Young People: A Focus on Implementation and Moderation. J Can Acad Child Adolesc Psychiatry 2016;25(2):80-86 [FREE Full text] [Medline: 27274743]
15. Rice SM, Goodall J, Hetrick SE, Parker AG, Gilbertson T, Amminger GP, et al. Online and social networking interventions for the treatment of depression in young people: a systematic review. J Med Internet Res 2014;16(9):e206 [FREE Full text] [doi: 10.2196/jmir.3304] [Medline: 25226790]
16. Tsai Y, Zhou F, Wortley P, Shefer A, Stokley S. Trends and characteristics of preventive care visits among commercially insured adolescents, 2003-2010. J Pediatr 2014 Mar;164(3):625-630. [doi: 10.1016/j.jpeds.2013.10.042] [Medline: 24286572]
17. Whitaker C, Stevelink S, Fear N. The Use of Facebook in Recruiting Participants for Health Research Purposes: A Systematic Review. J Med Internet Res 2017 Aug 28;19(8):e290 [FREE Full text] [doi: 10.2196/jmir.7071] [Medline: 28851679]
18. Deady M, Mills KL, Teesson M, Kay-Lambkin F. An Online Intervention for Co-Occurring Depression and Problematic Alcohol Use in Young People: Primary Outcomes From a Randomized Controlled Trial. J Med Internet Res 2016 Mar 23;18(3):e71 [FREE Full text] [doi: 10.2196/jmir.5178] [Medline: 27009465]
19. Robinson J, Hetrick S, Cox G, Bendall S, Yuen HP, Yung A, et al. Can an Internet-based intervention reduce suicidal ideation, depression and hopelessness among secondary school students: results from a pilot study. Early Interv Psychiatry 2016 Feb;10(1):28-35. [doi: 10.1111/eip.12137] [Medline: 24684946]
20. Robinson J, Hetrick S, Cox G, Bendall S, Yung A, Yuen HP, et al. The development of a randomised controlled trial testing the effects of an online intervention among school students at risk of suicide. BMC Psychiatry 2014 May 27;14:155 [FREE Full text] [doi: 10.1186/1471-244X-14-155] [Medline: 24884888]
21. Naslund JA, Aschbrenner KA, Marsch LA, McHugo GJ, Bartels SJ. Crowdsourcing for conducting randomized trials of internet delivered interventions in people with serious mental illness: A systematic review. Contemp Clin Trials 2015 Sep;44:77-88 [FREE Full text] [doi: 10.1016/j.cct.2015.07.012] [Medline: 26188164]
22. Bold KW, Hanrahan TH, O'Malley SS, Fucito LM. Exploring the Utility of Web-Based Social Media Advertising to Recruit Adult Heavy-Drinking Smokers for Treatment. J Med Internet Res 2016;18(5):e107 [FREE Full text] [doi: 10.2196/jmir.5360] [Medline: 27194456]
23. Moreno MA, Vanderstoep A, Parks MR, Zimmerman FJ, Kurth A, Christakis DA. Reducing at-risk adolescents' display of risk behavior on a social networking web site: a randomized controlled pilot intervention trial. Arch Pediatr Adolesc Med 2009 Jan;163(1):35-41. [doi: 10.1001/archpediatrics.2008.502] [Medline: 19124701]
24. Tumblr. URL: https://www.tumblr.com/ [WebCite Cache ID 6yL4XY6Fn]
25. Tumblr. Blog Management URL: https://tumblr.zendesk.com/hc/en-us/sections/205853348-Blog-management [WebCite Cache ID 6yL4mbcph]
26. Bell C. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. JAMA 1994 Sep 14;272(10):828. [doi: 10.1001/jama.1994.03520100096046]
27. Random.org. URL: https://www.random.org/ [WebCite Cache ID 6yL4fhVk1]
28. Richardson LP, McCauley E, Grossman DC, McCarty CA, Richards J, Russo JE, et al. Evaluation of the Patient Health Questionnaire-9 Item for detecting major depression among adolescents. Pediatrics 2010 Dec;126(6):1117-1123 [FREE Full text] [doi: 10.1542/peds.2010-0852] [Medline: 21041282]
29. Egan KG, Koff RN, Moreno MA. College students' responses to mental health status updates on Facebook. Issues Ment Health Nurs 2013 Jan;34(1):46-51. [doi: 10.3109/01612840.2012.718044] [Medline: 23301569]
30. Eysenbach G, CONSORT-EHEALTH Group. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. J Med Internet Res 2011 Dec 31;13(4):e126 [FREE Full text] [doi: 10.2196/jmir.1923] [Medline: 22209829]

Abbreviations

DSM-IV: Diagnostic and Statistical Manual
PHQ-9: Patient Health Questionnaire-9

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Original Paper

Diabetes-Specific Formulae Versus Standard Formulae as Enteral Nutrition to Treat Hyperglycemia in Critically Ill Patients: Protocol for a Randomized Controlled Feasibility Trial

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Abstract

Background: During critical illness, hyperglycemia is prevalent and is associated with adverse outcomes. While treating hyperglycemia with insulin reduces morbidity and mortality, it increases glycemic variability and hypoglycemia risk, both of which have been associated with an increase in mortality. Therefore, other interventions which improve glycemic control, without these complications should be explored. Nutrition forms part of standard care, but the carbohydrate load of these formulations has the potential to exacerbate hyperglycemia. Specific diabetic-formulae with a lesser proportion of carbohydrate are available, and these formulae are postulated to limit glycemic excursions and reduce patients' requirements for exogenous insulin.

Objective: The primary outcome of this prospective, blinded, single center, randomized controlled trial is to determine whether a diabetes-specific formula reduces exogenous insulin administration. Key secondary outcomes include the feasibility of study processes as well as glycemic variability.

Methods: Critically ill patients will be eligible if insulin is administered whilst receiving exclusively liquid enteral nutrition. Participants will be randomized to receive a control formula, or a diabetes-specific, low glycemic index, low in carbohydrate study formula. Additionally, a third group of patients will receive a second diabetes-specific, low glycemic index study formula, as part of a sub-study to evaluate its effect on biomarkers. This intervention group (n=12) will form part of recruitment to a nested cohort study with blood and urine samples collected at randomization and 48 hours later for the first 12 participants in each group with a secondary objective of exploring the metabolic implications of a change in nutrition formula. Data on relevant medication and infusions, nutrition provision and glucose control will be collected to a maximum of 48 hours post randomization. Baseline patient characteristics and anthropometric measures will be recorded. A 28-day phone follow-up will explore weight and appetite changes as well as blood glucose control pre and post intensive care unit (ICU) discharge.

Results: Recruitment commenced in February 2015 with an estimated completion date for data collection by May 2018. Results are expected to be available late 2018.

Conclusions: This feasibility study of the effect of diabetes-specific formulae on the administration of insulin in critically ill patients and will inform the design of a larger, multi-center trial.

Trial Registration: Australian New Zealand Clinical Trial Registry (ANZCTR):12614000166673; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12614000166673 (Archived by WebCite at http://www.webcitation.org/6xs0phrVu)

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KEYWORDS

nutrition; enteral formula; tube formula; low carbohydrate; glucose; glycemic control

Introduction

Background

Nutrition and adequate glycemic control are key management strategies associated with positive outcomes in the critically ill patient [1-4]. These components of patient management are linked since nutrition is the principal exogenous source of carbohydrate (CHO) in ventilated, tube fed patients. Nutritional formulae have the capacity to influence blood glucose control during critical illness [5]. Despite this, only a small number of studies have investigated the effect of manipulating nutritional formulae on blood glucose control in an intensive care unit (ICU) setting [6-8].

Critically ill patients experience marked changes in CHO metabolism, which contributes to hyperglycemia [9-12]. These include increased gluconeogenesis, non-insulin dependent enhanced peripheral glucose uptake, and utilization, insulin resistance and inversion of plasma glucagon to insulin ratio [11]. Hyperglycemia is prevalent in the critically ill, with up to three- quarters of patients having raised blood glucose concentrations [13]. Acute hyperglycemia is associated with various adverse outcomes including increased infectious complications, prolonged intensive care unit (ICU) and hospital stay, and an increased risk of mortality [14-16].

Historically, it was accepted as dogma that hyperglycemia was an adaptive response to stress or injury which did not require intervention [17]. This doctrine was challenged when a single center trial reported increased survival in critically ill surgical patients randomized to intensive insulin therapy aimed at maintaining blood glucose concentrations between 4.4 and 6.1mmol/L [18]. The study was pivotal to implementing strict glucose management protocols globally [19]. However, in the landmark multi-center NICE-SUGAR trial, intensive insulin therapy was linked to increased mortality compared to standard care of aiming for a blood glucose level between 6 and 10mmol/L [20]. Subsequent work has shown that it is not only hyperglycemia but also insulin-induced hypoglycemia that is strongly associated with adverse outcomes [21]. The latter has been found to be independently associated with increased mortality [22-24]. Considering that exogenous insulin affects glycemic variability [25] and, is associated with a higher risk of mortality in critically ill patients [26-28], it is appropriate to consider strategies that may facilitate reduced insulin requirements.

It has been postulated that one intervention may be substituting a more traditional exogenous nutrition with one that has a lower glycemic load and is specifically designed for hyperglycemic individuals (eg, diabetes-specific formulae [DSF]) [7]. DSF with lower CHO content has been shown to attenuate hyperglycemia and decrease glycemic variability in the non-acute setting [29-32]. However, there are limited studies evaluating the use of nutritional therapies, specifically DSF, as adjuncts to treatments for hyperglycemia in the critically ill prior to this proposed study.

Mesejo, et al. compared a high protein DSF to a standard ICU high protein formula in 50 eligible patients [7]. The aim of this open-label study was to maintain blood glucose levels between 5.5 and 11.1mmol/L through the administration of insulin as required, which is a range that varies from current practice [16,24,25]. Obese patients were excluded from participating, which has implications for the applicability of these data to countries with a greater proportion of overweight or obese patients in their ICU [33]. The investigators reported that less exogenous insulin was required to maintain acceptable glycemic control using the DSF.

De Azevedo, et al. conducted a randomized controlled trial (RCT) to assess the safety and efficacy of a CHO restrictive approach compared to intensive insulin therapy [6]. Patients allocated to the nutritional therapy group received Glucerna Select (Abbott Nutrition) and subcutaneous insulin to maintain blood glucose concentrations below 10mmol/L. The control group received an alternative formula and an insulin infusion aiming for a blood glucose target of 4.4 and 6.7mmol/L. Importantly, participants allocated to the lower target experienced a substantial increase in the frequency of hypoglycemia. These studies provide a foundation for further work investigating the role of nutrition support in the management of hyperglycemia.

In summary, glycemic control and adequate nutrition provision for critically ill patients are accepted elements of best clinical practice [34]. Hyperglycemia occurs frequently in this group, due to stress induced glucose intolerance, pre-existing diabetes mellitus and glucocorticoid therapy [18]. Management of hyperglycemia often involves exogenous insulin. Therefore, a balance of risks must be considered between hyperglycemia and treatment-induced hypoglycemia or glycemic variability [35]. The observed increase in mortality associated with insulin-induced hypoglycemia provides a strong incentive to

explore managing hyperglycemia with a reduced dependency on insulin [20].

Study Objectives

The primary aim of this study is to determine whether the administration of a DSF reduces insulin administered to critically ill patients with hyperglycemia during enteral nutrition compared to a standard liquid nutritional formula over a 48-hour period. Secondary outcomes will also be explored including the feasibility of study processes to build toward a future multi-site RCT.

A nested cohort study will also be conducted to facilitate a greater understanding of the underlying pathophysiology in critically ill patients. It will specifically seek to determine whether altered CHO and advanced glycation end product (AGE) intake, is associated with oxidative stress markers in addition to acute and chronic inflammatory biomarkers.

Methods

Overview

This is a prospective, double-blinded, single-center, two-phased, randomized controlled feasibility trial. It has been developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2013) [36] and the Consolidated Standards for Reporting of Trials CONSORT Guidelines [37]. The trial complies with the Australian National Statement on Ethical Conduct in Human Research [38] and is currently being undertaken in the two adult ICUs at Mater Health in Brisbane, Australia. Both ICUs are run by the same intensive care specialists and protocols/ procedures are identical across sites but the ICUs differ in the health insurance status of their patients, which may be reflected in patient demographics and clinical case-mix [39].

This study has undergone full ethical review by the Mater Human Research Ethics Committee (Mater HREC; Approval HREC/14/MHS/55) and also has approval from The University of Queensland (UQ HREC; Approval 2014001353) due to the interventional nature of the research. It is also registered on the Australia New Zealand Clinical Trials Registry with registration number ANZCTR:12614000166673.

Study Participants

Participants will be recruited following admission to Mater Adults Hospital or Mater Private Hospital ICU. Eligibility is determined by the following inclusion criteria – a patient is receiving exclusive enteral nutrition and requires an insulin infusion. The majority of patients with two consecutive blood glucose levels > 10mmol/L will commence on an insulin infusion as per the units' glucose management protocol. The exclusion criteria for this study include patients under the age of 18, declined consent by the patient or legally authorized representative, or if the treating physician deems participation clinically inappropriate for any patient.

Senior ICU medical staff (consultant or advanced trainee), research assistant(s) or dietitian(s) will seek informed consent from the patient preferentially where possible, or from a legally authorized representative if required where patients lack competence. Should the latter occur, patients will be approached for their consent to be followed once alert and able. A modification to the inclusion and exclusion criteria, primarily related to lowering the threshold of insulin dose used to determine eligibility, was made after commencement of this study to optimize recruitment of appropriate patients to this feasibility study.

Baseline Data Collection

Patient demographics including anthropometric data such as weight, height and body mass index will be collected at baseline. Additionally; admission diagnosis, acute physiology, age and chronic health evaluation (APACHE) III score, date of admission to hospital and the ICU, requirement for ventilation support, pre-existing comorbidities including pre-admission diabetic status, use of steroids and insulin at baseline will be recorded. Investigators will adopt the Patient Generated Subjective Global Assessment grading system for steroid dose which is as follows (in prednisone equivalents): low dose <10mg; moderate dose ≥10mg and <30mg and high dose ≥30mg [40].

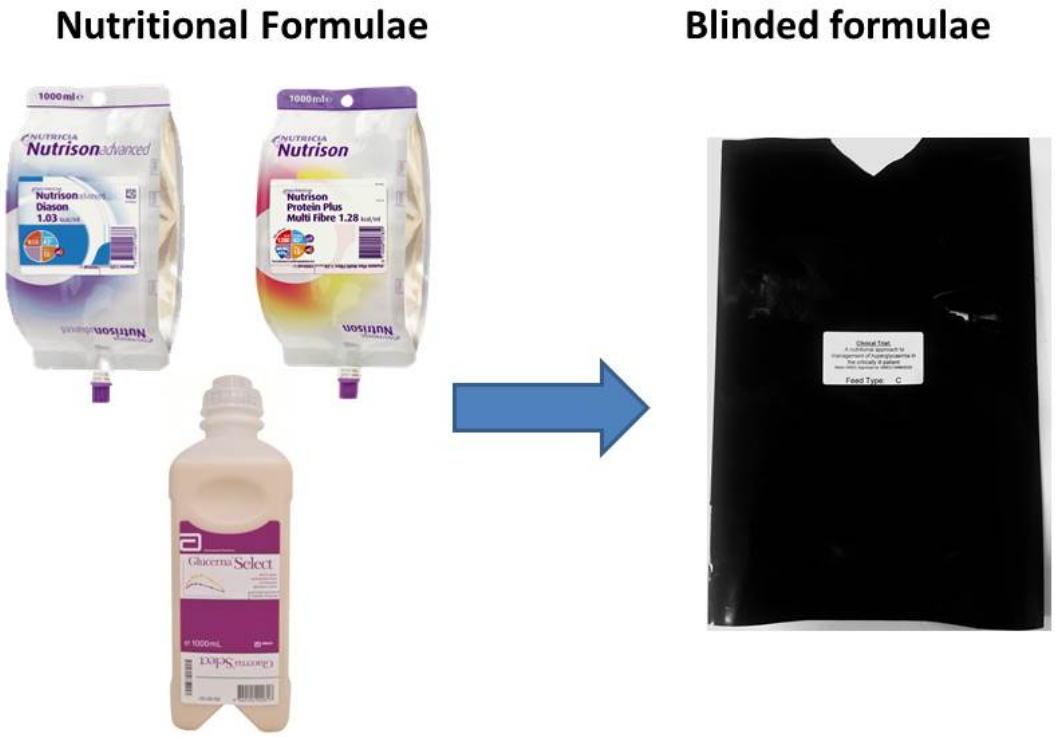
Randomization

Randomization between three arms will be performed initially 1:1:1 by a computer-generated sequence concealed within opaque sequentially numbered envelopes. Block randomization will be used to promote balanced patient numbers per arm. Envelopes will be prepared by a non-investigator and will include both the designated treatment arm (denoted as Feed A, Feed B or Feed C) as well as weight based recommended goal rates for administration of the formulae. Calculations of these prescribed rates are detailed in section 5. Once 12 patients have been recruited to the second intervention arm [Diason (Nutricia)], further recruitment to this treatment will cease, and the trial continues with the remaining interventional arm, Glucerna Select (Abbott Nutrition), and the control arm, Nutrison Protein Plus Multifibre (Nutricia).

Blinding

This study will attempt blinding of the form and appearance of the formula bags from patients and study investigators. Due to the different form factors of the formulae packaging - Glucerna Select (Abbott Nutrition) is retained in a hard-plastic bottle, while Nutricia formulae are available in soft satchels, formula containers will be placed within an opaque masking bag with an opening in the bottom to allow for connection to giving sets (Figure 1). Blinding of the formulae will be carried out by a non-investigator and the concealed bags marked with the study details and treatment arm. These will be placed into corresponding storage containers for nursing staff to access.

Figure 1. Blinding of formulae.



Study Design

Following consent participants will be randomized to either control, which is the unit's standard nutritional formula, Nutrison Protein Plus Multifibre (Nutricia), or the intervention, which is a low CHO, low glycemic index DSF, Glucerna Select (Abbott Nutrition). For the purpose of the nested cohort study, a second intervention arm using a different low glycemic index DSF will be used [Diason (Nutricia)]. Refer to Table 1 for a complete nutritional breakdown of these products. Varying advanced glycation end-product content of the differing DSF necessitates the third arm as part of this study. Randomization to the second intervention arm will be ceased once a complete set of blood and urine samples are available for a minimum of 10 participants in each group, with 12 patients set as the target recruitment to account for retracted/declined consent, incomplete sample sets in the instances of extubation or discharge to the ward prior to retrieval. These samples will be collected from all patients at randomization and 48 hours later. Once this has been achieved, randomization will revert to control [Nutrison Protein Plus Multifibre (Nutricia)] and intervention [Glucerna Select (Abbott Nutrition)] groups only. Collection of urine and blood samples for biomarker assay will also be discontinued at this point.

Each envelope will include detailed instructions for clinical staff regarding nutritional formula type labeled as Feed A, B or C and a protocolized delivery rate. The rate has been determined to minimize difference in protein provision in an effort to mitigate confounding factors based on studies identifying the protein as having a protective effect [2]. Once group allocation has occurred, participants will remain on their specified study formula as long as tube feeding continues in ICU or at the discretion of the treating clinician. If the participant were to withdraw from the study, clinical care would revert to usual practice such that the formula will be changed over to what would have otherwise been used had the trial not taken place (Nutrison Protein Plus® or Diason® - Nutricia). Due to the pragmatic nature of this study, all other aspects of care will occur as per routine clinical practice. That is, rates of feeding and treatment of intolerance to enteral nutrition will be as per the unit's standardized enteral feeding protocol.

Outcome Measures

Primary Outcome Measures

The primary outcome of this study is the difference in total amount of insulin per 24 hours administered to patients following commencement of the study formula until the 48-hour time period [7]. Pre-study insulin use will also be recorded from the patient charts for the 12 hours preceding randomization.

Secondary Outcome Measures

A range of secondary measures will be explored as outlined below.

Table 1. Nutritional composition of study feeds. RE: retinol equivalent. α-TE: alpha tocopherol equivalent. NE: niacin equivalent.

Formula Composition	Nutrison Protein Plus Multifibre (per 1000mL/per kcal/1000mL)	Glucerna Select (per 1000mL)	Diason (per 1000mL)
Energy (kJ)	5350/4180	4170	4350
Protein (g)	63/49 (20%E[a])	50 (20%E[a])	43 (17%E[a])
Carbohydrate (g)	141/110 (44%E[a])	75 (28.6%E[a])	113 (44%E[a])
Fat (g)	49/38 (34%E[a])	54 (48%E[a])	42 (36%E[a])
Saturated Fat(g)	13/10.2	4	5
Monounsaturated Fat(g)	27/21	Not specified	30
Polyunsaturated Fat(g)	9/7	Not specified	7
Fiber (g)	15/12	21	15
Micronutrients (Minerals and Vitamins)			
Sodium (mg)	1110/867	940	1000
Potassium (mg)	1680/1313	1300	1500
Calcium (mg)	900/703	700	800
Phosphorus (mg)	900/703	650	720
Magnesium (mg)	280/219	210	230
Chloride (mg)	800/625	1250	1250
Vitamin A (mcg RE)	1020/797	580	820
Vitamin D (mcg)	17/13	9.3	7
Vitamin E (mg α-TE)	16/13	19	25
Vitamin K (mcg)	66/52	100	53
Vitamin C (mg)	130/102	110	150
Thiamine (mg)	1.9/1.5	1.5	1.5
Riboflavin (mg)	2/1.6	1.8	1.6
Niacin (mg NE)	23/18	17	18
Vitamin B6 (mg)	2.1/1.6	2.1	1.7
Vitamin B12 (mcg)	2.6/2.0	3	5
Folic Acid (mcg)	330/258	250	380
Pantothenic Acid (mg)	6.6/5.2	7.5	5.3
Biotin (mcg)	50/39	40	40
Trace Elements			
Iron (mg)	20/15.5	13	16
Zinc (mg)	15/11.7	12	12
Manganese (mg)	4.1/3.2	3.5	3.3
Copper (mcg)	2250/1758	1400	1800
Iodine (mcg)	170/133	110	130
Molybdenum (mcg)	130/102	100	100
Selenium (mcg)	71/56	50	75
Chromium (mcg)	83/65	85	120
Osmolality (mOsmol/kg H_2O)	360	450	360

[a]Percentage of total calories; E: energy.

Scientific Measures

Many of the quantitative data measures will be collected within the first 48 hours post randomization including glycemic variability [41], tolerance of enteral nutrition and ability to meet nutritional requirements if there were no clinical contraindications [42]. Glycemic variability will be measured using routinely collected glucometer blood glucose readings which are taken between hourly and 4 hourly, depending on previous blood glucose and insulin rate. The mean and standard deviation of these values will be utilized to calculate the coefficient of variation which forms a surrogate marker of variability [43]. Tolerance of prescribed nutrition will be measured through establishing the incidence of diarrhea commencing post-randomization, the collection of gastric residual volumes [44,45] and potential subsequent use of prokinetics as well as ability to meet recommended goal rates of nutrition in the absence of any clinical contraindication. Goal rates are calculated based on protein requirements of 1.2-1.5g/kg body weight (BW) or adjusted ideal body weight (AIBW) and 25-30kcal/kg BW/AIBW [46]. Adjusted ideal body weight is to be used in the instance a patient has a body mass index greater than 25kg/m^2.

Process Measures Used to Assess Feasibility

Suitable patients, based on the inclusion and exclusion criteria, will be identified by clinical staff and subsequently eligibility and consent verified by the trial research staff. The eligibility criteria used in this study methodology will be assessed for sufficiency to ensure patients are appropriately screened, consented and recruited. Furthermore, data obtained from this study will be used to determine whether a pre-defined period of time expected on nutrition support is required as a component of the inclusion criteria. This will be assessed by the proportion of patients reaching the 48-hour mark on nutrition support. Recruitment rates will be determined by the number of eligible patients who consent in their own right or consent has been obtained from their legally authorized representative. Refusal of consent at either of these points will be recorded with reasons if provided. Based on predictive modelling of patient numbers for Mater Health ICUs to date it is expected that patients will be recruited over a two-and-a-half-year period. This can be extended for a further 6 months dependent upon recruitment rates. The pilot study intends to recruit a minimum of 54 patients.

Tertiary Outcome Measures

Length of ICU and hospital stay data as well as mortality outcomes will be investigated at 28 days through a follow up phone call in the instance a patient has been discharged from the hospital, or by access to medical records in the event of death before hospital discharge. Within scripted questions, data related to weight, weight history, diet and functional capacity pre and post ICU admission, will be collected, based on adaption from a validated malnutrition assessment tool (Patient-Generated Subjective Global Assessment) [47]. Blood glucose control including insulin/oral hypoglycemic use pre and post ICU admission will also be explored. The planned sub-study aims to analyze blood and urine samples to establish differences in acute and chronic inflammatory markers, cortisol, oxidative stress and anti-oxidant capacity between baseline and 48 hours later while on differing nutritional products [48-53]. Blood samples will be retrieved through existing arterial lines, centrifuged within 45 minutes and stored at negative eighty degrees Celsius until batch analysis. Urine samples will be taken and aliquots stored under the same conditions.

Statistical Considerations and Data Analysis

Sample Size

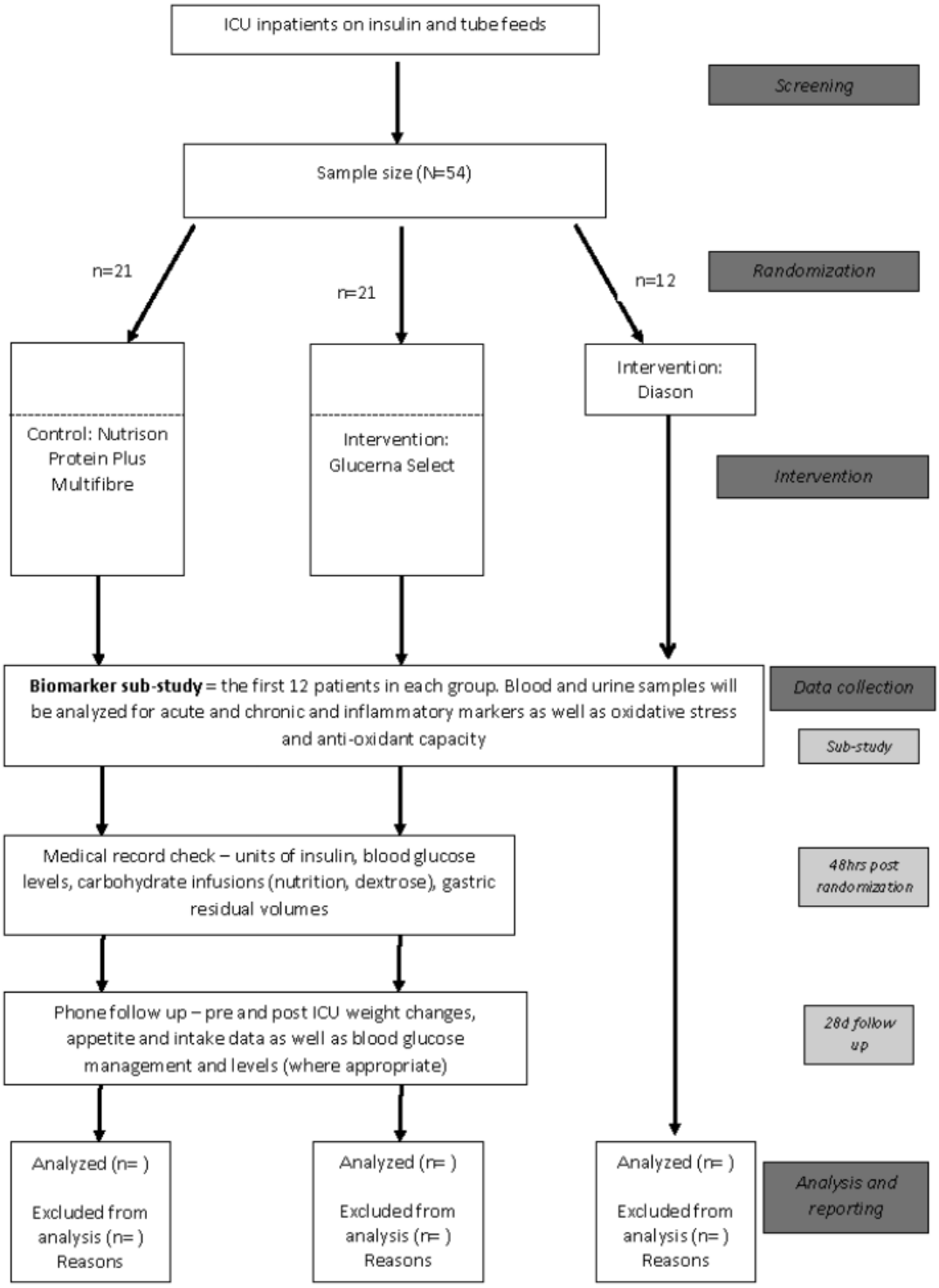
There is a minimum target recruitment of 54 patients for this pilot feasibility trial (refer to Figure 2). Two arms of this study will require nineteen patients each to detect a statistically significant difference (alpha 0.05) with a power of 80% based on a median difference of 21.5 units of insulin per day and a common standard deviation of 22.5 units. This has been modeled after the enteral formula study by Mesejo, et al. (2003). For the third arm, a sample size of 10 patients will be randomized for the nested cohort study investigating relevant biomarkers. A 10% buffer of two patients per arm, in the instance of retracted consent or earlier than expected cessation of nutrition, has been accounted for in the target sample size of 54 patients with 21 patients in the primary study (two arms) and 12 in the third arm forming part of the nested cohort study i.e. 2 additional patients per arm.

Data Analysis Plan

The analysis will be performed using R commander software or equivalent. Descriptive statistics (frequency, means and standard deviations, medians, interquartile ranges and full ranges) will be calculated for relevant demographic and baseline variables as well as for trial endpoints. Linear, logistic and time-to-event analyses will be performed using relevant data, returning point estimates of effect with associated 95% confidence intervals. Cross sectional analyses in cohort study data with equal follow-up time per subject will be analyzed with linear (for continuous outcomes) or logistic models (for categorical outcomes). Univariable time to event analyses will use Kaplan-Meier curves and differences will be tested using log rank tests.

Adjusted time-to-event analyses will use Cox proportional hazards models, with the assumed proportionality of the hazard subject to verification. Analyses using data collected over time within individual patients will be modeled using methods that account for patient-level clustering (generalized estimating equation methods or mixed linear or logistic models). In the event of non-negligible proportions of missing data, sensitivity analyses will present both the results of complete case analyses and multiple imputation analyses. Linear regression analyses will be used to analyze results from the nested cohort study to determine the contribution of AGE intake (total feed delivered accounting for formula content), AGE output (urine output accounting for AGE level in the urine) and insulin dose (area under the curve) on sRAGE levels.

Figure 2. Study flow diagram of recruitment, randomization and study conduct. Once consented patients will be randomized on a 1:1:1 ratio until there are 12 patients who have complete blood and urine sample sets from each group to form the biomarker sub-study. Thereafter the study will proceed with two arms as indicated. Finalized patient numbers have not been provided as this is a feasibility study.



Results

Recruitment to this study commenced in February 2015 and has an estimated completion date for data collection by May 2018. Results are expected to be available in late 2018.

Discussion

Expected Outcomes and Potential Significance

The findings of this feasibility study will be used to refine the design of a larger multi-center trial identifying protocol strengths and limitations and importantly returning preliminary study

effect estimates for sample size estimation. A more detailed budget will also be established using data from this initial study.

The pragmatic approach of negligible alterations to the pre-existing ICU policies and procedures regarding glucose management is intentional, aiming for this study to proceed with minimal disruption to standard ICU clinical work routines. If successful, a subsequent larger multi-center trial derived from the present proposed pilot study may clarify the efficacy of an intervention altering the composition of enteral nutrition in ICU patients as a standalone therapy for dysregulated glucose management in ICU patients.

Conclusion

Treatment of hyperglycemia, predominantly involving insulin therapy, remains controversial in the critically ill. While there is evidence to indicate diabetes specific enteral nutrition formulae are beneficial in reducing blood glucose levels in general patients with diabetes, at both a ward and community level, limited evidence supports this practice in the intensive care setting. At present, modification of the composition of enteral nutrition is rarely considered to be an efficacious mode of therapy for glucose control despite its significant contribution to total carbohydrate intake. This pilot study intends to investigate the feasibility and efficacy of diabetic specific nutrition formulations as an additional therapeutic measure in glucose management in the ICU.

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Authors' Contributions

RD, DS, AT, JF, JP, and AD contributed to study design. RD and DS drafted the manuscript. All authors critically reviewed the manuscript and agree to be accountable for the accuracy and integrity of the work. JP assisted with randomization and statistical input for this study.

Conflicts of Interest

None declared.

References

1. Dvir D, Cohen J, Singer P. Computerized energy balance and complications in critically ill patients: an observational study. Clin Nutr 2006 Feb;25(1):37-44. [doi: 10.1016/j.clnu.2005.10.010] [Medline: 16321459]
2. Wischmeyer PE. The evolution of nutrition in critical care: how much, how soon? Crit Care 2013;17 Suppl 1:S7 [FREE Full text] [doi: 10.1186/cc11505] [Medline: 23514524]
3. Al-Tarifi A, Abou-Shala N, Tamim HM, Rishu AH, Arabi YM. What is the optimal blood glucose target in critically ill patients? A nested cohort study. Ann Thorac Med 2011 Oct;6(4):207-211 [FREE Full text] [doi: 10.4103/1817-1737.84774] [Medline: 21977065]
4. Badawi O, Waite MD, Fuhrman SA, Zuckerman IH. Association between intensive care unit-acquired dysglycemia and in-hospital mortality. Crit Care Med 2012 Dec;40(12):3180-3188. [doi: 10.1097/CCM.0b013e3182656ae5] [Medline: 22971590]
5. Klein CJ, Stanek GS, Wiles CE. Overfeeding macronutrients to critically ill adults: metabolic complications. J Am Diet Assoc 1998 Jul;98(7):795-806. [doi: 10.1016/S0002-8223(98)00179-5] [Medline: 9664922]
6. de Azevedo JR, de Araujo LO, da Silva WS, de Azevedo RP. A carbohydrate-restrictive strategy is safer and as efficient as intensive insulin therapy in critically ill patients. J Crit Care 2010 Mar;25(1):84-89. [doi: 10.1016/j.jcrc.2008.10.011] [Medline: 19327317]
7. Mesejo A, Acosta JA, Ortega C, Vila J, Fernández M, Ferreres J, et al. Comparison of a high-protein disease-specific enteral formula with a high-protein enteral formula in hyperglycemic critically ill patients. Clin Nutr 2003 Jun;22(3):295-305. [Medline: 12765670]
8. Mesejo A, Montejo-González JC, Vaquerizo-Alonso C, Lobo-Tamer G, Zabarte-Martinez M, Herrero-Meseguer JI, et al. Diabetes-specific enteral nutrition formula in hyperglycemic, mechanically ventilated, critically ill patients: a prospective, open-label, blind-randomized, multicenter study. Crit Care 2015 Nov 09;19:390 [FREE Full text] [doi: 10.1186/s13054-015-1108-1] [Medline: 26549276]

9. Deane AM, Rayner CK, Keeshan A, Cvijanovic N, Marino Z, Nguyen NQ, et al. The effects of critical illness on intestinal glucose sensing, transporters, and absorption. Crit Care Med 2014 Jan;42(1):57-65. [doi: 10.1097/CCM.0b013e318298a8af] [Medline: 23963126]
10. Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. Am J Med 1995 Jan;98(1):75-84. [doi: 10.1016/S0002-9343(99)80083-7] [Medline: 7825623]
11. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. Crit Care Clin 2001 Jan;17(1):107-124. [Medline: 11219223]
12. van den Berghe G. How does blood glucose control with insulin save lives in intensive care? J Clin Invest 2004 Nov;114(9):1187-1195 [FREE Full text] [doi: 10.1172/JCI23506] [Medline: 15520847]
13. Plummer MP, Bellomo R, Cousins CE, Annink CE, Sundararajan K, Reddi BAJ, et al. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. Intensive Care Med 2014 Jul;40(7):973-980. [doi: 10.1007/s00134-014-3287-7] [Medline: 24760120]
14. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc 2004 Aug;79(8):992-1000. [doi: 10.4065/79.8.992] [Medline: 15301325]
15. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002 Mar;87(3):978-982. [doi: 10.1210/jcem.87.3.8341] [Medline: 11889147]
16. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med 2009 Dec;37(12):3001-3009 [FREE Full text] [doi: 10.1097/CCM.0b013e3181b083f7] [Medline: 19661802]
17. van Cromphaut SJ. Hyperglycaemia as part of the stress response: the underlying mechanisms. Best Pract Res Clin Anaesthesiol 2009 Dec;23(4):375-386. [Medline: 20108577]
18. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001 Nov 08;345(19):1359-1367. [doi: 10.1056/NEJMoa011300] [Medline: 11794168]
19. Niven DJ, Rubenfeld GD, Kramer AA, Stelfox HT. Effect of published scientific evidence on glycemic control in adult intensive care units. JAMA Intern Med 2015 May;175(5):801-809. [doi: 10.1001/jamainternmed.2015.0157] [Medline: 25775163]
20. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009 Mar 26;360(13):1283-1297. [doi: 10.1056/NEJMoa0810625] [Medline: 19318384]
21. Reddy P, Duggar B, Butterworth J. Blood glucose management in the patient undergoing cardiac surgery: A review. World J Cardiol 2014 Nov 26;6(11):1209-1217 [FREE Full text] [doi: 10.4330/wjc.v6.i11.1209] [Medline: 25429332]
22. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med 2007 Oct;35(10):2262-2267. [doi: 10.1097/01.CCM.0000282073.98414.4B] [Medline: 17717490]
23. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, et al. Hypoglycemia and outcome in critically ill patients. Mayo Clin Proc 2010 Mar;85(3):217-224 [FREE Full text] [doi: 10.4065/mcp.2009.0394] [Medline: 20176928]
24. Krinsley JS, Schultz MJ, Spronk PE, Harmsen RE, van BHF, van DSJP, et al. Mild hypoglycemia is independently associated with increased mortality in the critically ill. Crit Care 2011 Jul 25;15(4):R173 [FREE Full text] [doi: 10.1186/cc10322] [Medline: 21787410]
25. Hirsch IB. Sliding scale insulin--time to stop sliding. JAMA 2009 Jan 14;301(2):213-214. [doi: 10.1001/jama.2008.943] [Medline: 19141770]
26. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology 2006 Aug;105(2):244-252. [Medline: 16871057]
27. Krinsley JS. Glycemic variability and mortality in critically ill patients: the impact of diabetes. J Diabetes Sci Technol 2009 Nov 01;3(6):1292-1301 [FREE Full text] [doi: 10.1177/193229680900300609] [Medline: 20144383]
28. Lanspa MJ, Dickerson J, Morris AH, Orme JF, Holmen J, Hirshberg EL. Coefficient of glucose variation is independently associated with mortality in critically ill patients receiving intravenous insulin. Crit Care 2014 Apr 30;18(2):R86 [FREE Full text] [doi: 10.1186/cc13851] [Medline: 24886864]
29. Pohl M, Mayr P, Mertl-Roetzer M, Lauster F, Lerch M, Eriksen J, et al. Glycaemic control in type II diabetic tube-fed patients with a new enteral formula low in carbohydrates and high in monounsaturated fatty acids: a randomised controlled trial. Eur J Clin Nutr 2005 Nov;59(11):1221-1232. [doi: 10.1038/sj.ejcn.1602232] [Medline: 16077745]
30. Pohl M, Mayr P, Mertl-Roetzer M, Lauster F, Haslbeck M, Hipper B, et al. Glycemic control in patients with type 2 diabetes mellitus with a disease-specific enteral formula: stage II of a randomized, controlled multicenter trial. JPEN J Parenter Enteral Nutr 2009;33(1):37-49. [doi: 10.1177/0148607108324582] [Medline: 19011146]
31. Alish CJ, Garvey WT, Maki KC, Sacks GS, Hustead DS, Hegazi RA, et al. A diabetes-specific enteral formula improves glycemic variability in patients with type 2 diabetes. Diabetes Technol Ther 2010 Jun;12(6):419-425. [doi: 10.1089/dia.2009.0185] [Medline: 20470226]

32. Mori Y, Ohta T, Yokoyama J, Utsunomiya K. Effects of low-carbohydrate/high-monounsaturated fatty acid liquid diets on diurnal glucose variability and insulin dose in type 2 diabetes patients on tube feeding who require insulin therapy. Diabetes Technol Ther 2013 Sep;15(9):762-767. [doi: 10.1089/dia.2013.0066] [Medline: 23931715]
33. Dennis D, Trevenen M. Prevalence of obesity in an intensive care unit patient population. Intensive Crit Care Nurs 2016 Aug;35:52-56. [doi: 10.1016/j.iccn.2016.02.002] [Medline: 27210773]
34. Chase J, Shaw G, Le CA, Lonergan T, Willacy M, Wong X, et al. Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change. Crit Care 2008;12(2):R49 [FREE Full text] [doi: 10.1186/cc6868] [Medline: 18412978]
35. Hirsch I. Understanding low sugar from NICE-SUGAR. N Engl J Med 2012 Sep 20;367(12):1150-1152. [doi: 10.1056/NEJMe1208208] [Medline: 22992080]
36. Chan A, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586 [FREE Full text] [Medline: 23303884]
37. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001 Apr 18;285(15):1987-1991. [Medline: 11308435]
38. National Health and Medical Research Council, Australian Research Council, Australian Vice -Chancellors' Committee. National Statement on Ethical Conduct in Human Research (updated May 2015). 2007. URL: https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/e72_national_statement_may_2015_150514_a.pdf [accessed 2018-03-21] [WebCite Cache ID 6y5Il8abE]
39. Productivity Commission. Public and Private Hospitals - Research Report. URL: https://www.pc.gov.au/inquiries/completed/hospitals/report/hospitals-report.pdf [accessed 2018-03-21] [WebCite Cache ID 6y5J2jdzy]
40. Ottery F. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition 1996 Jan;12(1 Suppl):S15-S19. [Medline: 8850213]
41. Al-Dorzi H, Tamim H, Arabi Y. Glycaemic fluctuation predicts mortality in critically ill patients. Anaesth Intensive Care 2010 Jul;38(4):695-702 [FREE Full text] [Medline: 20715734]
42. Preiser JC, van Zanten ARH, Berger MM, Biolo G, Casaer MP, Doig GS, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care 2015 Jan 29;19:35 [FREE Full text] [doi: 10.1186/s13054-015-0737-8] [Medline: 25886997]
43. DeVries JH. Glucose variability: where it is important and how to measure it. Diabetes 2013 May;62(5):1405-1408 [FREE Full text] [doi: 10.2337/db12-1610] [Medline: 23613566]
44. Fruhwald S, Holzer P, Metzler H. Intestinal motility disturbances in intensive care patients pathogenesis and clinical impact. Intensive Care Med 2007 Jan;33(1):36-44. [doi: 10.1007/s00134-006-0452-7] [Medline: 17115132]
45. Desachy A, Clavel M, Vuagnat A, Normand S, Gissot V, François B. Initial efficacy and tolerability of early enteral nutrition with immediate or gradual introduction in intubated patients. Intensive Care Med 2008 Jun;34(6):1054-1059. [doi: 10.1007/s00134-007-0983-6] [Medline: 18210092]
46. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, Society of Critical Care Medicine, American Society for ParenteralEnteral Nutrition. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2016 Feb;40(2):159-211. [doi: 10.1177/0148607115621863] [Medline: 26773077]
47. Ferguson M. Patient-generated subjective global assessment. Oncology (Williston Park) 2003 Feb;17(2 Suppl 2):13-4; discussion 14 [FREE Full text] [Medline: 12632872]
48. Arabi YM, Dehbi M, Rishu AH, Baturcam E, Kahoul SH, Brits RJ, et al. sRAGE in diabetic and non-diabetic critically ill patients: effects of intensive insulin therapy. Crit Care 2011 Aug 26;15(4):R203 [FREE Full text] [doi: 10.1186/cc10420] [Medline: 21871056]
49. Cheng Y, Zhong J, Xiang Y, Zeng F, Cai D, Zhao L. Soluble receptor for advanced glycation end products in critically ill patients and its associations with other clinical markers and 28-day mortality. Clin Interv Aging 2014;9:1981-1986 [FREE Full text] [doi: 10.2147/CIA.S71130] [Medline: 25429209]
50. Uribarri J, Cai W, Ramdas M, Goodman S, Pyzik R, Chen X, et al. Restriction of advanced glycation end products improves insulin resistance in human type 2 diabetes: potential role of AGER1 and SIRT1. Diabetes Care 2011 Jul;34(7):1610-1616 [FREE Full text] [doi: 10.2337/dc11-0091] [Medline: 21709297]
51. Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc 2010 Jun;110(6):911-16.e12 [FREE Full text] [doi: 10.1016/j.jada.2010.03.018] [Medline: 20497781]
52. Leverve X. Hyperglycemia and oxidative stress: complex relationships with attractive prospects. Intensive Care Med 2003 Apr;29(4):511-514. [Medline: 12800829]
53. Galley HF. Oxidative stress and mitochondrial dysfunction in sepsis. Br J Anaesth 2011 Jul;107(1):57-64 [FREE Full text] [doi: 10.1093/bja/aer093] [Medline: 21596843]

Abbreviations

AIBW: adjusted ideal body weight
AGE: advanced glycation end product
APACHE: acute physiology, age and chronic health evaluation
BW: body weight
CHO: carbohydrate
DSF: diabetes-specific formula
HREC: Human Research Ethics Committee
ICU: intensive care unit
RCT: randomized controlled trial

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Protocol

Evaluating the Effectiveness of Text Messaging and Phone Call Reminders to Minimize No Show at Pediatric Outpatient Clinics in Pakistan: Protocol for a Mixed-Methods Study

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Abstract

Background: Missing health care appointments without canceling in advance results in a *no show*, a vacant appointment slot that cannot be offered to others. No show can be reduced by reminding patients about their appointment in advance. In this regard, mobile health (mHealth) strategy is to use text messaging (short message service, SMS), which is available on all cellular phones, including cheap low-end handsets. Nonattendance for appointments in health care results in wasted resources and disturbs the planned work schedules.

Objectives: The purpose of this study is to evaluate the efficacy of the current text messaging (SMS) and call-based reminder system and further explore how to improve the attendance at the pediatric outpatient clinics. The primary objectives are to (1) determine the efficacy of the current clinic appointment reminder service at pediatric outpatient clinics at Aga Khan University Hospital, (2) assess the mobile phone access and usage among caregivers visiting pediatrics consultant clinics, and (3) explore the perception and barriers of parents regarding the current clinic appointment reminder service at the pediatric outpatient clinics at Aga Khan University Hospital.

Methods: The study uses a mixed-method design that consists of 3 components: (1) retrospective study (component A) which aims to determine the efficacy of text messaging (SMS) and phone call–based reminder service on patient's clinic attendance during January to June 2017 (N=58,517); (2) quantitative (component B) in which a baseline survey will be conducted to assess the mobile phone access and usage among parents/caregivers of children visiting pediatrics consultant clinics (n=300); and (3) qualitative (component C) includes in-depth interviews and focus group discussion with parents/caregivers of children visiting the pediatric consultancy clinic and with health care providers and administrative staff. Main constructs will be to explore perceptions and barriers related to existing clinic appointment reminder service. Ethics approval has been obtained from the Ethical Review Committee, Aga Khan University, Pakistan (4770-Ped-ERC-17).

Results: Results will be disseminated to pediatric quality public health and mHealth communities through scientific meetings and through publications, nationally and internationally.

Conclusions: This study will provide insight regarding efficacy of using mHealth-based reminder services for patient's appointments in low- and middle-income countries setup. The finding of this study will be used to recommend further enhanced mHealth-based solutions to improve patient appointments and decrease no show.

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KEYWORDS

text messaging; mobile phone; mhealth; appointments and schedules; outpatient services; pediatrics

Introduction

Nonattendance for appointments in health care results in wasted resources and disturbs the planned work schedules. Missing health care appointments without canceling in advance results in a "no show," a vacant appointment slot that cannot be offered to others. In 2015, the UK Secretary of State for Health estimated that missed general practitioner and hospital appointments cost the National Health Service an estimated £912 million per year [1], and most appointments are missed due to simple reasons such as forgetfulness [2,3].

Mobile health, or mHealth, is defined as medical and public health practices supported by mobile devices. There has been a drastic increase in the usage of mobile phones with around 7 billion mobile phone subscribers globally, 89% of whom live in developing countries [4,5]. The portability of mobile phones makes this a flexible means of communication through which people can be contacted swiftly and can respond at their own convenience. The cost-effectiveness of this technology is reflected by the fact that even a substantial proportion of those living on less than US $1 per day have access to mobile phones and their SMS text messaging (short message service, SMS) [6]. A recent analysis assessing the socioeconomic impact of telecommunication in a developing country found that people living in rural areas benefit from telecommunication even more than those living in urban areas [6]. Mobile phones have thus changed the mode of communication among people worldwide and provide a great potential for engagement in care of patients with their health care provider [7]. SMS text messaging–based interventions have been quite effective in different programs, particularly in treatment adherence, nutrition programs, antenatal care attendance, and adherence for routine pediatric immunization [8]. In addition, available data show evidence for mobile phone–based SMS text messaging reminders to improve health care appointments' attendance and reduce "no shows" [9,10].

"No shows" can be reduced by engaging frequently with the patient, and reminding them about their appointment in advance. In this regard, one such health strategy is the use of SMS text messaging and phone calls. Various studies have shown how SMS text messaging reminders are effective for health care appointment attendance in different settings. A recent randomized controlled trial investigating the impact of SMS text messaging reminders on attendance rates at outpatient clinics in a psychiatric hospital found that receiving an SMS text messaging reminder independently reduces the chance of missing the next appointment by 50% [11]. Another study in a university setting in Switzerland found that both, SMS text messages and telephonic reminders were equally useful in reducing the number of missed appointments; however, SMS text messages were found to be more cost-effective [12]. SMS text messaging reminders at weekly intervals have also proven to be an efficacious method of improving adherence to antiretroviral therapy in patients with HIV [13]. Wang et al reported clinical attendance to be 72% versus 42% in those to whom SMS text messaging reminders were sent as compared with the control group with no intervention [14]. A meta-analysis and systematic review also found that SMS text messaging reminders serve as a simple and efficient method of improving health service delivery, as well as conferring health benefits to the patients who receive the reminders [15].

In recent years, mobile phone usage has boomed in Pakistan, with 140 million mobile phone subscribers and 237.58 billion person-to-person SMS text messages generated in 2011 [16,17]. A potential limitation to the use SMS text messaging based interventions is the level of literacy. However, there have been mixed inputs related to preference of phones calls as compared with SMS text messages in populations of low literacy and resource-constrained settings [18,19]. Mobile phone text messages in local languages or local language written in English in combination with phone call can further reduce this gap [20]. While one SMS text message has a maximum allowance of 160 characters only, this limit might help keep the messages short and easy to understand for a low literacy population [21].

To improve patient's clinic attendance and decrease "no show," the Aga Khan University outpatient clinic sends automated two-way SMS text messages or telephonic calls as appointment reminders. The cost of the SMS text messages and the phone calls is borne by the Aga Khan University Hospital (AKUH). However, the reply cost of the SMS text message is borne by the patient, in which an SMS text message is sent to the patient in English with a reply option of Yes or No for attending the clinic appointment. In 2016, around 70,000 appointments were given for pediatrics consultancy clinic, out of which 21,150 (30.21%) appointments resulted in "no show," despite the vigorous policies followed at the consultant clinic. Therefore, our aim is to evaluate the efficacy of the SMS text messaging and calls–based reminder system and further explore how to improve the attendance at the pediatric outpatient clinics at Aga Khan University Hospital, Karachi, Pakistan.

Methods

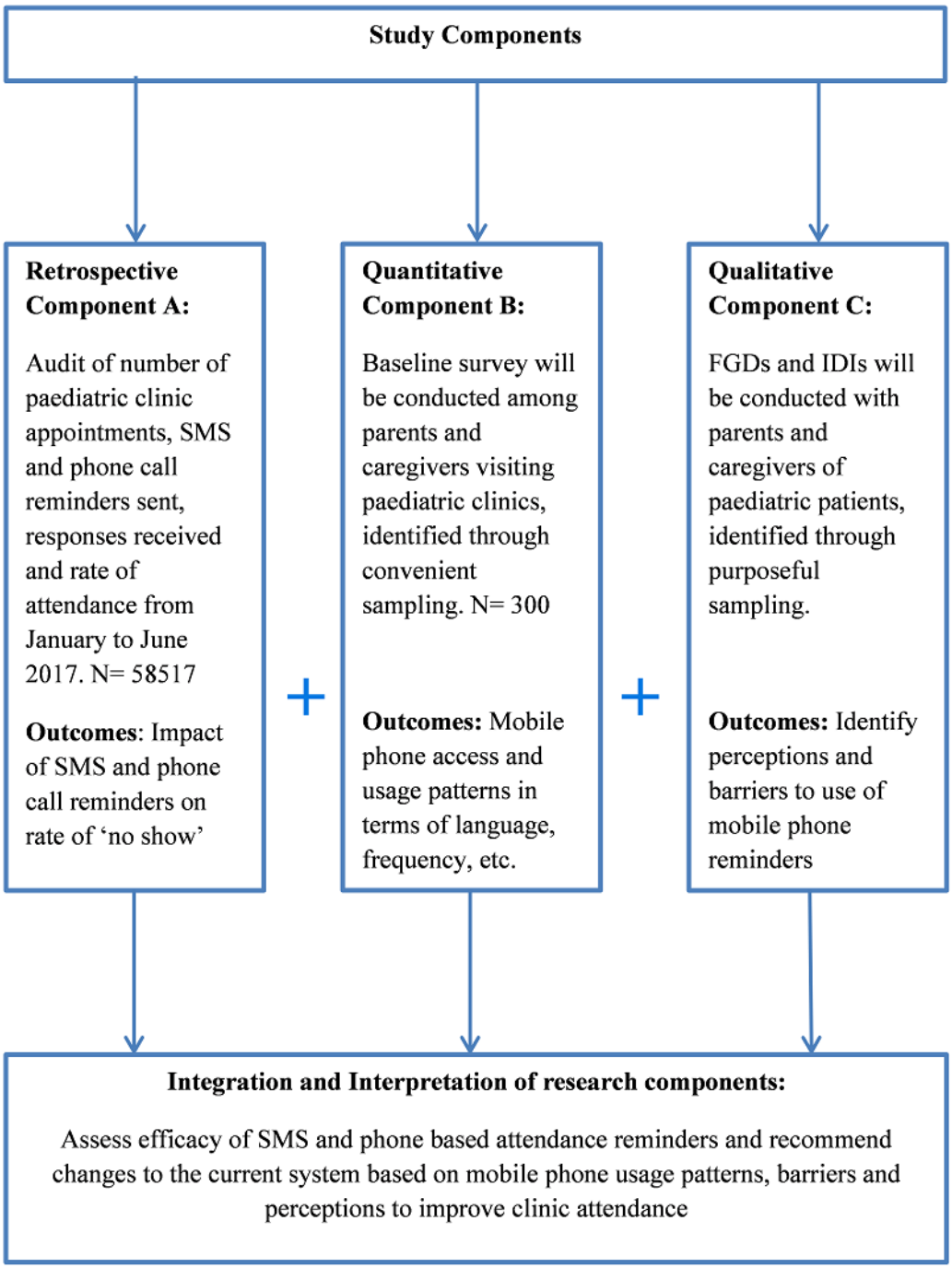
Study Setting

This study will be conducted at the pediatric consulting clinics of the Aga Khan University Hospital, Karachi, Pakistan. AKUH is a 560-bed tertiary care hospital that is accredited by the Joint Commission International (JCI) and is located in Karachi, the largest city of Pakistan with a population of over 14.9 million [22]. The Department of Pediatrics and Child health is one the biggest service providing facility across Pakistan with over 120-bed capacity. Along with general pediatrics, it provides a number of subspecialty services, including, Pediatric Neurology, Neonatology, Cardiology, Intensive care, Infectious diseases, Metabolic, Genetics, Endocrinology, Nephrology, Pediatric Surgery, and Rheumatology. The department provides extensive outpatient services in each of these specialties in the form of morning, afternoon, and evening clinics. Patient turnover last year (2016) in outpatient Pediatrics Clinics was 98,074.

Study Design

The study uses a mixed-method design which consists of 3 components (see Figure 1).

Figure 1. The mixed-method design of the study, which consists of three components: retrospective data, qualitative data, and quantitative data. SMS: short message service; FGD: focus group discussion; IDI: in-depth interview.



Retrospective Component A

A historical cohort data of pediatrics consultant clinic will be evaluated to determine the efficacy of phone-based reminders (SMS text messaging and call service) on patient's clinic attendance during period of January to June 2017 (N=58,517). Data regarding patient appointments, SMS text messaging and phone call reminders, and actual patient attendance at the clinic will be collected. The primary objective is to evaluate whether SMS text messages and phone calls can improve patients' appointment attendance at pediatric consulting clinic. The secondary objective is to compare the effect of SMS text messaging versus phone calls on improving clinic attendance.

The primary objective is to evaluate whether SMS text messages and phone calls can improve patients' appointment attendance at outpatient clinic. For reporting characteristics of patients attending outpatient clinics of AKUH, continuous variables will be expressed as mean and standard deviation or median and interquartile range as appropriate. Categorical variables will be presented as proportions. Chi-square test or Fisher exact test (if expected frequency of each cell is <5) will be employed to determine whether there is a statistical difference in outpatient

clinic attendance in group (1) receiving SMS text message, (2) receiving phone call, and (3) receiving both, SMS text message and phone call.

To study the association of patient-level characteristics with nonappearance at the clinic, a multivariable logistic regression will be applied to identify the predictors of patient's attendance taking into consideration the mode of reminders (SMS text messaging, phone call, or both) and other characteristics that can be adjusted in the model. All statistical tests will be performed on Statistical Package for Social Sciences for Windows version 19 (IBM Corporation). A *P* value of .05 or less will be considered significant.

Quantitative Component B

A baseline survey will be conducted among parents or care givers of children visiting the pediatric consultant clinic through convenient sampling strategy.

Study Design, Setting and Timeline

This will be a cross-sectional, questionnaire-based study. The study will be conducted at the outpatient pediatric consulting clinics of Aga Khan University Hospital, Karachi. Data will be collected prospectively in 2 months' time period.

Inclusion and Exclusion Criteria

Inclusion criteria comprised care givers visiting the Aga Khan University pediatric outpatient clinic for their children's appointment and the ability to provide informed consent. The exclusion criteria were as follows: caregivers of patients enrolled as inpatient, visiting pediatric oncology clinics, as it is located in a different location, and visiting outpatient clinic other than pediatrics outpatient clinic.

Sample Population and Size

Parents and caregivers of children visiting the pediatric consulting clinic at the AKUH after giving written, informed consent to be a part of this survey will be included as the study population.

Convenient sampling will be used to identify the 300 parents and caregivers who consented to be a part of this study. A formal sample size calculation is not done. Since there are no baseline data on mobile phone coverage among caregivers visiting a pediatric outpatient clinic in Pakistan, we followed the sample size strategy of similar baseline study conducted in Kenya [23].

Sampling Methodology

A baseline survey will be conducted among parents and caregivers of children visiting the pediatric consultant clinics. Consecutive convenience sampling will be used to recruit patients. In addition, the caregivers while waiting for the appointment will be approached by the study staff. A prepiloted, structured questionnaire will be used for data collection. Trained study staff will approach the parents/caregivers of patients who would be waiting for their appointment at the clinic and will ask for a dedicated time for the interview. The survey will comprise questions assessing patient demographics, mobile phone access and usage patterns, as well as acceptability and feasibility of an SMS text message and phone based system for appointment reminders.

Data Collection

Baseline data will be collected on a smart device. Business rules, consistence check, and skips will be incorporated, and important fields will be marked as must enter.

Data Analysis

Descriptive statistical analysis will be used and result will be expressed in frequencies and percentages. Further univariate analysis using chi-square tests and logistic regression model will be applied for dichotomous variables, whereas Mann Whitney *U* test and linear regression will be applied for continuous variables. *P* value of less than .05 will be considered as significant.

Component C (Qualitative)

The perceptions and barriers of parents/caregivers and health care providers about minimizing the "no show" in pediatric outpatient clinics at Aga Khan University Hospital, Karachi, and perceptions and barriers related to SMS text message and phone call–based clinic attendance reminders will be explored.

Study Design, Participants, Setting, and Duration

The proposed study is qualitative (exploratory) in nature. Data will be collected through interviews. Interviews will be conducted with the parents/caregivers visiting the pediatric consulting clinics and health care staff providing the services. We will explore the perceptions of the parents/caregivers visiting the pediatrics consulting clinics and health care providers. This component of the study will be completed in a period of 2 months that includes data collection, data analysis, and interpretation of data.

Inclusion and Exclusion Criteria

We will include parents/caregivers and health care providers visiting the Pediatric Consulting Clinics and health care staff providing the services. Parents/caregivers who refused to provide consent at the time of conducting the focus group discussions (FGDs) and in-depth interviews (IDIs) or caregivers who are visiting clinics other than Pediatrics Consultant Clinics will be excluded.

Data Collection Process and Tools

Data will be collected through conducting FGDs and IDIs, which will be conducted with parents/caregivers visiting the Pediatric Consulting Clinics and related health care providers (including consultants, paramedic, and management staff).

Data will be collected through semistructured interview guide; the focus of these interviews will be to explore perceptions of parents/caregivers and health care providers about the barriers related to "no show" and facilitators related to mobile phone–based SMS text message reminders, phone calls reminders, and the health care appointments attendance at the consultant clinics. FGDs and IDIs will be conducted with the parents/caregivers visiting Pediatric Consulting Clinics and health care providers at the Aga Khan University Hospital stadium road campus. Purposeful sampling will be used to identify parents and caregivers. In addition, sociodemographic information including participant's age, occupation, and education levels will be collected by using information sheet.

Data Analysis

All audio tapes will be transcribed by the research team as soon as possible after the data collection event. Qualitative data will be coded and analyzed through NVivo 11.4.1.1064 PRO for Windows (QSR International). Emerging themes and subthemes will be reported.

Ethical Considerations

The ethical approval for the study has been obtained from the Aga Khan University's Ethics Review Committee for approval before commencement of any study activities.

Patient Data Confidentiality

All the research documents will be held confidential and only shared with individuals who are directly involved in the study. Study questionnaire data in the tablets will be transferred on daily basis to the central database and the database will reside on a central computer managed by the study data manager. Participants' information will be given a study code, and data confidentiality will be maintained at all times. No personal identifiers will be used in any reports or publications of the study. For the qualitative component, unique ID will be allocated to the transcriptions and written notes. All the files will be kept in the password-protected computer.

Results

Results of this study will be disseminated to the government and private hospitals/clinics' pediatric and public health communities in Pakistan through scientific meetings and also submitted for publication in a peer-reviewed journal with an international public health audience. The results of this study may advise other organizations or countries to adopt this strategy to improve patient's attendance and decrease "no show" through sending automated two-way SMS text message along with the telephonic calls as appointment reminders.

Discussion

Strengths

The retrospective part of this data will capture massive data of Consulting Clinic Pediatrics, which will facilitate in generalizing our findings. To the best of our knowledge, this is one of the biggest SMS text messaging and phone call–based clinic appointment reminder database of a pediatric unit in low- and middle-income countries setup. Furthermore, the mixed-method design will help to explore mobile phone access and usage, as well as perceptions and barriers to improve the use of mobile phone reminders for clinic attendance.

Limitations

It is a single institution private sector study. Being a private sector hospital, we may not come across people with low socioeconomic background (cost perspective of nonresponders) having impact on mobile usage and ownership. There are chances of over- or underestimating a few barriers of nonresponding to the intervention.

Conflicts of Interest

None declared.

References

1. Zailinawati AH, Ng CJ, Nik-Sherina H. Why do patients with chronic illnesses fail to keep their appointments? A telephone interview. Asia Pac J Public Health 2006;18(1):10-15. [doi: 10.1177/10105395060180010301] [Medline: 16629433]
2. Martin SJ, Bassi S, Dunbar-Rees R. Commitments, norms and custard creams – a social influence approach to reducing did not attends (DNAs). J R Soc Med 2012;105(3):101-104. [doi: 10.1258/jrsm.2011.110250]
3. Cormick G, Kim NA, Rodgers A, Gibbons L, Buekens PM, Belizán JM, et al. Interest of pregnant women in the use of SMS (short message service) text messages for the improvement of perinatal and postnatal care. Reprod Health 2012 Aug 06;9:9 [FREE Full text] [doi: 10.1186/1742-4755-9-9] [Medline: 22866753]
4. Aranda-Jan CB, Mohutsiwa-Dibe N, Loukanova S. Systematic review on what works, what does not work and why of implementation of mobile health (mHealth) projects in Africa. BMC Public Health 2014 Feb 21;14:188 [FREE Full text] [doi: 10.1186/1471-2458-14-188] [Medline: 24555733]
5. International Telecommunication Union. 2012. Key statistical highlights: ITU data release June 2012 URL: https://www.itu.int/ITU-D/ict/statistics/material/pdf/2011%20Statistical%20highlights_June_2012.pdf [accessed 2018-03-24] [WebCite Cache ID 6y9MecB7y]
6. Malik S, Chaudhry I, Abbas Q. Socio-economic impact of cellular phones growth in Pakistan: an empirical analysis. PJSS 2009;29(1):23-37 [FREE Full text]
7. World Health Organization. Basic Newborn Resuscitation: a practical guide. Geneva: World Health Organization; 1997.
8. Déglise C, Suggs LS, Odermatt P. SMS for disease control in developing countries: a systematic review of mobile health applications. J Telemed Telecare 2012 Jul;18(5):273-281. [doi: 10.1258/jtt.2012.110810] [Medline: 22826375]
9. Gurol-Urganci I, de Jongh T, Vodopivec-Jamsek V, Atun R, Car J. Mobile phone messaging reminders for attendance at healthcare appointments. Cochrane Database Syst Rev 2013 Dec 05(12):CD007458. [doi: 10.1002/14651858.CD007458.pub3] [Medline: 24310741]

10. Siddiqui M, Islam MY, Mufti B, Khan N, Farooq M, Muhammad M, et al. Assessing acceptability of hypertensive/diabetic patients towards mobile health based behavioral interventions in Pakistan: A pilot study. Int J Med Inform 2015 Nov;84(11):950-955. [doi: 10.1016/j.ijmedinf.2015.08.009] [Medline: 26321485]
11. Thomas IF, Lawani AO, James BO. Effect of short message service reminders on clinic attendance among outpatients with psychosis at a psychiatric hospital in Nigeria. Psychiatr Serv 2017 Jan 01;68(1):75-80. [doi: 10.1176/appi.ps.201500514] [Medline: 27582239]
12. Junod PN, Dao M, Righini N, Humair J, Broers B, Narring F, et al. Text-messaging versus telephone reminders to reduce missed appointments in an academic primary care clinic: a randomized controlled trial. BMC Health Serv Res 2013 Apr 04;13:125 [FREE Full text] [doi: 10.1186/1472-6963-13-125] [Medline: 23557331]
13. Lester R, Ritvo P, Mills E, Kariri A, Karanja S, Chung M, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet 2010 Nov 27;376(9755):1838-1845. [doi: 10.1016/S0140-6736(10)61997-6] [Medline: 21071074]
14. Wang K, Wang C, Xi L, Zhang Y, Ouyang Y, Lou H, et al. A randomized controlled trial to assess adherence to allergic rhinitis treatment following a daily short message service (SMS) via the mobile phone. Int Arch Allergy Immunol 2014;163(1):51-58. [doi: 10.1159/000356317] [Medline: 24248037]
15. Guy R, Hocking J, Wand H, Stott S, Ali H, Kaldor J. How effective are short message service reminders at increasing clinic attendance? A meta-analysis and systematic review. Health Serv Res 2012 Apr;47(2):614-632 [FREE Full text] [doi: 10.1111/j.1475-6773.2011.01342.x] [Medline: 22091980]
16. PTA. Proliferation of SMS & MMS in Pakistan with emphasis on Premium Rate SMS services SMS/MMS Report 2012 URL: http://www.pta.gov.pk/media/sms_mms_report_130313_1.pdf [accessed 2018-02-28] [WebCite Cache ID 6xZM6lsXG]
17. Kazi AM, Jafri LA. The use of mobile phones in polio eradication. Bull World Health Organ 2016 Feb 01;94(2):153-154 [FREE Full text] [doi: 10.2471/BLT.15.163683] [Medline: 26908965]
18. Cormick G, Kim NA, Rodgers A, Gibbons L, Buekens PM, Belizán JM, et al. Interest of pregnant women in the use of SMS (short message service) text messages for the improvement of perinatal and postnatal care. Reprod Health 2012 Aug 06;9:9 [FREE Full text] [doi: 10.1186/1742-4755-9-9] [Medline: 22866753]
19. Wesolowski A, Eagle N, Noor AM, Snow RW, Buckee CO. Heterogeneous mobile phone ownership and usage patterns in Kenya. PLoS One 2012;7(4):e35319 [FREE Full text] [doi: 10.1371/journal.pone.0035319] [Medline: 22558140]
20. Stockwell MS, Fiks AG. Utilizing health information technology to improve vaccine communication and coverage. Hum Vaccin Immunother 2013 Aug;9(8):1802-1811 [FREE Full text] [doi: 10.4161/hv.25031] [Medline: 23807361]
21. Kazi AM. The role of mobile phone-based interventions to improve routine childhood immunisation coverage. Lancet Glob Health 2017 Apr;5(4):e377-e378 [FREE Full text] [doi: 10.1016/S2214-109X(17)30088-8] [Medline: 28288737]
22. Government of Pakistan, Statistics Division. 2017. Provisional summary results of 6th population and housing census-2017 URL: http://www.statistics.gov.pk/assets/publications/Population_Results.pdf [accessed 2018-03-24] [WebCite Cache ID 6y9NbeSl2]
23. Kazi A, Carmichael J, Hapanna G, Wangoo PG, Karanja S, Wanyama D, et al. Assessing mobile phone access and perceptions for texting-based mHealth interventions among expectant mothers and child caregivers in remote regions of northern Kenya: a survey-based descriptive study. JMIR Public Health Surveill 2017;3(1):e5. [doi: 10.2196/publichealth.5386]

Abbreviations

AKUH: Aga Khan University Hospital
FGD: focus group discussion
IDI: in-depth interview
mHealth: mobile health
SMS: short message service

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Protocol

An mHealth App for Decision-Making Support in Wound Dressing Selection (WounDS): Protocol for a User-Centered Feasibility Study

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Abstract

Background: Primary care health professionals, especially family physicians, see a variety of wounds, and yet—despite the frequency of providing wound care—many family physicians do not feel confident in wound care management. This is partly due to a lack of formal wound education in Family Medicine programs. While there are numerous electronic wound care resources available in the UK and North America, none were identified that address the specific need in supporting clinical decision-making in wound dressing selection. At the same time, healthcare providers are increasingly using technology in personal and professional contexts, and a logical extension is to use technology for knowledge translation strategies.

Objective: This work developed a prototype mobile health software application named *WounDS*, designed to support clinical decision-making in selecting wound dressings. This article presents the development and evaluation plan for the *WounDS* app.

Methods: *WounDS* has been developed on the iOS platform. The primary specification included ease of use, in that one of the primary influences in user adoption would be the ability to receive a wound dressing recommendation in under 30 seconds and under 5 taps on the screen. The *WounDS* app guides users through a series of binary decisions for assessing the wound and provides a wound dressing recommendation. The selection algorithm is based in best practices using the Wound Bed Preparation Paradigm.

Results: Current work is underway to examine the implementation needs for *WounDS* to be most effectively utilized and to pilot test its feasibility and use in clinical care. Data will be collected through user trials, focus groups, and user metadata will be collected within the app. Optimizing these preconditions will enable a subsequent phase of study to determine effects on clinical decision-making and clinical outcomes.

Conclusions: *WounDS* is designed for knowledge translation, use of technology in clinical decision-making, and continuity of care. The benefits of *WounDS* include the potential to improve healthcare providers' competency in wound management and to improve wound healing through better alignment with evidence-based best practices in wound dressing selection, consistency in care from primary to community care, and subsequent downstream impacts in quality of life for patients.

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KEYWORDS

mHealth; wounds; wound dressing; wound management

Introduction

This work developed a mobile health (mHealth) software application on the iOS platform, designed as a guide for selecting wound dressings that are maximally aligned with the patient's wound assessment, care plan, and best practice in wound healing—in short, a *Woun*d *D*ressing *S*election app (*WounDS*, or "the app"). *WounDS*, designed for iPhone and iPad, is currently a functional, stand-alone prototype app. It is designed to support (but not replace) clinical decision-making in wound dressing selections, particularly for healthcare providers with little education or experience in wound management. Current work is focused on evaluation of the app's use, and this article presents the development and evaluation plan for the *WounDS* app.

Primary care health professionals, especially family physicians, see a variety of wounds in their practices. These include skin abrasions, burns, lacerations secondary to trauma, leg ulcers, diabetic foot ulcers, and less commonly, pressure injuries. Family physicians can best serve their patients if they have access to current and comprehensive knowledge and skills in wound management [1-6]. Yet, family physicians do not feel confident in wound care management [7]. Currently, undergraduate medical students in Manitoba, Canada receive no formal wound care education in medical school. Family Medicine residents preparing to go into practice as family physicians receive only limited formal education on wound care, which includes up to 3 hours of content on differentiating wounds, causes of wounds, wound healing principles, and choosing the appropriate dressing for various types of wounds. The accreditation standards used by the College of Family Physicians do not include wound care education training as a curriculum requirement for Family Medicine residents [8].

An Ontario study (n=214) reported that only 16% (34/214) of family physicians felt confident in their ability to manage leg ulcers, 61% (130/214) did not feel they knew enough about wound care products, and more than 50% (107/214) were unaware of the use of compression as an effective treatment for venous ulcers [7]. Further, a national roundtable reported that appropriate dressing selection and use were identified for only 20% of wounds [9]. These findings supported the need for better guidance in wound management and dressing selection for decreased healing time, returning patients to optimal functioning sooner, and improved quality of life.

Little published data exists in Canada on the exact cost of wound care, although estimates are that wound care amounts to Can $3.9 billion per year in costs to the Canadian health care system [9]. An Ontario study estimates that lower limb ulcers alone cost Can $100 million per year [7]. More than 80% of chronic wounds such as leg ulcers occur in the community, and family physicians working in primary care are often patients' first contact for treatment. Chronic wounds are expected to become an increased economic burden given an aging population and co-morbid conditions such as diabetes and obesity [5,7]. The cost of wound care includes dressings and other materials, clinician time and hospitalization. Optimal wound management, from treatment to healing (if possible) requires careful assessment of the cause of the wound, person-centered concerns such as pain, and each wound's unique characteristics. When an advanced wound care dressing with a longer wear time is selected, the benefits outweigh the initial dressing costs, by having fewer dressing changes, maintaining an even temperature, reducing the exposure to contaminants, and reducing labor costs [10,11].

In healthcare delivery in Manitoba, Canada, wound care and wound management decisions may be made by both nurses and physicians, with nurses providing care in home care settings as well as clinics. When Family Medicine residents provide wound care in teaching clinics, they usually consult with on-site nurses with wound care skill sets to assist them in determining appropriate wound dressings for patients presenting to the clinic. Yet, not all teaching sites used in the Family Medicine residency program employ nurses; thus, wound care is then determined by the Family Medicine resident and the supervising physicians, who also often have limited wound dressing selection knowledge. In such cases, the wound care products may be selected on the basis of a practitioner's familiarity, preference and ease of use. Making informed, individualized wound dressing decisions based on best practices occurs less frequently despite resources and evidence-informed tools being available. On a practical level, it can be overwhelming for Family Medicine residents to evaluate the categories of wound care products for use, resulting in the default choices to the most familiar products.

There are numerous wound care resources available in the UK and North America, but we are not aware of any that address this specific need in supporting clinical decision-making in wound dressing selection. Currently, posters and other wound dressing product information (often from proprietary sources) exist to help guide in dressing selections. However, practitioners have indicated that adding these resources to busy units is a form of white noise. Concomitantly, there is an increasing emphasis on electronic communication in wound management to improve the efficiency of care, the patient and caregiver experience, and ultimately the clinical outcomes. Electronic Health (eHealth) and mHealth initiatives in wound care are conjectured to assist in prevention and treatment by facilitating different types of healthcare interventions, changing user behaviors, enhancing communication between patients and providers, and providing education [12-15].

Healthcare providers are increasingly using technology in personal and professional contexts, and a logical extension is to use technology for knowledge translation strategies, rather than continuing to rely on strategies that have not led to proven outcomes. There are several wound assessment apps on the market, including SmartWoundCare [16] (mobile app for handheld devices), How2Trak [17] (wound care software on a web-based interface), WoundRounds [18] (mobile app for handheld devices), and relative newcomers WoundMAP pump, Ulcercare, and Wound Mender in various stages of development [19]. These apps are all focused on assessing and documenting the wound, and none incorporate wound dressing selections. In areas outside of wound care, mobile consumer devices are increasingly capable of meaningful applications in mHealth, such as apps that range from allowing users to track diet and

fitness, health condition monitoring (eg, diabetes [20]; arthritis [21]), and the use of mobile devices to replace paper records and share information between healthcare providers (eg, [22-24]).

Within this context, *WounDS* was developed for primary care family physicians as well as other healthcare providers (eg, registered nurses (RNs), nurse practitioners, clinical nurse specialists and MDs) delivering wound care in tertiary- and long-term care facilities as well as community settings. *WounDS* is designed to support (but not replace) clinical decision-making by serving as a tool to update best practices in wound care. A healthcare provider may rely on it more heavily in the early stages of their training and practice, and over time they may use it to confirm decisions they reach based on repeated exposure to wounds and their concomitant accumulated knowledge and experience. For Family Medicine residents with little wound care education, *WounDS* can assist in developing competency in sound wound dressing selection over time, particularly in the absence of a nurse's or staff physician's expertise.

Methods

WounDS was developed to a functional prototype app on the iOS platform by an interdisciplinary development team with expertise in academic research and clinical practice in fields such as Nursing, Occupational Therapy, Wound Care, Computer Engineering, Biomedical Materials, and Family Medicine Research.

The *WounDS* app was designed using Xcode, Apple Inc's integrated development environment (IDE) for developing software for macOS, iOS, watchOS, and tvOS. The *WounDS* app uses Apple's Cocoa Touch software framework, which is the application programming interface (API) used for the iOS, watchOS, and tvOS operating systems. The language used to develop the *WounDS* app is Swift 3.0, the most current version of Apple's alternative to the Objective-C language. Swift 3.0 is designed to work cohesively with Apple's Cocoa Touch software framework and is included in Xcode. The source code is available from the authors and will be made available in GitHub.

WounDS was designed for task-technology fit, which asserts that a technology will be used and will have a positive impact on performance if its capabilities match the tasks to be performed. A number of factors contribute to task-technology fit. In *WounDS*, the quality and reliability of the app are facilitated by maintaining a small and simple software architecture and an uncomplicated user interface. The app is stored on the user's mobile device (phone or tablet) and is not server-based. This facilitates its accessibility and self-directed authorizations by the user. To support timeliness, updates to the app will be based on user reviews and feedbacks, as well as product changes in wound dressings used by the regional health authority. These updates will be available in the same way as app updates are available through the iOS App Store.

A significant focus has been placed on ease of use as a factor of task-technology fit. The conjecture is that one of the primary influences in user adoption would be the ability to receive a wound dressing recommendation in under 30 seconds and under 5 taps on the screen. This reflects a "lazy user model" in which a user will select a solution (eg, *WounDS*) from within a set of solutions (eg, *WounDS*, internet look-up, posters on the wall, etc) based on the amount of effort required. These targets (30 seconds and 5 taps) reflect what Family Medicine residents have reported for a similar app that provides decision support for pre-operative checklists in the regional health authority, relative to its appeal and likelihood of use in clinical practice. In general website navigation, the "3-click rule" assumes that users will become frustrated if they cannot find desired information in 3 clicks. In this work, 5 clicks (taps) is considered acceptable given the distinct difference between general internet browsing with no certainty that the desired information will be located, in contrast to the use of a tool in clinical practice for specific purposes and with certainty that a response will be available.

The *WounDS* app guides users through a series of binary decisions for assessing the wound, to limit the wound dressing options to those that are best aligned with the individual care plan, including both generic and proprietary options. Furthermore, it limits the options to those with which a health region may have purchasing contracts. Using preset options related to the health region's purchasing contracts is another factor of task-technology fit. The app is not associated with any patient per se, but rather serves as a deductive selection tool, akin to finding the correct recipe for something. *WounDS* will consider financial efficiencies when making suggestions, eg, less expensive dressings changed daily vs more expensive dressings that can stay on for multiple days. Integrated support features also increase the functionality and ultimate applicability of the *WounDS* app to others. These support features include help screens, glossary, links to external resources, and key salient content regarding wound management and the principles of wound dressing selection.

The selection algorithm is based on best practices using the Wound Bed Preparation Paradigm [11], as part of an overall patient-centered wound care approach which aims to treat the cause, treat the wound, and treat the patient's concerns (eg, pain). The healthcare provider considers wound type and status, size and colour, location, duration, skin and other tissue characteristics, moisture balance, infection and inflammation, and wound edges as the complex determinants for an individualized care plan which includes wound dressings. For example, in the area of tissue alone, practitioners assess the epithelium, granulation, exposed tissues (bone, muscle, or tendon), eschar or slough, and infection.

Other assessments towards wound dressing selection include wound temperature, moisture balance, exudate, and pain associated with a wound. There are numerous types of wound dressings, including but not limited to, acrylic, antimicrobial, foam, hydrocolloid, hydrofibre, hydrogel, and textile. This context demonstrates that there are dozens of possible interactions between dozens of parameters associated with the wound and with a particular dressing, and the *WounDS* app supports clinical decision-making towards an optimum selection for the individual's care plan.

Figures 1 and 2 display two representative pathways through the *WounDS* app. A key feature is that the user should be able to receive a recommendation in less than 30 seconds or 5 taps, for the app to be useful in day to day practice.

Figure 1. Sample user response pathway: infected - systemic - (okay) - drainage - significant - recommendation.

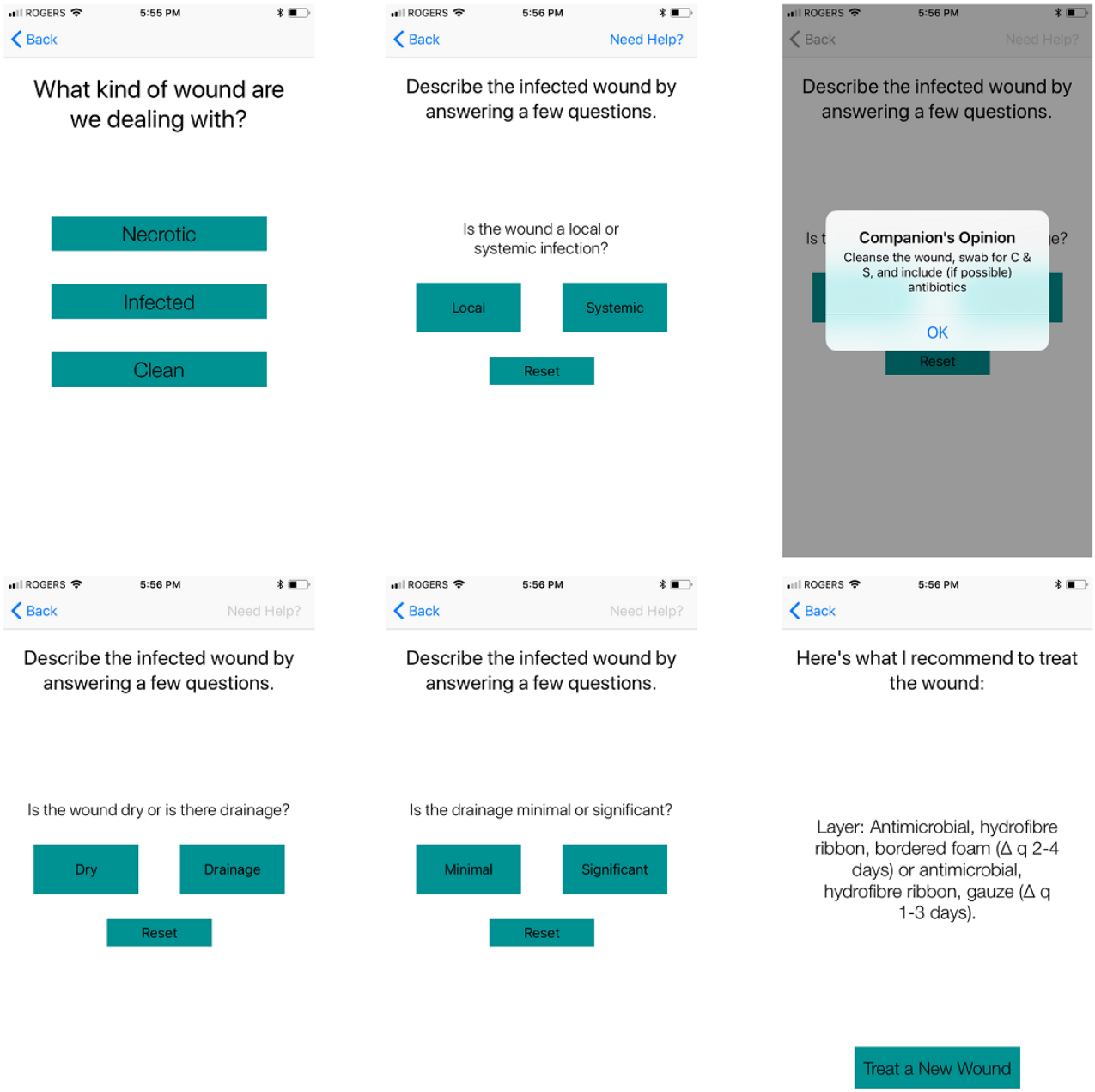
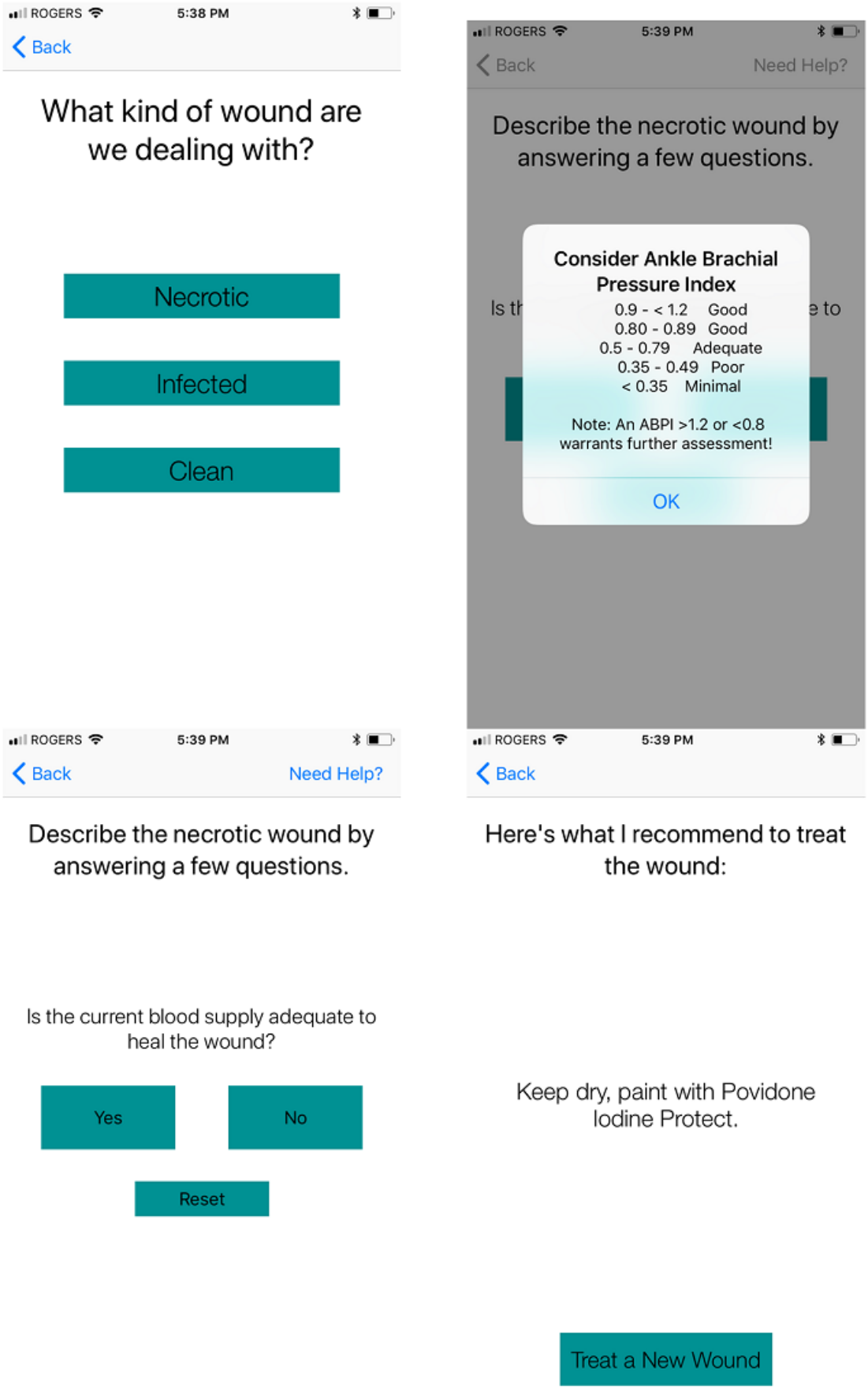


Figure 2. Sample user response pathway: necrotic - (okay) - no - recommendation.



Results

Currently, a study is underway to examine the implementation needs for *WounDS* to be most effectively utilized and to pilot test its feasibility and use in clinical care. Optimizing these pre-conditions will enable a subsequent phase of study to determine effects on clinical decision-making and clinical outcomes. Upon receipt of research ethics approval from the collaborating institutions, two phases will be undertaken.

In Phase 1, a qualitative usability study, design feedback from a focus group with Family Medicine residents and preceptors, including family physicians, nurses and nurse practitioners will be collected. Four case studies will serve as a basis upon which to examine the use of *WounDS* in a simulated context. The focus group participants will provide feedback to refine the app design, specifically advising on content, look-and-feel, and app functionality. They will also contribute to the design of an app support kit to accompany the use of *WounDS* and provide background information for the decision-making algorithm of *WounDS*. The Family Medicine residents are in an ideal position to provide feedback as they are generally high users of apps (thus providing a good comparison of *WounDS* usability and user interface to other apps). They will be asked to share their challenges in dressing selection following initial wound assessment. The preceptors are very involved in educating residents about wound management and will have valuable insights and suggestions for use among novice physicians as well as their own perspectives as a more experienced cohort of clinicians.

Phase 2 will involve implementing *WounDS* among a sample of 15 users (Family Medicine residents and home care nurses)—a sample size consistent with similarly designed studies [25-27] and appropriate for a purposeful sampling approach with the population of target users at the participating institutions. The users will be provided with the app support kit as part of their training for wound assessment and management and an introductory face-to-face training session. Users will be asked to trial *WounDS* in practice for up to four months. This timeframe was chosen to generate data on clinical utility quickly enough to capitalize on initial impressions and make changes. At the same time, the timeframe acknowledges that while home care nurses may see wounds on a near-daily basis, Family Medicine residents may not see wounds consistently or frequently, and a four-month timeframe will provide the opportunity for them to use the tool repeatedly. It is noteworthy that the infrequent presentation of wounds is exactly why the app is anticipated to be useful to Family Medicine residents, in that it supports information they do not use on a daily basis.

Following use in practice, the users will be invited to a focus group to determine whether and how the app was integrated into practice workflow, ease of use, and efficiency in helping to make best practice wound management decisions for various wound types. Members of the research team will be able to directly observe Family Medicine residents and document their use of *WounDS* in direct patient care. Their clinical expertise and in-depth familiarity with the clinical context will enable a rich textual narrative regarding the influence of implementation factors such as fit, how the app was used in practice, and its ability to be integrated into clinical flow.

In addition, *WounDS* will be designed to collect and store metadata from app use to gain a better understanding of users' navigation pathways and movement through the algorithm, number of times users logged into the app, and what information was provided. Using a unique identifier, we will be able to compare the app-facilitated dressing selection to actual dressing selection as indicated in the patient's medical record. This process of linking selections in the pilot phase will determine its research effectiveness for the larger subsequent study assessing service and client outcomes.

Both phases will provide an opportunity to address implementation issues as well as inform data collection for a subsequent clinical trial to examine patient outcomes.

Discussion

WounDS is designed for knowledge translation, use of technology in clinical decision-making, and continuity of care. The benefits of *WounDS* include the potential to improve wound healing through better alignment with evidence-based best practices in wound dressing selection, consistency in care from primary to community care, and subsequent downstream impacts in quality of life for patients. Furthermore, *WounDS* can enhance healthcare providers' capacity to deliver wound care and can enhance wound care knowledge transfer among healthcare providers and can potentially lead to cost savings for the health region. Current progress has resulted in a functioning prototype and an evaluation study in progress. It is noteworthy that Family Medicine residents are keen to engage with wound care specialists on this initiative.

WounDS is also the first known mHealth app of its type for wound dressing selection and it will serve as a proof-of-concept for this particular application. There are possible extensions for this concept that include integration with electronic medical record systems and integration with similar technology-based decision systems into other areas of clinical care. The latter could include assessment and treatment of specific wounds (pressure ulcers, diabetic foot ulcers) via SmartWoundCare [16], also developed within the research team, as well as blood glucose monitoring, blood pressure monitoring, and other self-monitoring tools.

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Conflicts of Interest

None declared.

References

1. Lees TA, Lambert D. Prevalence of lower limb ulceration in an urban health district. Br J Surg 1992 Oct;79(10):1032-1034. [Medline: 1422713]
2. Nelzén O, Bergqvist D, Lindhagen A, Hallböök T. Chronic leg ulcers: an underestimated problem in primary health care among elderly patients. J Epidemiol Community Health 1991 Sep;45(3):184-187 [FREE Full text] [Medline: 1757758]
3. Simon DA, McCollum CN. Approaches to venous leg ulcer care within the community: compression, pinch skin grafts and simple venous surgery. Ostomy Wound Manage 1996 Mar;42(2):34-8, 40. [Medline: 8703294]
4. McGuckin M, Kerstein MD. Venous leg ulcers and the family physician. Adv Wound Care 1998;11(7):344-346. [Medline: 10326351]
5. Sen C, Gordillo G, Roy S, Kirsner R, Lambert L, Hunt TK, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen 2009;17(6):763-771 [FREE Full text] [doi: 10.1111/j.1524-475X.2009.00543.x] [Medline: 19903300]
6. Little SH, Menawat SS, Worzniak M, Fetters MD. Teaching wound care to family medicine residents on a wound care service. Adv Med Educ Pract 2013;4:137-144 [FREE Full text] [doi: 10.2147/AMEP.S46785] [Medline: 23983497]
7. Graham ID, Harrison MB, Shafey M, Keast D. Knowledge and attitudes regarding care of leg ulcers. Survey of family physicians. Can Fam Physician 2003 Jul;49:896-902 [FREE Full text] [Medline: 12901487]
8. The COFPOC. The College of Family Physicians of Canada. The Red Book: Specific Standards for Family Medicine Residency Programs URL: http://www.cfpc.ca/red_book_TOC/ [accessed 2018-04-16] [WebCite Cache ID 6yj1NFVi3]
9. Ahearn P, Gardner P, Harley C, Latocki M, Paquette F, Stone J, et al. The perfect storm: Summary of a national wound care stakeholder round table. Wound Care Canada 2012;10(4):25-30.
10. Bryan J. Moist wound healing: A concept that changed our practice. Journal of Wound Care 2004;13(6).
11. Sibbald R, Goodman L, Woo K, Krasner DL, Smart H, Tariq G, et al. Special considerations in wound bed preparation 2011: An update. Advances in Skin and Wound Care 2011;24(9):415-436.
12. Friesen MR, Hamel C, McLeod RD. A mHealth application for chronic wound care: findings of a user trial. Int J Environ Res Public Health 2013 Nov 19;10(11):6199-6214 [FREE Full text] [doi: 10.3390/ijerph10116199] [Medline: 24256739]
13. White PJF, Podaima BW, Friesen MR. Algorithms for smartphone and tablet image analysis for healthcare applications. IEEE Access 2014;2(1):1-10.
14. Kratzke C, Cox C. Smartphone technology and apps: Rapidly changing health promotion. Int Electronic J of Health Educ 2012;15(72).
15. Berry D, Blumenstein B, Halpenny B, Wolpin S, Fann JR, Austin-Seymour M, et al. Enhancing patient-provider communication with the electronic self-report assessment for cancer: A randomized trial. J Clinical Oncology 2011;29(8):1029-1035.
16. SmartWoundCare. 2018. SmartWoundCare Mobile App for Healthcare Workers URL: http://www.smartwoundcare.com/ [accessed 2018-04-16] [WebCite Cache ID 6yjAMjtBO]
17. Health Outcomes Worldwide. how2trak Wound Care URL: https://www.healthoutcomesww.com/products/how2trak-wound-care [accessed 2018-04-15] [WebCite Cache ID 6yj1r9ulK]
18. WoundRounds. WoundRounds Care Management Solution URL: http://www.woundrounds.com/overview/ [accessed 2018-04-16] [WebCite Cache ID 6yj1s5xfG]
19. Mobihealth News. 2013 Jul. ONC names winners in pressure ulcer app challenge URL: http://www.mobihealthnews.com/news/onc-names-winners-pressure-ulcer-app-challenge [accessed 2018-04-16] [WebCite Cache ID 6yj2MB6Io]
20. Cafazzo JA, Casselman M, Hamming N, Katzman DK, Palmert MR. Design of an mHealth app for the self-management of adolescent type 1 diabetes: a pilot study. J Med Internet Res 2012 May;14(3):e70 [FREE Full text] [doi: 10.2196/jmir.2058] [Medline: 22564332]
21. Georgia Tech GVU Centre. RheumMate URL: https://gvu.gatech.edu/research/projects/rheummate [accessed 2018-04-16] [WebCite Cache ID 6yj1vu8j7]
22. Health Outcomes Worldwide. Software that improves health outcomes URL: https://www.healthoutcomesww.com/index.html [accessed 2018-04-16] [WebCite Cache ID 6yj2FnJld]
23. Olawale D, Ferens K, Griffith B, Podaima B. A smart shoe to prevent and manage diabetic foot diseases. 2015 Presented at: International Conference on Health Informatics and Medical Systems; 2015; Las Vegas.
24. Halas G, Katz A, Dean J. Computer-based risk assessment: Evaluating use in primary care. Electronic Healthcare 2010;9(2):e10-e15.
25. Zhang M, Ho R, Hawa R, Sockalingam S. Analysis of the information quality of bariatric surgery smartphone applications using the silberg scale. Obes Surg 2016;26:163 [FREE Full text]
26. Man C, Nguyen C, Lin S. Effectiveness of a smartphone app for guiding antidepressant drug selection. Fam Med 2014 Sep;46(8):626-630 [FREE Full text] [Medline: 25163042]

27. Brown B, Cheraghi-Sohi S, Jaki T, Su T, Buchan I, Sperrin M. Understanding clinical prediction models as 'innovations': a mixed methods study in UK family practice. BMC Med Inform Decis Mak 2016 Aug 09;16:106 [FREE Full text] [doi: 10.1186/s12911-016-0343-y] [Medline: 27506547]

Abbreviations

WounDS: Wound Dressing Selection prototype mobile app

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Protocol

Comparing a Mobile Decision Support System Versus the Use of Printed Materials for the Implementation of an Evidence-Based Recommendation: Protocol for a Qualitative Evaluation

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Abstract

Background: The distribution of printed materials is the most frequently used strategy to disseminate and implement clinical practice guidelines, although several studies have shown that the effectiveness of this approach is modest at best. Nevertheless, there is insufficient evidence to support the use of other strategies. Recent research has shown that the use of computerized decision support presents a promising approach to address some aspects of this problem.

Objective: The aim of this study is to provide qualitative evidence on the potential effect of mobile decision support systems to facilitate the implementation of evidence-based recommendations included in clinical practice guidelines.

Methods: We will conduct a qualitative study with two arms to compare the experience of primary care physicians while they try to implement an evidence-based recommendation in their clinical practice. In the first arm, we will provide participants with a printout of the guideline article containing the recommendation, while in the second arm, we will provide participants with a mobile app developed after formalizing the recommendation text into a clinical algorithm. Data will be collected using semistructured and open interviews to explore aspects of behavioral change and technology acceptance involved in the implementation process. The analysis will be comprised of two phases. During the first phase, we will conduct a template analysis to identify barriers and facilitators in each scenario. Then, during the second phase, we will contrast the findings from each arm to propose hypotheses about the potential impact of the system.

Results: We have formalized the narrative in the recommendation into a clinical algorithm and have developed a mobile app. Data collection is expected to occur during 2018, with the first phase of analysis running in parallel. The second phase is scheduled to conclude in July 2019.

Conclusions: Our study will further the understanding of the role of mobile decision support systems in the implementation of clinical practice guidelines. Furthermore, we will provide qualitative evidence to aid decisions made by low- and middle-income countries' ministries of health about investments in these technologies.

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KEYWORDS

practice guideline; implementation science; decision support systems; mhealth; technology acceptance; computer-interpretable clinical guidelines; Colombia

Introduction

Printed Materials for the Dissemination and Implementation of Clinical Practice Guidelines

Successful implementation of clinical practice guidelines (CPGs) has the potential to reduce health care costs and improve the quality of care by promoting the use of cost-effective, evidence-based interventions [1-3]. However, the extent of these benefits varies largely across implementation sites [1], and even between recommendations in the same guideline [2]. This variability could be attributed, in part, to the way CPGs are disseminated and implemented [1,4].

Distribution of printed materials has been the predominant CPG dissemination and implementation (D&I) strategy [2,3]. In 2004, Grimshaw et al [1] conducted an extensive literature review about the effectiveness of guideline D&I strategies. Among the studies evaluating the sole distribution of printed materials, the authors found that although most reports presented improvements in dichotomous process variables (eg, the proportion of patient encounters that follow the recommendation), the median effects were modest (8.1%, range 3.6% to 17.0%). Eight years later in 2012, literature reviews from Brusamento et al [5] and Giguère et al [6] found that this situation had not changed significantly.

Decision Support Systems for the Implementation of Clinical Algorithms

Some evidence-based recommendations ask the clinicians to implement clinical algorithms. In these cases, decision support systems (DSSs) provide an approach that facilitates the understanding of the recommendation among the intended users and its integration into their daily routine [7]. In 2005, Garg et al [8] conducted a review of trials evaluating the effect of DSSs in changing clinical practice. The authors found that these systems improved practitioner performance in 64% of the cases reported. Based on these results, Garg et al [8] highlighted the need for further research into the determinants of DSS acceptance and overall success.

Recent research has shown that it is feasible to use DSSs to support the implementation of clinical algorithms, even in resource-constrained environments [9,10]. Nevertheless, before these systems can be widely used as a D&I strategy, it is necessary to solve two informatics challenges.

The first of these challenges is that CPG recommendations are often unclear, ambiguous or incomplete [7,9,11-13], making it difficult to transform them into decision algorithms. This problem can be addressed through formalization processes that translate the recommendation into specific tasks and decision procedures while allowing for the identification of areas where the recommendations are ambiguous or evidence is missing [7].

The second challenge is that in many cases, DSSs rely on their integration into other clinical information systems, or at least on the availability of personal computers. This dependency on informatics infrastructure represents a barrier to the broad application of these systems as a D&I strategy. Most care centers in low-income countries do not have personal computers, let alone clinical information systems. Even in the case of middle-income countries, rural areas frequently present the same general shortage of computer infrastructure. Furthermore, although it is typical that urban care centers in middle-income countries and other technology-rich environments have electronic health records, these are often homegrown or produced by many different vendors. Consequently, the broad integration of DSSs into these systems would imply enormous investments, requiring the modification of many programs and coordination among many parties.

Mobile Decision Support Systems

Recent evidence suggests that mobile technologies could provide an approach to address these barriers, allowing DSSs to be implemented without requiring personal computers or its integration into other clinical information systems [9,14,15]. However, there is insufficient evidence supporting the effectiveness of these technologies [16,17]. This is in part due to a shortage of formal evaluations [18]. The authors of recent literature reviews have highlighted the need for theory-based research about the factors that may influence the adoption and scalability of these interventions [19], particularly those aimed at promoting practice changes [20].

Objective

Our goal is to provide qualitative evidence on the potential effect of mobile DSSs to facilitate the implementation of evidence-based recommendations, as well as the determinants of their adoption. To achieve this aim, we will compare the experience of primary care physicians while they try to implement a recommendation in their clinical practice using either a printout of the journal article containing the recommendation or a mobile DSS. This comparison will consider aspects related to the behavioral change intended and those related to the acceptance of each technology.

Methods

Overall Design

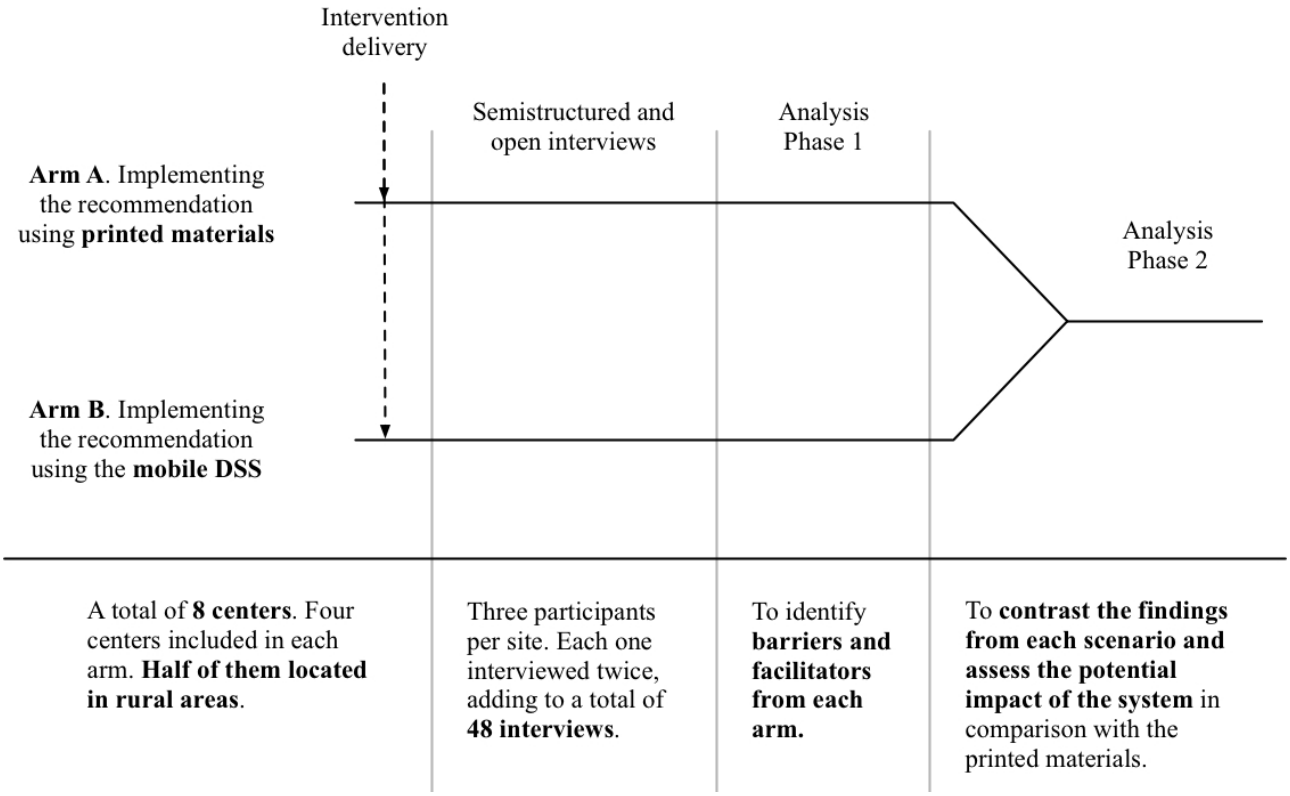
As shown in Figure 1, we will conduct a qualitative study with two arms. Participants will be asked to try to implement an evidence-based screening recommendation in their daily practice as primary care physicians, after being provided with either a journal article or a mobile DSS.

Arm assignment will be by center. Therefore, all participants from the same center will receive the same intervention. We will include a minimum of eight centers, half of them located in rural areas. We will assign centers to each arm iteratively as they enter the study, ensuring that half of the urban centers, as well as half of the rural centers, will be assigned to each arm.

Data will be collected through qualitative interviews, starting 1 month after the subjects received the article or the mobile app. During this time, the subjects will try to implement the screening recommendation during their daily practice as primary care physicians.

Analysis will focus on identifying barriers and facilitators for the implementation and contrasting these findings between the two arms.

Figure 1. Study design. DSS: decision support system.



Study Case

We will ask participants to try to implement the case finding recommendation included in the Colombian clinical practice guideline for chronic obstructive pulmonary disease. This recommendation instructs the physician to check a series of risk factors, signs, and symptoms in adults, 40 years or older. When the suspicion is established, the guide recommends ordering a spirometry test to confirm or rule-out the diagnosis [21].

The selection of this recommendation was arbitrary. The only criteria considered was that it included a clinical algorithm (in this case, the decision about ordering a spirometry test based on a series of risk factors, signs, and symptoms) and that it would be part of a Colombian CPG.

Interventions

Participants from centers assigned to arm A will be provided with a printout of the journal article in which the guideline was published [21]. Participants from centers assigned to arm B will be provided with a DSS implemented as a mobile app. As shown in Figure 2, the system will be developed following a process comprising four stages.

During the first stage, we will conduct a series of meetings with the guideline developers. Throughout these sessions, we will apply the cognitive analysis proposed by Patel et al [22] to formalize the recommendation into a clinical algorithm. Using this method, we will identify and encode the propositions stated in the text, and develop a conceptual model of the knowledge expressed. Throughout this process, we will identify and correct areas where the instructions allow different interpretations, the understanding depends on tacit knowledge, or the information is incomplete.

During the second stage, we will implement a mobile app that will support the participants in the implementation of the clinical algorithm. The app will be responsible for asking the user for information related to risk factors, signs, and symptoms, making calculations, and explaining the algorithm's end points. To improve the chances of acceptance, the app will be able to run on Android, iOS, and Windows Mobile devices, and will operate autonomously, without the need for internet connectivity. The latter requirement will ensure that participating in the study will not generate new or unexpected costs for our subjects.

During the third stage, we will inspect the usability of the app prototype by conducting a cognitive walkthrough [23,24]. This method will identify aspects of the app that could hinder its use. Two recently graduated physicians and a mobile app developer will attend the session, and the principal investigator will act as the facilitator. Finally, during the fourth stage, the findings from the cognitive walkthrough will be used to improve the app.

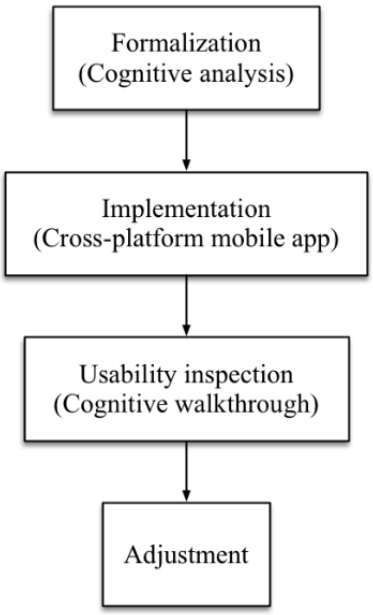
Selection of Sites and Participants

Our study will include a minimum of eight health centers, and a minimum of three participants per center, for a minimum sample of 24 participants. Half of the centers will be assigned to each arm.

We will conduct the study in Colombia. To explore the influence of the availability of informatics resources, half of the centers will be in Bogotá, while the other half will be in rural areas. The Bogotá sites will operate in a technology-rich environment that includes the use of clinical information systems and access to the internet during patient visits. In contrast, the rural sites

will fulfill the criteria of having neither clinical information systems nor access to the internet during patient visits.

Figure 2. Stages of the system development.



Our subjects will be general practitioners operating a regular primary care practice with adult patients.

Intervention Delivery

At each site, the study will start with a short talk with the subjects. During this meeting, the principal investigator will outline the study procedures, and 1 of the guideline developers will present the screening recommendation, including a summary of the literature supporting it. At the end of the meeting, we will provide the participants assigned to arm A with a printout of the journal article in which the practice guideline was published [21]. In sites assigned to arm B, we will demonstrate how to install the app, and if necessary, help the subjects until they have the system running on their phones. No other explanation about the app will be provided. Not having explained how to use the app, we expect to be able to explore aspects of the system's learnability [25]. In the case that a participant does not own an Android, iOS or Windows Mobile phone, we will provide them with a smartphone.

Recruitment

To gain access to the sites, we will arrange meetings with their directors. During the meeting, we will present the project, ask for permission to recruit participants among the primary care physicians, ask for the director's help in the recruitment process, and collect information about previous initiatives to implement CPGs, and the number of potential participants and their schedule.

The general practitioners from each center will be invited to participate by email (if possible, from the director of the respective site). The email will contain a description of the research goals, an outline of the study procedures (eg, the participant's attempt to implement the screening recommendation), the informed consent document, and contact information. The email will also ask the potential participant to respond, either by email or phone, to express their decision to participate or not. Two weeks after sending the email, we will visit potential participants who have not responded, to invite them personally.

To incentivize participation, potential subjects will be offered with two COP $100,000 prepaid cards from a local supermarket (worth approximately US $35).

Conceptual Framework

Our data collection and analysis will explore factors influencing the behavioral change intended by the recommendation, as well as those that regulate the system's acceptance among the intended users. To achieve this, we will develop a conceptual framework that will harmonize the Theoretical Domains Framework (TDF) [26,27], the Unified Theory of Acceptance and Use of Technology (UTAUT) [28], and constructs from recent literature reviews about the acceptance of mobile health (mHealth) systems and DSSs.

To harmonize the contributing frameworks, we will compare the constructs' descriptions. Based on these comparisons, we will define the harmonized constructs using the following strategies:

1. We will unify the name of constructs that refer to very similar concepts. Example: both the TDF and the UTAUT consider the extent to which the context provides support and resources to accomplish the behavior or to use the system effectively. However, the TDF calls this construct "environmental context and resources," while the UTAUT calls it "facilitating conditions."
2. We will include constructs that we consider relevant to understand the determinants of behavioral change and technology acceptance, but are not included in all contributing frameworks. Example: a recent literature review from Khong et al [29] identified "threats to professional autonomy" as a determinant of the acceptance of DDSs. It could be argued that this construct could be

considered part of the UTAUT's "performance expectancy." However, it could be useful to include this construct in the final framework specifically.

3. We will map constructs that we consider too specific to more abstract constructs included in other frameworks. Example: the same review from Khong et al [29] includes "usability" and "computer experience or computer skill" as determinants for DSS acceptability. These two constructs could be mapped to the UTAUT's "effort expectancy." Therefore, it could be argued that it would not be necessary to include them in the final framework.

The decisions about using strategies 2 and 3 will consider the usefulness of the resulting constructs in developing questions for data collection and their relevance in the context of the project's scope.

Contributing Frameworks

Determinants of Behavioral Change

The TDF was proposed by Michie et al [26] in 2005 to organize theoretical constructs included in classic psychological theories about behavior change and make them more accessible to implementation researchers from other fields. In 2012, Cane and Michie [27] produced a revised version of the TDF, containing 84 determinants of behavioral change, grouped in 14 domains: Knowledge, Skills, Social/Professional Role and Identity, Beliefs about Capabilities, Optimism, Beliefs about Consequences, Reinforcement, Intentions, Goals, Memory, Attention and Decision Processes, Environmental Context and Resources, Social Influences, Emotions, and Behavioral Regulation.

Determinants of Technology Acceptance

In 2003, Venkatesh et al [28] reviewed and combined the eight predominant models at the time, to integrate the fragmented theory on technology acceptance. The resulting theory (ie, UTAUT) states that the regular use of a technology is determined by the performance gain the user expects to obtain (Performance Expectancy), the level of effort they expect using the system will demand (Effort Expectancy), the influence of important others (Social Influence) and the level of support they will obtain (Facilitating Conditions). The first three influence the user's intention to use the tool, whereas the last modulates the actual use, independently of the intention.

UTAUT's constructs are general enough to be applied to any technology. However, to focus our research, we will also include specific concepts that have been identified as influencing the acceptance of mobile and decision support systems.

Determinants of the Acceptance of mHealth Systems

In 2016, Gagnon et al [30] published a systematic review of the literature reporting factors that modulate health care professionals' acceptance of mHealth systems. The authors identified 49 barriers and facilitators. Some examples of these determinants are: interoperability, design and technical concerns, physician salary status and reimbursement, and support and promotion of mHealth by colleagues [30].

Determinants of the Acceptance of Decision Support Systems

Finally, in 2015, Khong et al [29] published a systematic literature review about factors affecting the adoption of clinical decision support systems. They recognized 42 determinants, including: patient clinical status, fitness of task, credibility of system, and patient-user's relationship.

Data Collection

Data will be collected through qualitative interviews, starting 1 month after the intervention delivery. To leverage the conceptual framework, we will conduct semistructured interviews, which have a loose structure based on a set of open-ended questions that define the area to be explored, but allows divergence to explore new ideas or gather more detail [31]. However, to address the potential bias derived from the use of a predefined set of constructs, we will also conduct in-depth interviews [31], which will start with an open question about the subject's experience implementing the recommendation using either the app or the journal article. From this point on, participant's answers will dictate the course of the interview.

Each participant will be interviewed twice, the first interview concerning aspects of behavioral change, while the second, focused on aspects of technology acceptance. Before each interview round, the participants from the respective site will be assigned at random to attend a semistructured or in-depth interview. All interviews will be recorded and transcribed verbatim.

Analysis Plan

The analysis will be comprised of two phases. During phase one, we will perform a template analysis [32], based on the conceptual framework, to identify barriers and facilitators to the implementation in each scenario. This technique is especially useful to leverage an extant conceptual framework in the thematic analysis of qualitative data. In template analysis, the researcher starts with an a priori code book (or template) representing topics to look for in the data. This code book is refined during the analysis, to allow for the inclusion of new topics, the removal of codes that prove to be unnecessary, and the reorganization of codes to reflect the importance of specific concepts [32]. We will conduct this phase in parallel with the data collection, allowing for the adjustment of the interview guides according to preliminary results.

Coding will be conducted independently by 2 researchers. We will use NVivo version 11 (QSR International) to support analysis and data management. Consensus meetings will be held after coding every 4 transcripts. Before each meeting, the intercoder agreement for each transcript will be assessed using the Coding Comparison tool provided by NVivo. During the meeting, the researcher will discuss changes to the coding template and review transcripts with kappa coefficients below .7.

During the second phase, we will assess the potential impact of the system by contrasting the beliefs of the participants from the two arms, across the constructs in the conceptual framework and the emerging categories identified during the first phase. This comparison will allow us to propose hypotheses about the

underlying mechanisms that operate over the implementation process, as well as the effects of using each tool. Specifically, those barriers and facilitators that are not present in one scenario or to which the subjects refer to with contrasting emphasis will form the basis of hypotheses about the impact of the DSS in comparison with the printed materials. Barriers and facilitators that seem to have the same emphasis in both scenarios will form the basis of hypotheses concerning determinants not related to the implementation tool.

Additionally, the analysis in both phases will consider the type of center the subject belongs to (ie, urban or rural), the number of years the subject has used smartphones, and whether the subject was provided with a smartphone to participate in the study.

Protection of Human Subjects

We do not expect that participating in the study will put the subjects at a greater risk of harm or discomfort than what they encounter in their daily working life. Therefore, under the Federal Policy for the Protection of Human Subjects [33] and the Colombian regulation [34], it could be considered that this research does not involve more than minimal risk.

The process of informed consent to participate will start before collecting any data and will continue through the entire study. Before being interviewed, the participants will have time to read the consent document and ask questions about the study goals, the procedures in which they will be involved, and the measures undertaken to protect their rights as human subjects. At any time during the study, the participants will be free to withdraw their consent to participate and leave the study, stop the recording, order the destruction of any audio records they have participated in, and terminate or reschedule an interview.

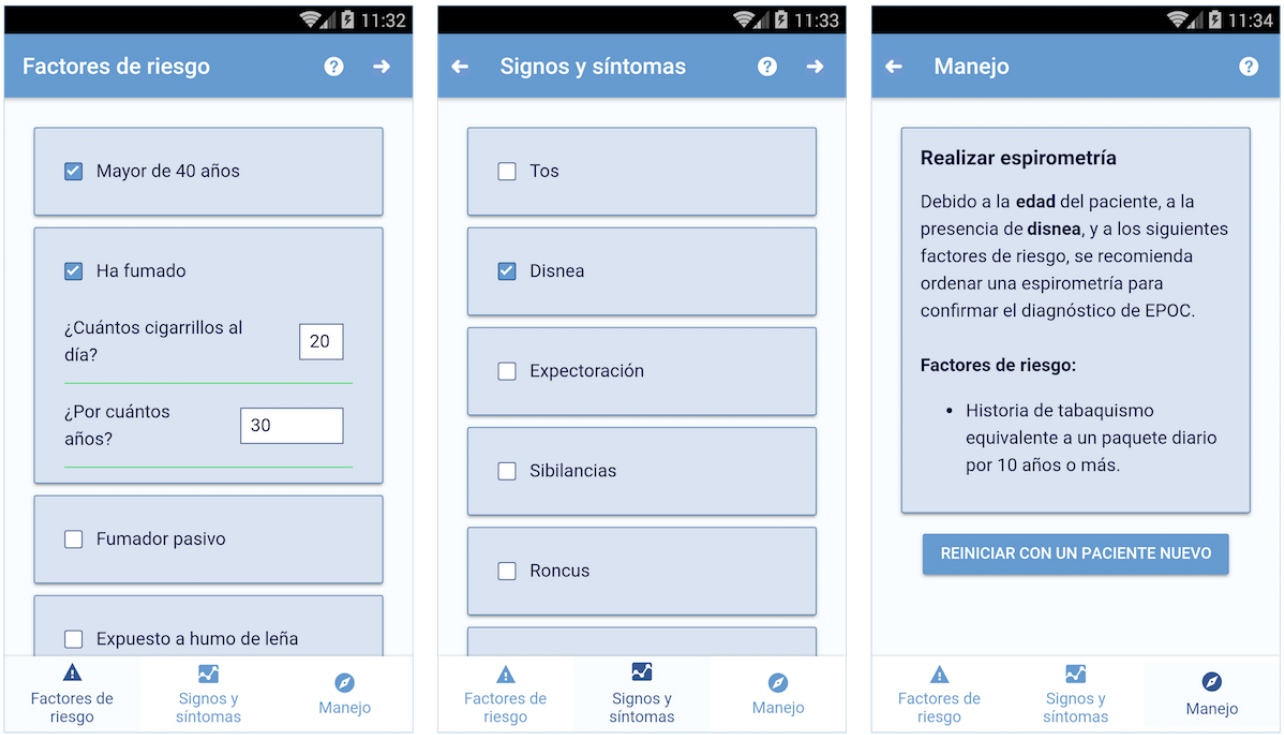
The interviews will be scheduled at the participants' convenience, with special attention given to not disrupting clinical practice. Audio records and transcripts will be securely stored and will not be shared with persons other than the 2 researchers involved in the analysis. Additionally, no publication will mention the participants' names or the names of the study sites. Although we will offer an economic incentive for participation, its value is small in comparison to the participants' monthly income. Therefore, we do not expect the compensation to compel subjects to participate. Finally, this research protocol has been approved by the institutional review boards of the Pontificia Universidad Javeriana in Bogotá, Colombia and the University of Pittsburgh in Pittsburgh, PA, USA.

Results

Intervention Design

We designed and implemented the mobile DSS, following the process presented in Figure 2. During the first stage, we had four meetings, with the participation of 1 engineer (with graduate-level training in biomedical informatics) and 2 pulmonologists who participated in the guideline development. These sessions resulted in a complete algorithm, including the formal definition of risk factors, signs, and symptoms. Some of these definitions were tacit in the text (eg, the number of years spent as a passive smoker that constitutes a risk factor). The algorithm also included previously undefined end points (eg, how patients with a risk factor but no symptoms should be managed).

Figure 3. Screenshots of the app.



During stage two, we implemented the algorithm in the form of a mobile app. To fulfill the requirement of being cross-platform (ie, being able to run on iOS, Android, and Windows Mobile), while reducing the development effort, we programmed the app using the IONIC 2 platform [35].

As presented in Figure 3, the app consists of three sections. In the example, the user is stating that the patient is older than 40 years (in Spanish: "Mayor de 40 años"), and has smoked approximately 20 cigarettes per day for 30 years (in Spanish: "¿Cuantos cigarrillos al día? 20" and "¿Por cuántos años? 30").

The first two sections contain checklists. The first captures the information related to risk factors, while the second concerns signs and symptoms. Some items include second level questions. For instance, when the user indicates that the patient has smoked (in Spanish: "Ha fumado"), the app asks how many cigarettes and for how many years. Finally, the third section presents the algorithm end points depending on the information entered. In the example, due to patient's age, his smoking history and the presence of dyspnea, the app recommends the user to order a spirometry test.

Next Steps

We are in the process of harmonizing the concepts from the contributing conceptual frameworks [27-30]. Data collection is expected to occur during 2018, with the first phase of analysis running in parallel. The second phase is scheduled to conclude in July 2019.

Discussion

Dissemination and implementation of CPGs is recognized as a challenging problem [1], and sometimes, a moving target [2]. Many governments and organizations are turning their attention to mobile DSSs hoping to find an effective, affordable, and scalable solution [9,14,36]. However, there is little evidence to support that expectation [16,17].

Our study will provide qualitative evidence about the potential effects of mobile DSSs in the context of a middle-income country. Furthermore, since the study design considers environments with constraints in informatics resources, our results may be used to inform decisions in low-income countries.

Finally, several authors have highlighted the need for theory-based research about the determinants of the effectiveness and adoption of these interventions [18-20]. Being based on a comprehensive conceptual framework, which considers determinants of behavioral change and technology acceptance, our study will provide actionable evidence that may be translated into concrete programs to promote practice change.

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Conflicts of Interest

None declared.

References

1. Grimshaw J, Thomas R, MacLennan G, Fraser C, Ramsay C, Vale L, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess 2004 Feb;8(6):1-72. [doi: 10.3310/hta8060]
2. Lugtenberg M, Burgers J, Westert G. Effects of evidence-based clinical practice guidelines on quality of care: a systematic review. Qual Saf Health Care 2009 Oct;18(5):385-392. [doi: 10.1136/qshc.2008.028043] [Medline: 19812102]
3. Gagliardi A, Alhabib S, members of Guidelines International Network Implementation Working Group. Trends in guideline implementation: a scoping systematic review. Implement Sci 2015 Apr 21;10:54 [FREE Full text] [doi: 10.1186/s13012-015-0247-8] [Medline: 25895908]
4. Prior M, Guerin M, Grimmer-Somers K. The effectiveness of clinical guideline implementation strategies--a synthesis of systematic review findings. J Eval Clin Pract 2008 Oct;14(5):888-897. [doi: 10.1111/j.1365-2753.2008.01014.x] [Medline: 19018923]
5. Brusamento S, Legido-Quigley H, Panteli D, Turk E, Knai C, Saliba V, et al. Assessing the effectiveness of strategies to implement clinical guidelines for the management of chronic diseases at primary care level in EU Member States: a systematic review. Health Policy 2012 Oct;107(2-3):168-183. [doi: 10.1016/j.healthpol.2012.08.005] [Medline: 22940062]
6. Giguère A, Légaré F, Grimshaw J, Turcotte S, Fiander M, Grudniewicz A, et al. Printed educational materials: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev 2012 Oct 17;10:CD004398. [doi: 10.1002/14651858.CD004398.pub3] [Medline: 23076904]
7. Peleg M, González-Ferrer A. Guidelines and Workflow Models. In: Greenes RA. editor. Clinical Decision Support: The Road to Broad Adoption: Second Edition. Academic Press; 2014:435-464.
8. Garg A, Adhikari N, McDonald H, Rosas-Arellano M, Devereaux P, Beyene J, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA 2005 Mar 09;293(10):1223-1238. [doi: 10.1001/jama.293.10.1223] [Medline: 15755945]

9. Mitchell M, Lesh N, Cranmer H, Fraser H, Haivas I, Wolf K. Improving care – improving access: the use of electronic decision support with AIDS patients in South Africa. IJHTM 2009;10(3):156-168. [doi: 10.1504/IJHTM.2009.025819]
10. Shao A, Rambaud-Althaus C, Samaka J, Faustine A, Perri-Moore S, Swai N, et al. New Algorithm for Managing Childhood Illness Using Mobile Technology (ALMANACH): A Controlled Non-Inferiority Study on Clinical Outcome and Antibiotic Use in Tanzania. PLoS One 2015;10(7):e0132316 [FREE Full text] [doi: 10.1371/journal.pone.0132316] [Medline: 26161535]
11. Codish S, Shiffman RN. A model of ambiguity and vagueness in clinical practice guideline recommendations. 2005 Presented at: AMIA Annu Symp Proc. Jan; 2005; Washington, DC p. 146-150.
12. Lee P, Liew S, Abdullah A, Abdullah N, Ng C, Hanafi N, et al. Healthcare professionals' and policy makers' views on implementing a clinical practice guideline of hypertension management: a qualitative study. PLoS One 2015;10(5):e0126191 [FREE Full text] [doi: 10.1371/journal.pone.0126191] [Medline: 25942686]
13. Solà I, Carrasco J, Díaz DCP, Gracia J, Orrego C, Martínez F, et al. Attitudes and perceptions about clinical guidelines: a qualitative study with Spanish physicians. PLoS One 2014;9(2):e86065 [FREE Full text] [doi: 10.1371/journal.pone.0086065] [Medline: 24505253]
14. Rambaud-Althaus C, Shao AF, Kahama-Maro J, Genton B, d'Acremont V. Managing the Sick Child in the Era of Declining Malaria Transmission: Development of ALMANACH, an Electronic Algorithm for Appropriate Use of Antimicrobials. PLoS One 2015;10(7):e0127674 [FREE Full text] [doi: 10.1371/journal.pone.0127674] [Medline: 26161753]
15. Ginsburg AS, Delarosa J, Brunette W, Levari S, Sundt M, Larson C, et al. mPneumonia: Development of an Innovative mHealth Application for Diagnosing and Treating Childhood Pneumonia and Other Childhood Illnesses in Low-Resource Settings. PLoS One 2015;10(10):e0139625 [FREE Full text] [doi: 10.1371/journal.pone.0139625] [Medline: 26474321]
16. Mechael P, Batavia H, Kaonga N, Searle S, Kwan A, Goldberger A, et al. Barriers and gaps affecting mHealth in low and middle income countries: Policy white paper. Columbia University, Earth Institute: Center for Global Health and Economic Development (CGHED); 2010.
17. Free C, Phillips G, Watson L, Galli L, Felix L, Edwards P, et al. The effectiveness of mobile-health technologies to improve health care service delivery processes: a systematic review and meta-analysis. PLoS Med 2013;10(1):e1001363 [FREE Full text] [doi: 10.1371/journal.pmed.1001363] [Medline: 23458994]
18. World Health Organization. mHealth New horizons for health through mobile technologies. Geneva, Switzerland: World Health Organization; 2011.
19. Peiris D, Praveen D, Johnson C, Mogulluru K. Use of mHealth systems and tools for non-communicable diseases in low- and middle-income countries: a systematic review. J Cardiovasc Transl Res 2014 Nov;7(8):677-691. [doi: 10.1007/s12265-014-9581-5] [Medline: 25209729]
20. Chib A, van VM, Car J. mHealth adoption in low-resource environments: a review of the use of mobile healthcare in developing countries. J Health Commun 2015;20(1):4-34. [doi: 10.1080/10810730.2013.864735] [Medline: 24673171]
21. Londoño D, García O, Celis C. Guía de práctica clínica basada en la evidencia para la prevención, diagnóstico, tratamiento y seguimiento de la enfermedad pulmonar obstructiva crónica (EPOC) en población adulta. Acta Med Colomb. (Supl 3) 2014;39:1-48 [FREE Full text]
22. Patel VL, Arocha JF, Diermeier M, Greenes RA, Shortliffe EH. Methods of cognitive analysis to support the design and evaluation of biomedical systems: the case of clinical practice guidelines. J Biomed Inform 2001 Feb;34(1):52-66 [FREE Full text] [doi: 10.1006/jbin.2001.1002] [Medline: 11376543]
23. Wilson C. Chapter 4 - Cognitive Walkthrough. In: User interface inspection methods: a user-centered design method. Oxford, UK: Newnes; 2013.
24. Spencer R. The streamlined cognitive walkthrough method, working around social constraints encountered in a software development company. In: Proceedings of the SIGCHI conference on Human factors in computing systems. New York, New York, USA: ACM Press; 2000 Presented at: SIGCHI conference on Human factors in computing systems; 2000; The Hague, The Netherlands p. 00-09.
25. ISO/IEC 25010Systems and software engineering -- Systems and software Quality Requirements and Evaluation (SQuaRE) -- System and software quality models. 2011 URL: https://www.iso.org/standard/35733.html [accessed 2018-02-20] [WebCite Cache ID 6xNMbQ60q]
26. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A. Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual Saf Health Care 2005 Feb;14(1):26-33 [FREE Full text] [doi: 10.1136/qshc.2004.011155] [Medline: 15692000]
27. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. Implement Sci 2012 Apr 24;7:37 [FREE Full text] [doi: 10.1186/1748-5908-7-37] [Medline: 22530986]
28. Venkatesh V, Morris M, Davis G, Davis F. User acceptance of information technology: toward a unified view. MIS Q 2003;27(3):425-478 [FREE Full text]
29. Khong PCB, Holroyd E, Wang W. A Critical Review of the Theoretical Frameworks and the Conceptual Factors in the Adoption of Clinical Decision Support Systems. Comput Inform Nurs 2015 Dec;33(12):555-570. [doi: 10.1097/CIN.0000000000000196] [Medline: 26535769]

30. Gagnon M, Ngangue P, Payne-Gagnon J, Desmartis M. m-Health adoption by healthcare professionals: a systematic review. J Am Med Inform Assoc 2016 Jan;23(1):212-220. [doi: 10.1093/jamia/ocv052] [Medline: 26078410]
31. Britten N. Qualitative Interviews. In: Pope C, Mays N, editors. Qualitative Research in Health Care. Hoboken, New Jersey: Wiley-Blackwell; 2006.
32. King N, Cassell C, Symon G. Using Templates in the Thematic Analysis of Texts. In: Cassell C, Symon G, editors. Essential guide to qualitative methods in organizational research. London: Sage Publications; 2004:256-270.
33. US Department of Health & Human Services. Federal Policy for the Protection of Human Subjects ('Common Rule') URL: http://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html# [WebCite Cache ID 6xNMs0Jdp]
34. Ministerio de Salud – República de Colombia. Resolución numero 8430 de 1993 URL: https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/DIJ/RESOLUCION-8430-DE-1993.PDF [WebCite Cache ID 6xNNAeKVe]
35. Ionic. Ionic Framework. IONIC - Build Amazing Native Apps and Progressive Web Apps with Ionic Framework and Angular URL: https://ionicframework.com/ [accessed 2018-02-20] [WebCite Cache ID 6xNNKDoD7]
36. Schweitzer J, Synowiec C. The economics of eHealth and mHealth. J Health Commun 2012;17 Suppl 1:73-81. [doi: 10.1080/10810730.2011.649158] [Medline: 22548602]

Abbreviations

CPG: clinical practice guideline
D&I: dissemination and implementation
DSS: decision support system
mHealth: mobile health
TDF: Theoretical Domains Framework
UTAUT: Unified Theory of Acceptance and Use of Technology

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Protocol

Cultural and Contextual Adaptation of an eHealth Intervention for Youth Receiving Services for First-Episode Psychosis: Adaptation Framework and Protocol for Horyzons-Canada Phase 1

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Abstract

Background: eHealth interventions have the potential to address challenges related to access, service engagement, and continuity of care in the delivery of mental health services. However, the initial development and evaluation of such interventions can require substantive amounts of financial and human resource investments to bring them to scale. Therefore, it may be warranted to pay greater attention to policy, services, and research with respect to eHealth platforms that have the potential to be adapted for use across settings. Yet, limited attention has been placed on the methods and processes for adapting eHealth interventions to improve their applicability across cultural, geographical, and contextual boundaries.

Objective: In this paper, we describe an adaptation framework and protocol to adapt an eHealth intervention designed to promote recovery and prevent relapses in youth receiving specialized services for first-episode psychosis. The Web-based platform, called Horyzons, was initially developed and tested in Australia and is now being prepared for evaluation in Canada.

Methods: Service users and service providers from 2 specialized early intervention programs for first-episode psychosis located in different provinces will explore a beta-version of the eHealth intervention through focus group discussions and extended personal explorations to identify the need for, and content of contextual and cultural adaptations. An iterative consultation process will then take place with service providers and users to develop and assess platform adaptations in preparation for a pilot study with a live version of the platform.

Results: Data collection was completed in August 2017, and analysis and adaptation are in process. The first results of the study will be submitted for publication in 2018 and will provide preliminary insights into the acceptability of the Web-based platform (eg, perceived use and perceived usefulness) from service provider and service user perspectives. The project will also provide knowledge about the adaptations and process needed to prepare the platform for evaluation in Canada.

Conclusions: This study contributes to an important gap in the literature pertaining to the specific principles, methods, and steps involved in adapting eHealth interventions for implementation and evaluation across a diverse range of cultural, geographical, and health care settings.

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KEYWORDS

mental health; young adult; telemedicine; eHealth; social support; therapy; psychology

Introduction

Background

eHealth interventions have the potential to address challenges related to access, service engagement, and continuity of care in the delivery of mental health services [1,2]. However, the initial development and evaluation of such interventions can require substantive amounts of financial and human resource investments to bring them to a level of scale. It is therefore important to consider alternative avenues to advance the practice of eHealth in a global context. One possibility for health system planners and service providers is leveraging the existing eHealth interventions that have been developed and tested in one country or jurisdiction and adapting these interventions for use in different communities and settings. This would reduce duplication of efforts at a global scale in terms of spending public, industry, and philanthropic resources to produce seemingly novel services and products that have already been developed elsewhere. It would also be in alignment with how health care innovations have traditionally been scaled up. However, more attention on how best to transport promising eHealth innovations across geographical, cultural, and contextual boundaries is warranted.

There are two general approaches to transporting eHealth interventions from one context to another: adoption and adaptation [3]. Adoption refers to a direct transport of the intervention by the developer or importation by the new context without systematically or extensively considering how the innovation fits with the needs and characteristics of the local service context, culture, and population. Adaptation involves making changes to the intervention to increase its fit with the local population and setting in which it is to be newly implemented and tested for its efficacy and effectiveness. It involves, for example, consideration of language, culture, and context [4,5]. Building on the definition of intervention adaptation from Sundell et al [3] and cultural adaptation from Bernal et al [4] and Castro et al [5], we define *eHealth adaptation* as the systematic, purposeful, and collaborative process of making changes to increase the relevance and acceptability of an eHealth innovation to a local population and health care setting and ultimately increase its effectiveness.

Thus, the purpose of adapting an intervention is to ensure that it is meaningful and satisfactory for a population that is different from the population for which the intervention was originally developed [6]. It has been suggested that acceptability of an intervention may influence the extent to which individuals engage with and participate in an intervention, which can ultimately affect its effectiveness [5]. Moreover, engaging in an adaptation process could help increase ownership of the intervention by the local setting and improve its sustainability especially if conducted using a collaborative and shared decision-making process [3,7]. Interventions that are matched in terms of linguistic, educational, and developmental needs of a population, and that have content that is perceived as interesting, useful, and relevant to a population's everyday life may elicit higher levels of engagement, and ultimately contribute to effectiveness [3].

In fact, recent systematic reviews indicate that the effectiveness of mental health–related interventions (in-person or Web-based) developed in one context and evaluated in another, are influenced by whether the intervention was adapted before the implementation [3,6,8,9]. In other words, those studies that involved cultural and contextual adaptations of interventions yielded larger effect sizes when compared with interventions that were not adapted for the same clientele group; however, it is important to note that these results have not been consistent across studies. As such, scholars have argued for more research to determine the effect of adaptations when transferring interventions across populations, settings, and countries [3,5]. This can help in determining whether the benefits of adaptation are worth the costs [5] and also to begin identifying what types of adaptations contribute the most toward outcomes.

Part of the challenge in reviewing the effectiveness of intervention adaptation is that there is limited consensus on the methods and processes for adapting an intervention. This is particularly the case for the eHealth field as many of the adaptation frameworks that have been developed were originally meant for face-to-face interventions. For example, Harper Shehadeh et al [6] highlight that some of the elements proposed in the cultural adaptation framework documented by Bernal and colleagues [4] may not be applicable in minimally guided interventions (including those delivered online). The cultural adaptation framework documented by Bernal and colleagues is widely cited in the psychosocial intervention literature pertaining to cultural adaptation. A second challenge in this field is limited documentation on adaptations undertaken by researchers when transporting or importing innovations from one context to another. For example, 2 recent systematic and meta-analytic reviews [3,6] on the adaptation of mental health interventions, including those delivered online, found few studies reporting details on the methods and processes of adaptation. This type of information is needed to inform the interpretation of findings as well as implementation and scale-up [6]. The lack of documentation on adaptations undertaken may in part be due to the dearth of guidance on the methods, processes, and impact of adapting eHealth interventions when implementing them across populations, settings, and countries.

In summary, more information and research attention are needed on the steps involved in transporting or importing interventions from one context to another, as well as the influence of adaptation on acceptability and outcomes. Toward this end, we report on an eHealth adaptation research framework and protocol for a Web-based intervention developed in Australia, Horyzons, in preparation for a pilot implementation study in Canada.

Description of the Intervention

Horyzons is a Web-based therapeutic platform designed to sustain the treatment benefits of specialized services for psychosis especially in relation to relapse prevention and social functioning through the provision of psychosocial interventions during transitions from specialized to regular mental health care. Horyzons was originally developed in Australia by coauthors (A2, A7), an interdisciplinary team of experts (professional writers, clinical psychologists, comic developers, artists, experts in computer science and human computer interaction), and codeveloped with young people who have received specialized services for a first-episode psychosis (FEP). The team worked iteratively over a 30-month period following participatory design principles, positive psychology, evidence-based interventions (eg, mindfulness), and strengths-based models [10,11]. The Web-based portal consists of interactive strengths-based psychosocial interventions, peer-to-peer Web-based social networking, as well as clinical and peer moderation to provide guidance and ensure safety. The moderation approach of the intervention is informed by self-determination theory and supportive accountability to enhance engagement with the Web-based intervention and motivation in social and psychological functioning [12,13]. It has been tested on a sample of 20 young Australian adults for its feasibility, acceptability, utility, and safety [10,14]. Further details on the Horyzons platform and its core features are provided in Textbox 1 and illustrated in Multimedia Appendices 1 and 2.

Our aim is to create an adapted version of Horyzons that is tailored for a Canadian young adult population. It could be argued that cultural, language, and contextual differences between Westernized countries such as Australia and Canada are minimal as, for instance, both countries have publicly funded health care and a high proportion of cultural and ethnic diversity. However, there are differences in relation to how mental health services are implemented at the front-line, which may influence implementation of the intervention. Moreover, Canada has a history of both French and British colonization whereas Australian colonial history is British, which highlights the importance of attending to communication practices and related linguistic considerations in the context of transporting or importing an eHealth intervention.

The adaptation of the Horyzons platform is the first step in a multiphased, international research program.

Textbox 1. Overview of the Horyzons system.

Purpose: To promote long-term recovery in youth with psychosis.

Developers: Multidisciplinary development team comprising of software developers, mobile developers, novelists, comic artists, clinical psychologists, experts in human computer interaction, experts in machine learning and natural language processing, young people with lived experience.

Original population: Youth with first-episode psychosis (FEP) living in Melbourne, Australia.

Main components:

- Therapy modules (steps): discrete, interactive, evidence-based therapy modules addressing, for example (1) personal strengths (eg, identifying personal strengths via an interactive card-sort game based on the strengths-based frameworks; (2) mindfulness (eg, activities to enhance self-compassion); and (3) connecting with others (eg, modules providing guidance on how to respond to the good news expressed by others; how to respond empathically to others). Content is conveyed through text, video, audio, and interactive visual graphics.
- Persuasive system features ("do its," "playlist") to promote behavioral change: behavioral prompts that support the implementation of a "step" in real-life contexts (eg, following a step about identifying personal strengths, the user is prompted to exercise a core personal strength such as kindness in specific contexts such as at school or work). A "playlist" stores and schedules any "do-it" the young person wants to complete in the future. Behavior change is also promoted through social network features described below.
- Social network features ("the café," "team up," "talk it out"): Users are encouraged to communicate with one another through the Web-based social network or "café" to foster social support and connectedness. Each user creates her or his own profile with images (as on Facebook) and can visit the wall of fellow users, where their posts and general activity are displayed. Users can rate, comment on, and share any step with others via the social networking newsfeed. Users can also support others' efforts to engage in specific behavioral changes via the "team up" function. A group problem-solving function (Talk it out) aims to promote social self-efficacy and interpersonal problem solving. It allows users to nominate issues (eg, "how to deal with low self-esteem about your body?").
- Moderation ("expert moderators" and "super-users"): Expert moderation is by mental health professionals experienced in treating patients with psychosis. Their role is to provide guidance, monitor participants' clinical status, and ensure the safety of the social network. Each expert moderator is assigned a caseload (a full-time moderator can manage 100 users). Expert moderators develop brief case formulations that are presented at weekly supervision meetings with senior clinicians. Moderators send each client tailored content suggestions weekly based on the clients' needs, interests, and strengths. Suggestions appear on the user's home page, and they receive a text notification via an inbuilt text-messaging (short message service) function. Super-users are young people with lived experience of FEP who have received peer-support training. Their role includes providing support and fostering engagement (eg, reaching out to reticent users, posting "ice-breakers," commenting and liking posts, and modeling activity). The site is monitored by moderators 7 days a week during moderating hours. The system is set up to send automatic notifications to the moderator when posts have words that could be indicative of risk; these posts are blocked until the moderator can assess the post and its related risk following a clinical safety protocol.

Specifically, the aim of this phase I study is to assess the initial acceptability of the platform by analyzing perspectives of Canadian young adults receiving specialized services for FEP and service providers on the Horyzons platform (eg, in relation to perceived usefulness and ease of use), and to adapt the platform in preparation for evaluation. The results will then inform the design for phase II, a pilot test of the adapted platform with a small sample of mental health service users. Subsequently, these results will support detailed planning for controlled evaluations of the intervention (eg, randomized controlled trial).

Conceptual Framework

To inform and guide the adaptation, we conducted a literature review on research pertaining to adapting interventions across cultural and contextual settings. We identified several models on the adaptation process developed across a range of different fields (eg, psychology, education); for example, in relation to psychotherapy and evidence-based health interventions [4,15-23]. We also identified frameworks evaluating Web-based tools [24,25], implementation research models (eg, Revised Ottawa Model of Research Use) [26], and technology and innovation models (eg, technology acceptance model) [27]. Some of the key elements drawn from this review are summarized in the sections below followed by a presentation of the eHealth adaptation framework that will be used in this study.

According to Castro et al [5], there are 3 broad elements that need to be considered when adapting interventions: characteristics of the population that will receive the intervention; the staff that would be involved in delivering the intervention; and other administrative, contextual, and community factors. Where there are mismatches between aspects of the current intervention with these 3 elements, adaptations should be considered. Moreover, several models suggest a staged process for adaptation that incorporates qualitative and quantitative data over the course of a series of steps leading to changes in an intervention [5,15,16]. A synthesis of these models suggests the following steps that are important to consider in the adaptation process: (1) assess and generate knowledge from target population, program implementers, and stakeholders; (2) determine the need to adopt or adapt the intervention; (3) identify elements to adapt, respect core elements of the original intervention, pilot-test adaptations with target population, program implementers, and stakeholders; (4) integrate adaptations into the intervention; (5) conduct a formal evaluation of the adapted intervention (eg, pilot study); (6) refine the intervention if necessary; and (7) conduct efficacy, effectiveness, and implementation trials.

In terms of specific elements to assess, the Ecological Validity Model from Bernal et al [4] suggests culturally sensitive elements, such as language, concepts, and content, to address during the adaptation process, whereas the Framework for Evaluating the Quality of Multimedia Learning Resources [24] and the Mobile Assessment Rating Scale [25] identify several items that help evaluate users' experiences of a Web-based platform, for example, motivation, aesthetics, accessibility, interaction, quality and credibility of information, and usability. The Revised Ottawa Model of Research Use [26] highlights the importance of considering barriers and supports, including the adaptors, the practice environment, and implementation strategies. Finally, the technology acceptance model suggests that the perceived ease of use and perceived usefulness of an information technology will influence users' acceptance of a technology [27].

Moreover, before engaging in an adaptation of an eHealth intervention, it is important to clarify the therapeutic intervention principles upon which it is based, including what the intervention aims to achieve and how it achieves it [28]. For example, Horyzons is based on supportive accountability principles that highlight that human support (ie, social presence of an individual online that is seen as trustworthy and having expertise, such as a clinician moderator) increases motivation to engage in the intervention, which is important for clinical outcomes [13]. Thus, to maintain internal validity of an eHealth intervention, adaptations would not focus on the core principles (eg, supportive accountability through clinician moderation) but rather on content and features of the platform to enhance its usability, interactivity, relevance to a local population and context, and alignment with current technologies.

These aforementioned principles and models were used to develop our research framework, which is organized into the following 3 objectives and stages: (1) to assess initial perspectives of service users and providers of the eHealth intervention (without any modifications) following a brief overview and interaction with the website, (2) to assess perspectives of the eHealth intervention after an extended exploration, and (3) to adapt the eHealth intervention based on feedback from key stakeholder groups (while respecting its core therapeutic elements and principles, and considering feasibility of adaptations in terms of resources available). The second objective is important as it provides an opportunity for participants to explore the platform in the community at their own pace and more extensively, which could help elicit additional perspectives pertinent for adaptation. Further details on the eHealth adaptation framework in terms of methods and processes are provided in Table 1. All stages of the study seek to better understand participant perspectives of all 4 components of the platform. We anticipate that most of the adaptations that will be recommended will be in relation to the therapeutic modules; however, this remains to be assessed based on the results of the study.

Table 1. eHealth adaptation framework. ICT: information and communication technology; N/A: not applicable.

Framework components	Stage 1	Stage 2	Stage 3
Objectives	To assess initial perceptions and experiences of the original Web-based platform from the perspectives of service users and service providers following a brief overview, including the core therapeutic principles and features it is based on, and exposure to it.	To assess perceptions and experiences of the original Web-based platform after engaging with it over a duration of 2 weeks.	To adapt the Web-based platform based on stakeholder feedback, while respecting its core elements and feasibility of resources.
Questions	What are the perceptions of mental health service users and service providers regarding the Web-based platform?	What are the perceptions of mental health service users and service providers regarding the Web-based platform following an extended personal exploration of 2 weeks?	What are the recommendations of mental health service users and service providers on adapting the Web-based platform to enhance its relevance and acceptability?
Topics	• Language; culture • Likes, dislikes, facilitators, barriers • Usefulness • Safety • Design, ease of use • Therapeutic alignment • Organizational factors	• Language; culture • Likes, dislikes, facilitators, barriers • Usefulness • Safety • Design, ease of use • Therapeutic alignment • Organizational factors	Targeted features and content for adaptation based on stage 1 data.
Participants	Service users, service providers	Service users, service providers	Service users, service providers
Data collection			
Activity	ICT use survey, platform introduction, brief exploration and guided activities, feedback forms, group discussion	Extended exploration and feedback forms	Consultation meetings
Methods of collection			
Service providers and users	*Survey*: Topics include • Access to technology • Use of Internet and related technologies • Barriers and facilitators to using technology *Focus group*: Questions include • What do you like the most about the platform? • What do you dislike the most about the platform? • How is the content helpful? (probe: images, audio, videos) • How are the features helpful? • What are your thoughts on: how motivating and engaging it is to use; what could hinder motivation to use the platform; how safe the platform is to use; the support that is offered on this platform; the design and layout; and, how easy it is to use? • If you could make one change or add something to the platform, what would it be? • Please identify any words, expressions, or parts of the platform that seem unclear • What are your suggestions for adaptations (eg, in relation to language, metaphor, images, ease of use, content, the way information is presented)?	N/A	Identify modules, features, content, activity that needs adaptation. For each adaptation, the following topics will be discussed in an iterative manner • Relevancy or fit for Canadian context • Written feedback on each adaptation (likes, dislikes, content difficult to understand) • Content, links to add or delete; general comments

Framework components	Stage 1	Stage 2	Stage 3
Service providers only	N/A	• Explore 4 features, activities, modules to evaluate (2 preselected by the researchers based on service provider expertise and 2 selected by the service provider). • Complete written feedback form for each activity identified in terms of suggested adaptations; reasons why they are important; general comments.	N/A
Users only	N/A	• Explore 4 features, activities, modules to evaluate (2 preselected by the researchers and 2 selected by the service user). • Complete written feedback form for each activity identified in terms of content, sentences, or words that are not clear or difficult to understand: What you like?; What you dislike?; and general comments. • Additional questions: Which other activities did you try on the website?; What are your comments related to these other activities (eg, likes, dislikes, recommendations for changes)?; Please share any other comments or suggestions.	*Questionnaire*: • Would you recommend the use of this platform to others? (5-point Likert scale) Please elaborate • Would you feel safe on this platform? Y or N—Please elaborate • Please list 3 key obstacles that might prevent an individual from using this platform • Please list 3 strategies that would encourage a young person to use this platform • What would be an ideal total number of participants using this platform at the same time? • How would you use this platform? Please select from the following: Learning about what happened to you, and how to get better; Social networking (meeting other youth that have gone through similar experiences; Support from other youth; Support from mental health service providers; Other purpose, specify

Methods

Participants and Setting

This research will take place in 2 specialized early intervention clinics for FEP, 1 urban and 1 semirural, located in different provinces. Both programs provide a comprehensive range of services for young people diagnosed with FEP and follow best practice guidelines for real-world settings [29,30]. Service users and providers from both sites will take part in the study. Eligibility criteria for service users are as follows: diagnosed with a psychotic disorder, within their first 3 years of treatment and currently followed by a clinician, considered to be symptomatically stable and capable of participating in focus groups as judged by their primary treating clinician, and 18 years of age and older. Eligible service providers include psychiatrists, case managers, or other health care professionals with a minimum of 2 years of experience working in the field of specialized early intervention for FEP and regularly involved in delivering services to youth with FEP. We aim to recruit a minimum of 11 service providers (6 urban and 5 rural) and 11 service users (6 urban and 5 rural).

Ethics approval has been obtained from the ethics review board of the primary recruitment site and from the ethics review board of the secondary site. All participants will provide written, informed consent before participating in the study.

The same data collection activities will be conducted at both sites and with both groups separately on a beta-version of the eHealth intervention: sociodemographic and technology use questionnaire, focus group discussions with written feedback forms, and extended explorations of the platform with written feedback forms.

Stage 1: Assessing Initial Perspectives and Experiences of the eHealth Intervention

To address the first objective, service users and providers will respond to a survey and take part in focus group sessions. In addition to collecting sociodemographic information, the survey will assess participants' access, experiences, and attitudes on their use of information and communication technology (ICT) as well as their use of ICT in relation to obtaining mental health information, services, and supports. The focus group sessions with service users and providers will take place separately in a computer lab with approximately 4 to 5 participants per session

and will last approximately 90 min. Each participant will be assigned to their own computer station (or laptop) and logged into the platform as an individual user with a personalized access code. The focus groups will be led by 2 facilitators and will include a brief tutorial on the core features of the intervention, for instance, the persuasive system, the social networking features, the role of moderators, the main content areas, and the core therapeutic principles. The facilitator will also describe how the platform is envisioned to be implemented in the future pilot study and a subsequent randomized controlled trial. The aim of this first step is 2-fold: first, to help participants understand the intention and functioning of the platform as well as the overall vision for its future implementation before considering local and contextual adaptations; and second, to provide participants with a general understanding of how the website is organized to facilitate their subsequent individual explorations of the website. Next, participants will individually explore the platform at their workstations and provide feedback on the following: general impressions (likes, dislikes, questions, comments); usefulness, safety and support; design, layout, and navigations; ease of use; and suggestions for modifications and adaptations (Canadian context and language). Patient participants will receive $25 CAD, and clinician participants will be offered lunch for their participation in this component of the study.

Stage 2: Assessing Perspectives and Experiences of the eHealth Intervention After an Extended Exploration

At the end of the focus group session, service providers and service users will be invited to individually explore a beta version of the eHealth intervention for a maximum of 120 min over a 2- to 4-week period from a personal computer. Each participant will be given personal log-in information (username and password) to access the platform providing them with the opportunity to continue their exploration of the platform's therapeutic content and activities. Participants will be given either an email or electronic copy of a feedback form with detailed instructions and questions to capture their impressions and suggestions for modifications and adaptations. Patient participants will receive $50 CAD for their participation in this component of the study.

Data obtained during stages 1 and 2 of the research will provide insights on whether the platform and its aims as a whole are understandable and whether participants would be interested in using the platform as a complement to the services they receive. The qualitative data from the focus groups will be recorded and transcribed verbatim, and the written feedback responses (from the focus groups and extended explorations) will be organized into tables. The data will be managed using Atlas.ti (Scientific Software Development GmbH, Version 7.5.6), and a coding framework will be developed based on the interview guide and a thematic analysis approach. The quantitative data will be assessed using descriptive statistics. In line with the convergent mixed-methods model, the quantitative and qualitative data will first be analyzed separately and then considered for an integrated analysis of the findings [31].

Stage 3: Adapting the eHealth Intervention

The adaptations identified in stages 1 and 2 will be considered in relation to the feasibility of making the adaptations as well as how they might affect the core features of the intervention (eg, fidelity). The adaptations that are suggested by participants will be discussed with the intervention authors to assess the extent to which these adaptations would affect fidelity of the platform. Moreover, results from this initial adaptation study will provide insights on strategies that may need to be implemented to ensure fidelity of the intervention during the pilot implementation.

If needed, an additional process of consensus discussion will be added to prioritize the adaptations that will be pursued. Service providers who take part in the focus groups will first be consulted on an individual basis to identify the details of the adaptations that will be made. Service users will be invited to assess the usefulness and accessibility of the adapted content and to share their feedback. Patient participants will receive $25 CAD for their participation in this final stage of the study. The adapted eHealth intervention will be further assessed during the second phase of the research program, that is, a small pilot study using a live version of the site. A live version of the site will provide participants access to the full range of social media features of the platform such as communicating with others, as well as posting images, videos, and links. Moreover, a live version would also provide access to a Web-based peer support worker and clinician moderator.

Results

The project was funded March 2015 and data collection was completed in August 2017. Analysis and adaptations are currently under way, and the first results are expected to be submitted for publication in 2018.

Discussion

Study Rationale and Significance

This protocol addresses an important gap in the eHealth intervention literature in terms of frameworks, methods, and processes used by researchers to adapt an eHealth intervention before its implementation and evaluation in different contexts and settings. Although more research is needed on the effectiveness of adapting interventions, there is a general consensus by several authors of systematic and meta-analytical reviews of psychological and health-promotion interventions (eg, [3,6]) that considering adaptation when transporting interventions and programs is well-warranted. Moreover, not only is there a "moral case to test and demonstrate the appropriateness, acceptability, and harmlessness of interventions up front" [6], there is increasing evidence indicating that such a process can positively impact the effectiveness of an intervention. We believe this would extend similarly to the adaptation of eHealth innovations when considering their implementation across geographical, cultural, and contextual settings, particularly those that are based on psychological and social therapy principles and interventions.

Access to details on the adaptation of eHealth interventions is important for supporting the interpretation of results obtained from effectiveness studies when an innovation is implemented and studied across different settings. Although the importance of retaining therapeutic principles and mechanisms of an intervention when scaling up evaluation are recognized, there are limited examples of how changes to increase relevancy, alignment with current technologies, interactivity, and fit can be considered when scaling up evaluation of eHealth innovation across cultural and contextual settings. The eHealth adaptation framework that we have developed for this study provides a concrete example of the process and methods for how adaptations to psychological, social, and educational interventions in the field of eHealth could be addressed. It highlights the importance of considering the therapeutic principles and mechanisms upon which the intervention is based; the population, the service providers, and the setting (eg, urban, rural, program delivery model) in which the innovation will be implemented; extended opportunities to explore the eHealth intervention at a pace that is more reflective of real-life implementation; considering the perspectives of different stakeholder groups, including their experiences, skills, access, and attitudes toward the use of technology; and, providing different media and methods through which to collect data pertaining to adaptation (eg, focus groups, written feedback, consultation).

In addition, we will be able to compare adaptations suggested across settings (eg, urban, multiethnic vs semirural). Our framework also attends to the various types of media that participants can access on the website, including the visual images, audio, and video supports, and the importance of understanding whether these media are presented in a manner that is relatable to different audience groups. For example, given that the graphics are created by an Australian visual artist, it is possible that some of the imagery and symbolism may not be readily understandable to the Canadian population. Also, the voice recordings for therapeutic activities (eg, mindfulness, breathing) have an Australian accent, and this might hinder participation and engagement. The study will also provide information on words that may need to be added or rephrased in accordance with Canadian English language. The system has a database of synonyms obtained from Web-based dictionaries and can make suggestions on aspects of the website that may be of interest to participants based on their posts (by matching words used in their posts and related synonyms from the dictionary to therapeutic content on the website). As such, it will be important to assess the appropriateness of the dictionary being used by the system during the adaptation of the intervention.

Limitations and Future Research

Certain limits of the adaptation protocol are also acknowledged. For example, the protocol invites participants to reflect on features of the platform that would be available during the live implementation (eg, clinician moderator, peer support worker); in this regard, some of their perspectives will be based on projections into the future, rather than actual experience. To mitigate this limitation, we plan to pilot-test the adapted version, with all features accessible, with a small sample (n=20) of participants over a period of 8 weeks. The pilot study will also have a qualitative component assessing participants' experiences of all aspects of the platform, for example, interactions with peers, peer support worker, and clinician moderators. This will facilitate obtaining additional data on the acceptability of the eHealth intervention and any further adaptations needed before conducting controlled evaluations.

Conclusions

The results of this study will provide preliminary insights into the acceptability of the Horyzons Web-based platform (eg, perceived use and perceived usefulness) and knowledge about the adaptations and process needed to prepare the platform for evaluation in Canada. Moreover, this protocol contributes to an important gap in the literature pertaining to the specific principles, methods, and steps involved in the adaptation process for scaling up evaluation of eHealth innovations. This type of research is novel from a Canadian and international eHealth perspective and is increasingly relevant in a global environment where eHealth innovations are being considered for implementation across a range of cultural, geographical, and health system contexts.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Horyzons' Screenshot: How Horyzons Works.

[PNG File, 151KB - resprot_v7i4e100_app1.png]

Multimedia Appendix 2

Horyzons' Screenshot: Strengths.

[PNG File, 207KB - resprot_v7i4e100_app2.png]

References

1. Lal S, Adair CE. E-mental health: a rapid review of the literature. Psychiatr Serv 2014 Jan 1;65(1):24-32. [doi: 10.1176/appi.ps.201300009] [Medline: 24081188]
2. Lal S, Malla A. Service engagement in first-episode psychosis: current issues and future directions. Can J Psychiatry 2015 Aug;60(8):341-345 [FREE Full text] [doi: 10.1177/070674371506000802] [Medline: 26454555]
3. Sundell K, Beelmann A, Hasson H, von Thiele Schwartz U. Novel programs, international adoptions, or contextual adaptations? Meta-analytical results from German and Swedish intervention research. J Clin Child Adolesc Psychol 2016;45(6):784-796. [doi: 10.1080/15374416.2015.1020540] [Medline: 25864716]
4. Bernal G, Bonilla J, Bellido C. Ecological validity and cultural sensitivity for outcome research: issues for the cultural adaptation and development of psychosocial treatments with Hispanics. J Abnorm Child Psychol 1995 Feb;23(1):67-82. [Medline: 7759675]
5. Castro FG, Barrera M, Holleran Steiker LK. Issues and challenges in the design of culturally adapted evidence-based interventions. Annu Rev Clin Psychol 2010;6:213-239 [FREE Full text] [doi: 10.1146/annurev-clinpsy-033109-132032] [Medline: 20192800]
6. Harper Shehadeh M, Heim E, Chowdhary N, Maercker A, Albanese E. Cultural adaptation of minimally guided interventions for common mental disorders: a systematic review and meta-analysis. JMIR Ment Health 2016 Sep 26;3(3):e44 [FREE Full text] [doi: 10.2196/mental.5776] [Medline: 27670598]
7. Durlak JA, DuPre EP. Implementation matters: a review of research on the influence of implementation on program outcomes and the factors affecting implementation. Am J Community Psychol 2008 Jun;41(3-4):327-350. [doi: 10.1007/s10464-008-9165-0] [Medline: 18322790]
8. Chowdhary N, Jotheeswaran AT, Nadkarni A, Hollon SD, King M, Jordans MJ, et al. The methods and outcomes of cultural adaptations of psychological treatments for depressive disorders: a systematic review. Psychol Med 2014 Apr;44(6):1131-1146 [FREE Full text] [doi: 10.1017/S0033291713001785] [Medline: 23866176]
9. Smith TB, Rodríguez MD, Bernal G. Culture. J Clin Psychol 2011 Feb;67(2):166-175. [doi: 10.1002/jclp.20757] [Medline: 21105069]
10. Alvarez-Jimenez M, Bendall S, Lederman R, Wadley G, Chinnery G, Vargas S, et al. On the HORYZON: moderated online social therapy for long-term recovery in first episode psychosis. Schizophr Res 2013 Jan;143(1):143-149. [doi: 10.1016/j.schres.2012.10.009] [Medline: 23146146]
11. Fredrickson BL, Losada MF. Positive affect and the complex dynamics of human flourishing. Am Psychol 2005 Oct;60(7):678-686 [FREE Full text] [doi: 10.1037/0003-066X.60.7.678] [Medline: 16221001]
12. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol 2000 Jan;55(1):68-78. [Medline: 11392867]
13. Mohr DC, Cuijpers P, Lehman K. Supportive accountability: a model for providing human support to enhance adherence to eHealth interventions. J Med Internet Res 2011;13(1):e30 [FREE Full text] [doi: 10.2196/jmir.1602] [Medline: 21393123]
14. Gleeson JF, Lederman R, Wadley G, Bendall S, McGorry PD, Alvarez-Jimenez M. Safety and privacy outcomes from a moderated online social therapy for young people with first-episode psychosis. Psychiatr Serv 2014;65(4):546-550. [doi: 10.1176/appips.201300078] [Medline: 24687106]
15. Barrera Jr M, Castro FG, Strycker LA, Toobert DJ. Cultural adaptations of behavioral health interventions: a progress report. J Consult Clin Psychol 2013 Apr;81(2):196-205 [FREE Full text] [doi: 10.1037/a0027085] [Medline: 22289132]
16. Wingood GM, DiClemente RJ. The ADAPT-ITT model: a novel method of adapting evidence-based HIV Interventions. J Acquir Immune Defic Syndr 2008 Mar 01;47 Suppl 1:S40-S46. [doi: 10.1097/QAI.0b013e3181605df1] [Medline: 18301133]
17. Hwang WC. The psychotherapy adaptation and modification framework: application to Asian Americans. Am Psychol 2006 Oct;61(7):702-715. [doi: 10.1037/0003-066X.61.7.702] [Medline: 17032070]
18. Domenech Rodríguez MM, Baumann AA, Schwartz AL. Cultural adaptation of an evidence based intervention: from theory to practice in a Latino/a community context. Am J Community Psychol 2011 Mar;47(1-2):170-186. [doi: 10.1007/s10464-010-9371-4] [Medline: 21116707]
19. Bowen SA, Saunders RP, Richter DL, Hussey J, Elder K, Lindley L. Assessing levels of adaptation during implementation of evidence-based interventions: introducing the Rogers-Rütten framework. Health Educ Behav 2010 Dec;37(6):815-830. [doi: 10.1177/1090198110366002] [Medline: 21051771]
20. Marsiglia FF, Booth JM. Cultural adaptation of interventions in real practice settings. Res Soc Work Pract 2015 Jul 01;25(4):423-432 [FREE Full text] [doi: 10.1177/1049731514535989] [Medline: 26213454]

21. McKleroy VS, Galbraith JS, Cummings B, Jones P, Harshbarger C, Collins C, ADAPT Team. Adapting evidence-based behavioral interventions for new settings and target populations. AIDS Educ Prev 2006 Aug;18(4 Suppl A):59-73. [doi: 10.1521/aeap.2006.18.supp.59] [Medline: 16987089]
22. Poulsen MN, Vandenhoudt H, Wyckoff SC, Obong'o CO, Ochura J, Njika G, et al. Cultural adaptation of a U.S. evidence-based parenting intervention for rural Western Kenya: from parents matter! To families matter!. AIDS Educ Prev 2010 Aug;22(4):273-285. [doi: 10.1521/aeap.2010.22.4.273] [Medline: 20707689]
23. Robinson BE, Galbraith JS, Lund SM, Hamilton AR, Shankle MD. The process of adaptation of a community-level, evidence-based intervention for HIV-positive African American men who have sex with men in two cities. AIDS Educ Prev 2012 Jun;24(3):206-227. [doi: 10.1521/aeap.2012.24.3.206] [Medline: 22676461]
24. Leacock TL, Nesbit JC. A framework for evaluating the quality of multimedia learning resources. J Educ Techno Soc 2007;10(2):44-59 [FREE Full text]
25. Stoyanov SR, Hides L, Kavanagh DJ, Zelenko O, Tjondronegoro D, Mani M. Mobile app rating scale: a new tool for assessing the quality of health mobile apps. JMIR Mhealth Uhealth 2015;3(1):e27 [FREE Full text] [doi: 10.2196/mhealth.3422] [Medline: 25760773]
26. Santesso N, Tugwell P. Knowledge translation in developing countries. J Contin Educ Health Prof 2006;26(1):87-96. [doi: 10.1002/chp.55] [Medline: 16557514]
27. Holden RJ, Karsh BT. A theoretical model of health information technology usage behaviour with implications for patient safety. Behav Inf Technolol 2009 Jan;28(1):21-38. [doi: 10.1080/01449290601138245]
28. Mohr DC, Schueller SM, Riley WT, Brown CH, Cuijpers P, Duan N, et al. Trials of intervention principles: evaluation methods for evolving behavioral intervention technologies. J Med Internet Res 2015;17(7):e166 [FREE Full text] [doi: 10.2196/jmir.4391] [Medline: 26155878]
29. Malla A, Lal S, Vracotas NC, Goldberg K, Joober R. Early intervention in psychosis: specialized intervention and early case identification. Encephale 2010 Mar;36 Suppl 3:S38-S45. [doi: 10.1016/S0013-7006(10)70029-4] [Medline: 21095391]
30. Malla A, Norman R, McLean T, Scholten D, Townsend L. A Canadian programme for early intervention in non-affective psychotic disorders. Aust N Z J Psychiatry 2003 Aug;37(4):407-413. [doi: 10.1046/j.1440-1614.2003.01194.x] [Medline: 12873324]
31. Creswell JW, Klassen AC, Plano Clark VL, Smith KC. Best Practices for Mixed Methods Research in the Health Sciences. Bethesda, Maryland: National Institutes of Health; 2011.

Abbreviations

FEP: first-episode psychosis
ICT: Information and communication technology

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Protocol

The Effect of Occupational Lifting on Hypertension Risk: Protocol for a Project Using Data From the Copenhagen City Heart Study

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Abstract

Background: Hypertension is a major risk factor for cardiovascular disease and is responsible for 14% of all annual deaths globally. The prevalence of hypertension varies across occupational groups, possibly affected by differences in the working environment. One work-related factor that might impose a risk for hypertension is lifting due to the acute large increases in blood pressure (BP) during lifting.

Objective: The aim of this study is to explore associations between heavy occupational lifting and hypertension in the Copenhagen City Heart Study.

Methods: This study will use data from the third, fourth, and fifth examination of the Copenhagen City Heart Study. The dataset contains person-based information on health as well as a large variety of biological, environmental, and lifestyle-related factors. Using a cross-sectional design, we will investigate the association between heavy occupational lifting and hypertension, defined as using antihypertensive drugs or having a measured systolic BP (SBP) ≥140 mm Hg or diastolic BP (DBP) ≥90 mm Hg. Furthermore, in a prospective design, we will investigate the association between heavy occupational lifting and risk of becoming an SBP case, defined as the shift from not using antihypertensive drugs in examination n to use of antihypertensive drugs in examination n+1 or an above median delta value of SBP (SBP in examination n+1−SBP in examination n).

Results: In the third examination in 1991-1994, 10,135 out of 16,560 participants attended (61.20%), in the fourth examination in 2001-2003, 6237 out of 12,599 participants attended (49.50%), and in the fifth examination in 2011-2015, 4550 out of 9765 participants attended (46.59%). On the basis of the inclusion criteria of answering to the level of occupational physical activity, 5031 observations were excluded from examination 3, 2600 from examination 4, and 1621 from examination 5. Hence, the final populations for the cross-sectional and prospective analysis are assumed to include less than 7166 participants in the cross-sectional analysis and less than 1850 participants in the prospective analysis due to the additional inclusion criteria of measured BP and use of antihypertensive drugs.

Conclusions: One-third of the workforce in Europe reports to carry or move heavy loads regularly during working hours (6th survey in Eurofound). Thus, if this study shows occupational lifting to increase the risk for hypertension, the prevention for hypertension can be improved.

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KEYWORDS

occupational exposure; blood pressure; Copenhagen City Heart Study; cardiovascular diseases; manual handling; blue collar; occupational epidemiology; heavy lifting; cohort study

Introduction

Background

Hypertension is a major risk factor for cardiovascular diseases [1,2] and is responsible for 14% of all annual deaths globally [1]. The prevalence of hypertension varies across occupational groups, possibly affected by differences in the working environment. One work-related factor that might impose a risk for hypertension is lifting [3,4]. Heavy lifting causes acute large increases in blood pressure (BP) [5]. These increases in BP during heavy lifting are explained by the constriction of the vessels due to contraction of muscle fibers surrounding the vessels as well as the pressor reflex, both leading to an increased peripheral resistance and thereby also an increased BP [5]. Thus, because some workers perform occupational lifting for several hours per day, many days per week, higher BP or hypertension is likely to occur [6]. Yet, scientific knowledge of the relation between heavy occupational lifting and hypertension is limited. Previous studies investigating this relation have found occupational lifting to increase risks for myocardial infarction [3] and ischemic heart disease [4] in population studies including both sexes and workers from white- and blue-collar occupations. However, one study, only including males from blue-collar occupations did not find increased risk for ischemic heart disease from occupational lifting [7]. As the study by Petersen and colleagues [4] found the risks from lifting to be most pronounced among workers with low occupational physical activity (OPA) but high exposure to lifting, it seems that investigations of associations between occupational lifting and risk for hypertension benefit from populations including both sexes and a variety of occupations.

Conversely, heavy lifting might also impose beneficial effects on BP, since resistance training involving heavy lifting has been shown to reduce resting BP [8,9]. Additionally, it is also unknown whether effects of exposure to heavy occupational lifting differ between participants with and without preexisting hypertension. A Danish survey from 2016 [10] concludes that 22% of the Danish workforce are exposed to occupational lifting during ≥25% of their working hours. Likewise, 32% of European workers report to carry or move heavy loads regularly during working hours (6th survey in Eurofound). Thus, an investigation of the association between occupational lifting and risk of hypertension in population studies including both sexes and both blue- and white-collar occupations, might uncover a potential for prevention of cardiovascular diseases for a quite large proportion of the working population.

Objective

The aim of this study is to explore associations between heavy occupational lifting and hypertension in the Copenhagen City Heart Study. Associations will be investigated both cross-sectionally and prospectively, among randomly selected citizens from two districts of Copenhagen, Denmark.

For the cross-sectional analysis, the primary null-hypothesis is that there is no association between heavy occupational lifting and hypertension. For the prospective analysis, the primary null-hypothesis is that there is no association between heavy occupational lifting at baseline and increased resting systolic BP (SBP) 10 years later.

Methods

Overview

This study will use data from the Copenhagen City Heart Study, which have been collected via health examinations and questionnaires in five examinations, namely 1976-1978, 1981-1983, 1991-1994, 2001-2003, and 2011-2014, on random population samples from two districts of Copenhagen. The sample of the first examination consisted of approximately 20,000 people in the age range of 20 to 93 years. The samples of the other examinations consisted of all previously invited people plus a new sample of people, who were younger than 20 years at the time of the first examination. In the first examination, 73.58% responded (14,223/19,329), this dropped to 49.50% (6237/12,599) in the fourth examination [11]. The dataset contains person-based information on health, as well as a large variety of biological, environmental, and lifestyle-related factors. This study will include data from the third, fourth, and fifth examination of the Copenhagen City Heart Study for the analysis of the association between heavy occupational lifting and hypertension without inclusion of effect of time. Using a cross-sectional design, we will investigate the association between heavy occupational lifting and hypertension, defined as using antihypertensive drugs or having a measured SBP ≥140 mm Hg or DBP ≥90 mm Hg. Furthermore, in a prospective design, we will investigate the association between heavy occupational lifting and risk of becoming an SBP case across a time span of approximately 10 years. An SBP case will be defined as the shift from not using antihypertensive drugs in examination n to use of antihypertensive drugs in examination n+1 or an above median delta value of SBP (SBP in examination n+1−SBP in examination n). Analyses of associations both cross-sectional and prospectively hold the potential of evaluating associations both with and without inclusion of the effect of time.

Inclusion Criteria

For the cross-sectional analysis, the criteria for inclusion will be participation in the BP measurement and having responded to the questions regarding level of OPA (also including heavy lifting) and antihypertensive drug usage.

Inclusion criteria for the prospective analysis will be (1) that the participant answered the question regarding level of OPA at the third examination and/or fourth examination (n); (2) that he or she was normotensive at examination n; and (3) that he or she participated in the BP measurement and gave a valid answer to the questions regarding antihypertensive drug usage in examination n and n+1.

We believe that potential effects of heavy occupational lifting on BP may be concealed, reversed, or otherwise distorted by effects from antihypertensive drugs. The reason for excluding participants with hypertension at baseline from the prospective analysis is that they either are treated with antihypertensive drugs at examination n or, due to being detected as hypertensive at the health examination, are likely to receive treatment with

antihypertensive drugs in the time period between examination n and examination n+1.

Assessment of Exposure

In all 3 examinations, the self-reported information on level of OPA was obtained by asking the question: "Please describe your level of OPA within the past year" with the following response categories: "(1) predominantly sedentary; (2) sitting or standing, some walking; (3) walking, some handling of material; (4) heavy manual work." If answering 3 or 4, an additional question regarding heavy occupational lifting was applied. The question was: "Do you lift heavy burdens?" with the response categories: "(1) yes and (2) no." Participants will be classified as exposed to heavy occupational lifting by answering "yes" to the question concerning heavy burdens, and those participants answering 1, 2, and 3 or 4 in combination with not lifting heavy burdens will be classified as the reference group.

Between the examinations of data collection, we do not have any information about their exposure to OPA or lifting. However, for the prospective analysis, a measure of the stability of exposure was accounted for by cross-tabulating the self-reported exposure at examination 3 by exposure at examination 4 and also the self-reported exposure at examination 4 by exposure at examination 5. Among those participants responding to the self-reported exposure to OPA at examinations 3 and 4, 13.4% (329/2459) stated to be exposed to heavy lifting in examination 3 and 12.0% (295/2459) in examination 4. Among those participants responding to the self-reported exposure to OPA at examinations 4 and 5, 8.29% (146/1762) stated to be exposed to heavy lifting in examination 4 and 6.81% (120/1762) in examination 5. An evaluation of the agreement (Cohen kappa) between exposure to heavy occupational lifting in examinations 3 and 4 was .30, and the agreement between exposure to heavy occupational lifting in examinations 4 and 5 was .40, indicating a fair agreement between exposure to heavy occupational lifting across examinations (see Tables 1-4) [12].

Table 1. Number of participants who responded to the questions on level of occupational physical activity (OPA) at examinations 3 and 4.

Examination 3 (1991-1994)	Examination 4 (2001-2003)			
	1[a]	2	3	4
1	599	223	45	9
2	173	511	123	8
3	57	210	367	34
4	3	21	26	50

[a]1=predominantly sedentary; 2=sitting or standing, some walking; 3=walking, some handling of material; 4=heavy manual work.

Table 2. Number of participants who reported to have heavy occupational lifting at examinations 3 and 4.

Examination 3 (1991-1994)	Examination 4 (2001-2003)	
	Yes	No
Yes	236	93
No	59	90

Table 3. Number of participants who responded to the questions on level of occupational physical activity (OPA) at examinations 4 and 5.

Examination 4 (2001-2003)	Examination 5 (2011-2015)			
	1[a]	2	3	4
1	523	163	30	1
2	175	352	73	3
3	43	112	219	13
4	7	13	13	22

[a]1=predominantly sedentary; 2=sitting or standing, some walking; 3=walking, some handling of material; 4=heavy manual work.

Table 4. Number of participants who reported to have heavy occupational lifting at examinations 4 and 5.

Examination 4 (2001-2003)	Examination 5 (2011-2015)	
	Yes	No
Yes	94	52
No	26	95

Assessment of Outcome

The primary outcome in the cross-sectional analysis will be hypertensive status. Participants will be classified as hypertensives if they use antihypertensive drugs or they had a measured SBP ≥140 mm Hg or DBP ≥ 90 mm Hg.

In the prospective analysis, the primary outcome will be classified as an SBP case. The SBP case definition is the shift from no use of antihypertensive drugs in examination n to use of antihypertensive drugs in examination n+1 or an above median delta value of SBP (SBP in examination n+1−SBP in examination n).

In addition, secondary analyses will be conducted with pulse pressure (pulse pressure=SBP−DBP), mean arterial pressure (mean arterial pressure=([2 × DBP] + SBP/3) and mid BP (½ SBP + ½ DBP) as outcomes [13].

Assessment of Covariates

Previously a number of factors have been shown to be associated both with occupational workload and BP. Thus, those factors will be included as covariates: sex (male or female) [14,15]; age (categories of <40, 50-59, 60-69, 70-79, and >80 years) [16]; body mass index (BMI; categories of <18.5, 18.5-24.9, 25.0-29.9, and ≥30kg/m^2) [17,18] calculated from objectively measured body height and weight; smoking (categories of nonsmoking and currently smoking) [19,20]; length of education (categories of uneducated, low educated up to 3 years, vocationally educated 1-3 years, higher educated, and academically educated) [1,21]; for the prospective analysis only, additional adjustment for vital exhaustion, split in 4 categories defined elsewhere (0, 1-4, 5-9, and 10-17) [22,23]; self-rated cardiorespiratory fitness (categories of lower, similar, and higher cardiorespiratory fitness compared with peers of same sex and age) [24]; SBP at baseline (categories of 80-89, 90-99, 100-109, 110-119, 120-129, 130-139, and ≥140 mm Hg) [13]; and DBP at baseline (categories of 40-49, 50-59, 60-69, 70-79, 80-89, and ≥90 mm Hg).

Criteria for Statistical Significance

The overall significance level will be set at .05. A Bonferroni correction will be applied, due to the similarity of the two proposed hypotheses, which means that each of the two primary hypotheses will be tested at a significance level of P=.025. Secondary analyses will be regarded as exploratory and will therefore not be tested for statistical significance, but the precision will be reported by 95% CI. They may influence the interpretation of findings of the primary analyses.

Primary Statistical Analyses

Logistic regression will be used to estimate the odds of becoming a case from examination n to n+1 as a function of heavy occupational lifting. For the cross-sectional analysis, there will be a possibility of 3 observations per participant, 1 from each examination. For the prospective analysis, there will be a possibility of 2 observations per participant, 1 from the third to the fourth examination and one from the fourth to the fifth examination. The cross-sectional analysis will be controlled for sex, age, BMI, smoking, and education. The prospective analysis will, in addition to the variables of the cross-sectional analysis, be controlled for self-rated cardiorespiratory fitness, vital exhaustion, and BP at baseline. Self-rated cardiorespiratory fitness and vital exhaustion will only be included as covariates in the prospective analysis where the main point of interest is new cases and not prevalent cases as in the cross-sectional analysis. Generalized estimating equations will be used to estimate the parameters. Observations from the same person will be treated as repeated measurements. A first order autoregressive correlation structure is assumed. Should the estimated covariance matrix fail to converge, then we will resort to a variance component correlation structure.

The significance test will be based on the empirical SE and the Wald Statistic. The odds ratio (OR) between the exposed and the nonexposed will be calculated and presented with a 95% CI. The CI will be based on the empiric SE.

Statistical Power

The power calculations are based on, inter alia, the following assumptions:

- In total, 20% of the participants were hypertensive at baseline [16].
- In total, 15.68% (1830/11,670) participants performed heavy occupational lifting at baseline (Table 2).
- In total, 55% of the participants who were normotensive at examination n would meet the case criteria (antihypertensive drug usage or an above median delta of SBP) at examination n+1.
- The intraperson correlation coefficient equals .5 in the cross-sectional analysis and .1 in the prospective analysis.

Table 5 shows the expected numbers of observations, participants, and “cases” that will be included in the primary analyses. It also shows the variance inflation factor, which is a function of the assumed intraperson correlation and the mean numbers of observations per participant.

Table 5. Number of observations, participants, and estimated cases that we expect to include in the primary analyses.

Analysis	Number of observations	Number of participants	Observations/Participants	Estimated number of cases[a]	Variance inflation factor
Cross-sectional	11,670	7166	1.63	2334	1.31
Prospective	4746	3271	1.45	2610	1.05

[a]A case in the primary analysis will be defined as the shift from no use of antihypertensive drugs in examination n to use of antihypertensive drugs in examination n+1 or an above median delta value of systolic blood pressure (systolic blood pressure in examination n+1-systolic blood pressure in examination n).

Figure 1. Statistical power of detecting a cross-sectional association between heavy occupational lifting and hypertension, as a function of the underlying odds ratio between exposed and unexposed participants in the target population.

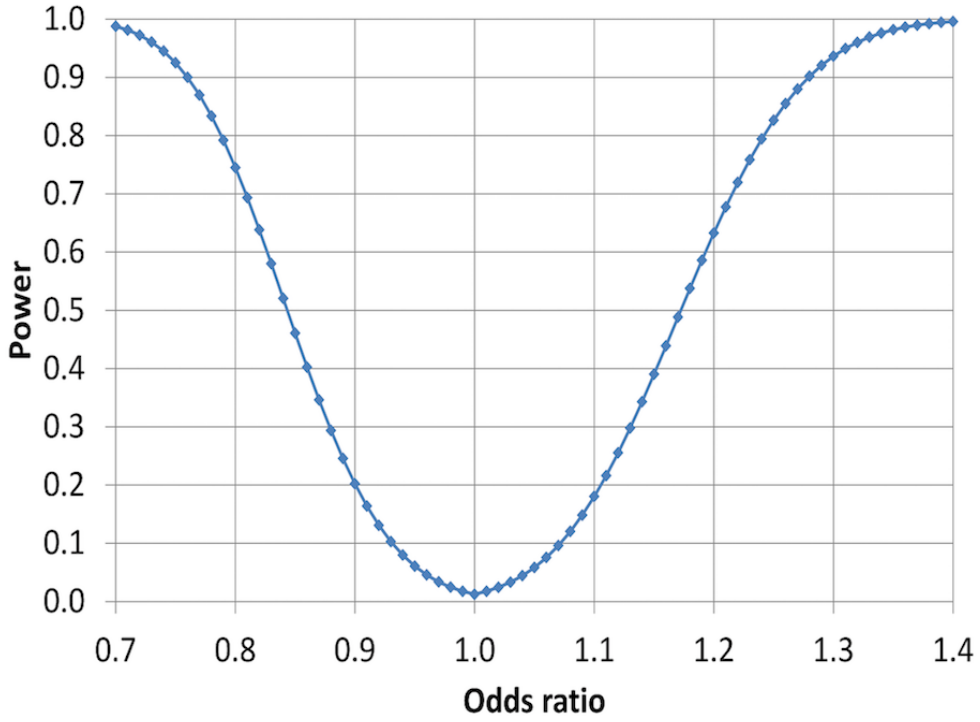
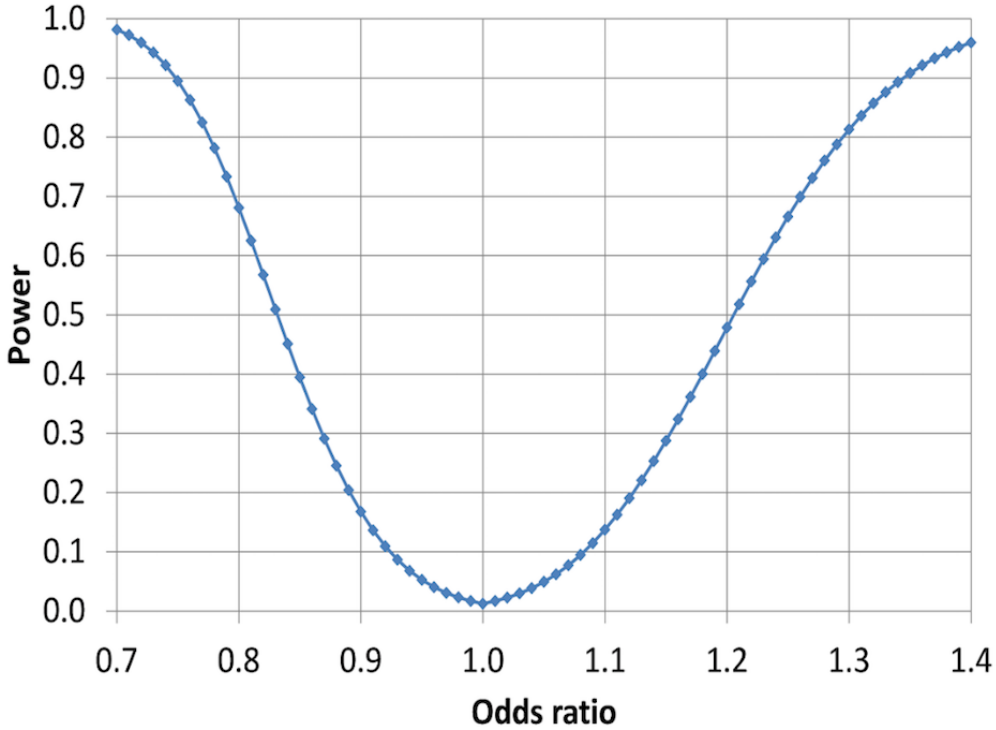


Figure 2. Statistical power of detecting an association between heavy occupational lifting at examination n and antihypertensive drug usage or an above median delta of systolic blood pressure (SBP) at examination n+1, as a function of the underlying odds ratio between exposed and unexposed participants in the target population.



The statistical powers of the primary hypotheses are given in Figures 1 and 2. The calculations are based on the above assumptions, the propagation of error formulas, the central limit theorem, and a two-tailed significance level at P=.025, for each of the two hypotheses.

Secondary Analyses

Linear Regression on Systolic Blood Pressure

It has been suggested that each mm Hg increase in resting SPB is associated with an approximately 3.5% increased risk of death due to ischemic heart disease (IHD) [13]. It has moreover been

suggested that the relative effect of a 1 mm Hg increase is quite independent of the level of SBP; a change in SBP from 120 to 121 would, for example, cause the same relative risk increase as a change from 139 to 140 [13]. From this viewpoint, it would be of interest to estimate the expected effect of heavy occupational lifting on resting SBP in a linear regression model and thereby obtain an estimate that could be directly translated into relative risks of death due to IHD. There are, however, some problems with this approach:

If occupational lifting is associated with risk of hypertension and we exclude participants who are treated for hypertension, then the participants who had been most affected by their occupational lifting status would be more likely to be excluded than the ones who had been least affected, and this would bias the estimation toward unity.

If we do not exclude participants who are treated for hypertension then the potential effects of occupational lifting on BP may be concealed, reversed, or otherwise distorted by effects from antihypertensive drugs and other types of heart medications.

It was the above mentioned problems that made us refrain from linear regression in the primary analyses. We recognize, however, that a conservative estimation of the effect of heavy occupational lifting on resting SBP in a linear regression model may provide meaningful information if the bias is taken into account in the interpretation of the results. We will therefore conduct a secondary analysis, in which the association between heavy occupational lifting and SBP will be investigated, first cross-sectionally and then prospectively (change in SBP [mm Hg] from examination n to examination n+1), by use of linear regression. Observations from participants who are treated with antihypertensive drugs or other types of heart medications will be excluded from an analysis similar to the primary analysis and performed both cross-sectionally and prospectively.

Generalized estimating equations will be used to estimate the parameters. Observations from the same person will be treated as repeated measurements. A first-order autoregressive correlation structure is assumed. Should the estimated covariance matrix fail to converge then we will resort to a variance component correlation structure. The expected difference between the exposed and the nonexposed will be estimated and presented with a 95% CI, based on the empiric SE.

Analysis on Other Types of Blood Pressure Measurements

It is presently not known if and how a person's resting BP is influenced by occupational lifting activities. It is therefore of interest to also regard potential effects of occupational lifting on mean arterial pressure, DBP, and pulse pressure. For this reason, we will repeat the linear regression analyses described above on each of these outcomes. Furthermore, a prospective analysis will be applied where the outcome will be classified as a DBP case, similar to the analysis aforementioned relating occupational lifting to the risk of becoming an SBP case. The DBP case will be defined by the shift from no use of antihypertensive drugs in examination n to use of antihypertensive drugs in examination n+1 or an above median delta value of DBP (DBP in examination n+1−DBP in examination n).

Sensitivity to Choice of Comparison Group

According to our primary assessment of exposure, the exposed group would consist of participants whose work entailed heavy occupational lifting combined with walking, some handling of material, or heavy manual work. The comparison group would consist of the rest of the occupationally active participants, regardless of their type of occupational activity. We want to know how sensitive our analyses are to the choice of comparison group after adjustment for the included covariates. To shed some light on this issue, we plan to perform an additional set of linear regressions on SBP. In these particular analyses, we will split the comparison group into three different subgroups and thereby create an exposure variable with 4 instead of 2 categories. The statistical models, covariates, and inclusion criteria will otherwise be the same as they are in our previously defined linear regression analyses. The results will be presented as outlined in Table 6.

Sensitivity to the Definition of Hypertension

In our primary cross-sectional analysis, we will define hypertension as the use of antihypertensive drugs or a measured consultation SBP ≥140 mm Hg or DBP ≥90 mm Hg [25]. We recognize, however, that the cut-points could have been defined differently, eg, SBP ≥160 mm Hg or DBP ≥100 mm Hg [25]; SBP ≥180 mm Hg or DBP ≥110 mm Hg [25,26]; and SBP ≥130 mm Hg or DBP ≥80 mm Hg [27].

Table 6. Dummy table for the reporting of results of linear regressions on systolic blood pressure (SBP) as a function of occupational physical activity.

Occupational physical activity	Cross-sectional differences in SBP			Prospective differences in delta SBP		
	N[a]	Diff[b]	95% CI	N	Diff	95% CI
Heavy lifting		Ref[c]	—		Ref	—
Walking, some handling of material or heavy manual work but no heavy lifting						
Sitting or standing, some walking						
Predominantly sedentary work						

[a]Number of observations.

[b]Difference in mm Hg.

[c]Reference group.

We want to know whether the OR for hypertension as a function of heavy occupational lifting is sensitive to the definition of hypertension. We will therefore conduct two additional cross-sectional logistic regression analyses, which will be performed in the same way as the primary cross-sectional analysis but with the cut-points SBP ≥160 mm Hg or DBP ≥100 mm Hg and SBP ≥130 mm Hg or DBP ≥80 mm Hg instead of the traditional SBP ≥140 mm Hg or DBP ≥90 mm Hg.

Stratification by Age

A potential effect of occupational exposures might be more pronounced among people who are likely to be occupationally active throughout the approximately 10-year period that passes between the baseline and follow-up examinations than it is among people who have fulfilled the requirements for old-age pension (65 years of age) or early retirement (60 years of age) at the time of the follow-up examination. It is therefore possible that this study is more relevant among participants who are younger than 50 years at baseline than it is among those who are 50 years or older. For this reason, we will perform a sensitivity analysis in which the sample is stratified by age at baseline (≥ vs <50 years). The outcome, statistical model, inclusion criteria, and covariates will otherwise be the same as they were in the primary prospective analysis.

Linear Regression on Systolic Blood Pressure Without Exclusion of Participants Treated With Antihypertensive Drugs

As previously mentioned, we believe that any potential effect of occupational lifting on SBP may be concealed, reversed, or otherwise distorted by effects from antihypertensive drugs and other types of heart medications. It is, however, relevant to investigate the effect of the decision to exclude participants who were treated for antihypertensive drugs from sensitivity analysis 1 and, therefore, we will repeat the steps of that analysis, without the exclusion of medically treated participants.

Substudy on Cardiac Damage

Data from the fourth and fifth examinations of the Copenhagen City Heart Study will be included for the cross-sectional and long-term associations between heavy occupational lifting and cardiac damage in a nested design. Early subclinical structural changes of the heart will be recognized by advanced echocardiographic analyses. We will compare participants exposed to heavy occupational lifting (cases) with matched participants who are not exposed to heavy occupational lifting (controls) both in the cross-sectional and longitudinal study. Controls will be matched on age and sex. Echocardiographic assessment will focus on early subclinical changes in cardiac structure primarily assessed by cardiac mass, indices of diastolic function, and global strain assessments. Analyses will be adjusted for confounders, including hypertension, diabetes, and BMI. With 200 exposed and 200 unexposed participants included in the echocardiographic analyses, we will have 80% power to detect a between-group difference of 1 in global longitudinal strain (equal to 5% difference based on an expected mean of 20) with a significance level (alpha) of 1.25%. The choice of alpha is adjusted to allow for comparison over several parameters of subclinical structural changes.

Results

Flow of Participants

In the third examination in 1991-1994, 10,135 out of 16,560 (61.20%) participants attended; in the fourth examination in 2001-2003, 6237 out of 12,599 (49.50%) participants attended; and in the fifth examination in 2011-2015, 4550 out of 9765 (46.59%) participants attended. On the basis of the inclusion criteria of responding to the level of OPA, 5031 observations were excluded from examination 3; 2600 from examination 4; and 1621 from examination 5. Hence, the final populations for the cross-sectional and prospective analysis are assumed to include less than 7166 participants in the cross-sectional analysis and less than 1850 participants in the prospective analysis (Figure 3), due to the additional inclusion criteria of measured BP and use of antihypertensive drugs. The information on BP and use of antihypertensive drugs will be provided after submission of this protocol paper.

Descriptive Information of the Included Population

The population which will be included in the analysis will be set by the criteria for inclusion, described previously. Therefore, it is assumed that fewer participants will be included in the analysis than the amount of participants answering on the level of OPA, described in Tables 7 and 8.

Differences in the Study Population

Smaller numerical differences were observed between the participants answering on the level of OPA and the attending participants.

Cross-sectionally, the participants responding to the level of OPA were 9.8 years younger (mean age 49.0 years among the participants answering on the level of OPA and 58.8 years among the attending), had a higher level of education than the attending participants (13.87% [1619/11,670] participants responding to the level of OPA were noneducated and 20.69% [4328/20,922] among the attending), and a higher proportion of the participants responding to the level of OPA stated to be exposed to heavy occupational lifting (14.04% [1638/11,670] among the participants responding to the level of OPA and 8.48% [1774/20,922] among the attending participants).

Figure 3. Flow of the observations and participants in the third, fourth, and fifth examinations of the Copenhagen City Heart Study. OPA: occupational physical activity; obs: observation.

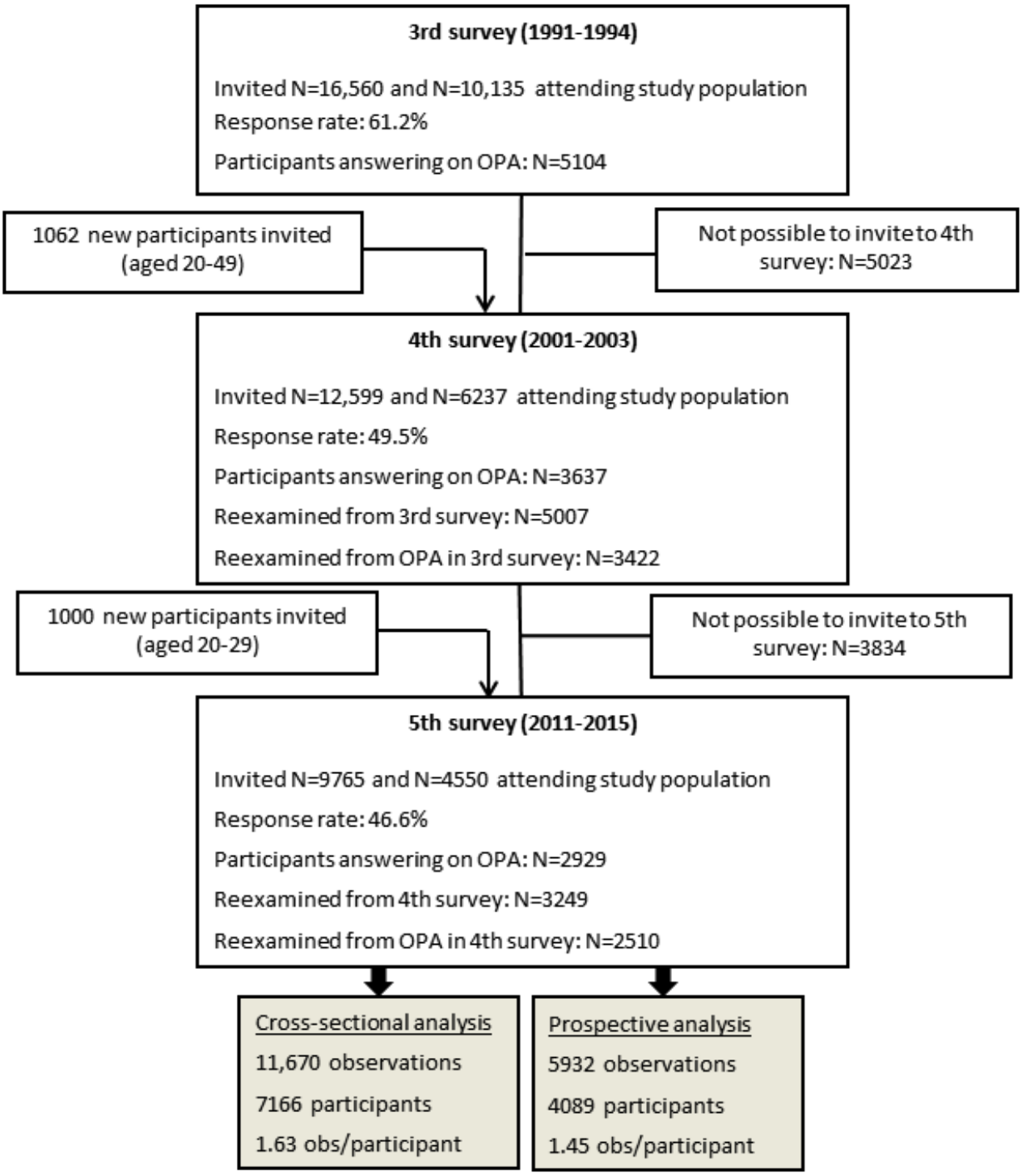


Table 7. Baseline characteristics of the participants responding to the level of occupational physical activity for the cross-sectional analysis; 11,670 observations on 7166 participants.

Cross-sectional analysis	Mean (SD)	n (%)	Range
Age (years)	49.0 (13.8)		20.3-99.7
Sex (% female)		5330 (54.3)	
Body mass index (kg/m^2)	25.2 (4.3)		12.8-56.6
Smoking (% current smokers)		4292 (36.9)	
Education			
Uneducated		1619 (14.1)	
Low educated, <3 years		1806 (15.7)	
Vocational education, 1-3 years		3123 (27.2)	
Higher education, >3 years		2103 (18.3)	
Academic education		2837 (24.7)	
Occupational physical activity			
Predominantly sedentary		4407 (37.8)	
Sitting or standing, some walking		4079 (35.0)	
Walking, some handling of material		2729 (23.4)	
Heavy manual work		455 (3.9)	
Occupational heavy lifting (% yes)		1830 (15.7)	
Vital exhaustion (sum, 0-17)	3.0 (3.5)		0-17
Cardiorespiratory fitness (% similar level as peers)		6390 (54.8)	
Observation per participant	2.0 (0.8)		1-3

Prospectively, the participants answering on the level of OPA were 11.0 years younger (mean age 48.0 years among participants responding to the level of OPA and 59.0 years among the attending). The smokers were 2.31 percentage points higher (38.96% [2311/5932] of the participants responding to the level of OPA were current smokers and 36.65% [6930/18,908] among the attending); they had a higher level of education than the attending participants (12.39% [735/5932] of the participants responding to the level of OPA were noneducated and 19.76% [3737/18,908] among the attending). A higher proportion of the participants responding to the level of OPA stated to be exposed to heavy occupational lifting (17.52% [1039/5932] among the participants responding to the level of OPA and 8.34% [1576/18,908] among the attending participants), and a higher proportion of the participants responding to the level of OPA stated to have a level of cardiorespiratory fitness similar to their peers (57.67% [3421/5932] among the participants responding to the level of OPA and 45.57% [8617/18,908] among the attending).

These nonsignificant differences between the attending participants and participants responding to the level of OPA in the cross-sectional and prospective populations may affect the prevalence of hypertension. The younger age of the participants responding to the level of OPA as well as their higher proportion of being educated might lower the prevalence of hypertension among these participants compared with those attending [28]. Conversely, may those participants responding to the level of OPA have a higher prevalence of hypertension due to their higher exposure to heavy occupational lifting than among the attending participants. In the prospective population, the small difference in proportion of participants stating to have a level of cardiorespiratory fitness similar to their peers, is not believed to affect the prevalence of hypertension, as the proportion of participants stating to have a higher level of cardiorespiratory fitness than their peers is similar among those participants responding to the level of OPA and those attending.

Table 8. Baseline characteristics of the participants responding to the level of occupational physical activity for the prospective analysis; 5932 observations on 4089 participants.

Prospective analysis	Mean (SD)	n (%)	Range
Age (years)	48.0 (11.8)		20.3-84.3
Sex (% female)		3301 (55.7)	
BMI (kg/m^2)	25.0 (4.0)		16.0-52.5
Smoking (% current smokers)		2311 (39.1)	
Education			
Uneducated		735 (12.6)	
Low educated, <3 years		2142 (36.7)	
Vocational education, 1-3 years		1983 (34.0)	
Higher education, >3 years		380 (6.5)	
Academic education		590 (10.1)	
Occupational physical activity			
Predominantly sedentary		2113 (35.6)	
Sitting or standing, some walking		2086 (35.2)	
Walking, some handling of material		1497(25.2)	
Heavy manual work		234 (3.9)	
Occupational heavy lifting (% yes)		1039 (17.5)	
Vital exhaustion (sum, 0-17)	2.9 (3.3)		0-17
Cardiorespiratory fitness (% similar level as peers)		3421 (57.7)	
Observation per participant	1.5 (0.5)		1-2

Discussion

Study Protocol

This study aims to contribute to the knowledge of risk for hypertension from heavy occupational lifting, and possibly thereby contribute to the prevention of cardiovascular disease by giving recommendations for participants exposed to heavy occupational lifting.

Methodological Challenges

In the primary prospective analysis, the power would be insufficient if the outcome had been defined as hypertensive (yes or no). Therefore, we chose a case definition which included both hypertension and an above median increase in SBP of the study population from examination n to n+1. The proposed analyses have some limitations, such as the self-reported exposure to occupational lifting and level of cardiorespiratory fitness. Previous studies show that self-reported exposure to occupational lifting may be affected by recall bias [29,30]. Also the collection of BP only in consultation during rest is a limitation due to the lower prognostic value than obtained by monitoring of 24 hours BP or BP during sleep [31,32]. Furthermore, a previous study has shown occupational lifting to reduce the odds for having prolonged working hours [33]; however, this is not possible to adjust for in this analysis due to the lack of information on amount of weekly working hours. It could also be speculated that the range and variety of the exposure to occupational lifting could be limited due to the Danish Working Environment Authority guideline for occupational lifting [34], stating that carrying, lifting, pulling, and pushing of nonliving burdens below 3 kg are not classified as heavy lifting, and workers should not lift or carry burdens heavier than 20 kg.

Some of the strengths in the proposed analysis are the follow-up time of 8 to 10 years and the determination of hypertension based both on the use of prescription medicine and the resting BP in mm Hg. This limits the risk of classifying a participant as false negative (eg, using antihypertensives and therefore having a resting BP below the threshold). Another strength is the randomly selected study population.

Implications of the Proposed Analysis

Since one-third of the workforce in Europe reports to carry or move heavy loads regularly during working hours (6th survey in Eurofound) and hypertension is a major risk factor for cardiovascular disease and mortality [1;2], a positive association between occupational lifting and risk for hypertension could reveal a potential for improved prevention for hypertension by reducing exposure to occupational lifting in the population. This could, for example, be achieved by using technical lifting devices and automatization of manual work tasks currently requiring heavy lifting. This is particularly the case because a positive association could be considered as a reflection of a physiological mechanism and therefore must be assumed to apply for the majority of humans exposed to occupational lifting. Conversely, a negative association would not be assumed as a

reflection of a physiological mechanism before the negative association had been verified in populations not subject to restrictive regulations of occupational lifting, as employees in Denmark are. Moreover, a null finding would also propose a need for additional investigations of this association in populations with wider ranges of exposure to occupational lifting. Since these proposed analyses will be applied to a randomly selected adult population and is planned to be verified in another randomly selected adult Danish population, these results may be generalized to the Danish adult population engaged in work including occupational lifting.

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Conflicts of Interest

None declared.

References

1. Olsen MH, Angell SY, Asma S, Boutouyrie P, Burger D, Chirinos JA, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. Lancet 2016 Dec 26;388(10060):2665-2712 [FREE Full text] [doi: 10.1016/S0140-6736(16)31134-5] [Medline: 27671667]
2. Antikainen RL, Moltchanov VA, Chukwuma C, Kuulasmaa KA, Marques-Vidal PM, Sans S, WHO MONICA Project. Trends in the prevalence, awareness, treatment and control of hypertension: the WHO MONICA Project. Eur J Cardiovasc Prev Rehabil 2006 Feb;13(1):13-29. [Medline: 16449860]
3. Fransson E, De Faire U, Ahlbom A, Reuterwall C, Hallqvist J, Alfredsson L. The risk of acute myocardial infarction: interactions of types of physical activity. Epidemiology 2004;15(5):573-582 [FREE Full text] [doi: 10.1097/01.ede.0000134865.74261.fe] [Medline: 15308957]
4. Petersen CB, Eriksen L, Tolstrup JS, Søgaard K, Grønbaek M, Holtermann A. Occupational heavy lifting and risk of ischemic heart disease and all-cause mortality. BMC Public Health 2012 Dec 11;12:1070 [FREE Full text] [doi: 10.1186/1471-2458-12-1070] [Medline: 23231790]
5. MacDougall JD, Tuxen D, Sale DG, Moroz JR, Sutton JR. Arterial blood pressure response to heavy resistance exercise. J Appl Physiol (1985) 1985 Mar;58(3):785-790 [FREE Full text] [doi: 10.1152/jappl.1985.58.3.785] [Medline: 3980383]
6. Clays E, De Bacquer D, Van Herck K, De Backer G, Kittel F, Holtermann A. Occupational and leisure time physical activity in contrasting relation to ambulatory blood pressure. BMC Public Health 2012 Nov 20;12:1002 [FREE Full text] [doi: 10.1186/1471-2458-12-1002] [Medline: 23164344]
7. Hannerz H, Holtermann A. Ischaemic heart disease among workers in occupations associated with heavy lifting. Int J Occup Med Environ Health 2016;29(1):129-136 [FREE Full text] [doi: 10.13075/ijomeh.1896.00472] [Medline: 26489949]
8. Williams M, Haskell W, Ades P, Amsterdam E, Bittner V, Franklin B. Resistance exercise in individuals with and without cardiovascular disease update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. Circulation 2007;116(5):2007. [doi: 10.1161/CIRCULATIONAHA.107.185214] [Medline: 17638929]
9. Cornelissen V, Fagard R, Coeckelberghs E, Vanhees L. Impact of resistance training on blood pressure and other cardiovascular risk factors: a meta-analysis of randomized, controlled trials. Hypertension 2011;58(5):950-958. [doi: 10.1161/HYPERTENSIONAHA.111.177071] [Medline: 21896934]
10. The National Research Centre for the Working Environment. Copenhagen, Denmark; 2014 Jan 01. Work and Health URL: http://www.arbejdsmiljoforskning.dk/da/arbejdsmiljoedata/arbejdsmiljoe-og-helbred-20/rapporten--danskernes-arbejdsmiljoe-2014 [accessed 2018-03-15] [WebCite Cache ID 6xvmy26wV]
11. Schnohr P. Physical activity in leisure time: impact on mortality. Risks and benefits. Dan Med Bull 2009 Feb;56(1):40-71. [Medline: 19232166]
12. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977 Mar;33(1):159-174. [Medline: 843571]
13. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360(9349):1903-1913 [FREE Full text] [doi: 10.1016/S0140-6736(02)11911-8] [Medline: 12493255]
14. Doumas M, Papademetriou V, Faselis C, Kokkinos P. Gender differences in hypertension: myths and reality. Curr Hypertens Rep 2013 Aug;15(4):321-330. [doi: 10.1007/s11906-013-0359-y] [Medline: 23749317]
15. Quan H, Chen G, Walker RL, Wielgosz A, Dai S, Tu K, Hypertension Outcome and Surveillance Team. Incidence, cardiovascular complications and mortality of hypertension by sex and ethnicity. Heart 2013 May;99(10):715-721. [doi: 10.1136/heartjnl-2012-303152] [Medline: 23403406]

16. Kronborg CN, Hallas J, Jacobsen IA. Prevalence, awareness, and control of arterial hypertension in Denmark. J Am Soc Hypertens 2009;3(1):19-24.e2. [doi: 10.1016/j.jash.2008.08.001] [Medline: 20409941]
17. Papathanasiou G, Zerva E, Zacharis I, Papandreou M, Papageorgiou E, Tzima C, et al. Association of high blood pressure with body mass index, smoking and physical activity in healthy young adults. Open Cardiovasc Med J 2015;9:5-17 [FREE Full text] [doi: 10.2174/1874192401509010005] [Medline: 25834651]
18. Chen J, Das S, Barlow CE, Grundy S, Lakoski SG. Fitness, fatness, and systolic blood pressure: data from the Cooper Center Longitudinal Study. Am Heart J 2010 Jul;160(1):166-170. [doi: 10.1016/j.ahj.2010.04.014] [Medline: 20598988]
19. Saladini F, Benetti E, Fania C, Mos L, Casiglia E, Palatini P. Effects of smoking on central blood pressure and pressure amplification in hypertension of the young. Vasc Med 2016;21(5):422-428 [FREE Full text] [doi: 10.1177/1358863X16647509] [Medline: 27197683]
20. Dochi M, Sakata K, Oishi M, Tanaka K, Kobayashi E, Suwazono Y. Smoking as an independent risk factor for hypertension: a 14-year longitudinal study in male Japanese workers. Tohoku J Exp Med 2009;217(1):37-43 [FREE Full text] [doi: 10.1620/tjem.217.37] [Medline: 19155606]
21. Tang K, Rashid R, Godley J, Ghali W. Association between subjective social status and cardiovascular disease and cardiovascular risk factors: a systematic review and meta-analysis. BMJ Open 2016;6(3):e010137 [FREE Full text] [doi: 10.1136/bmjopen-2015-010137] [Medline: 26993622]
22. Appels A. Mental precursors of myocardial infarction. Br J Psychiatry 1990 Apr;156:465-471. [Medline: 1974819]
23. Prescott E, Holst C, Grønbaek M, Schnohr P, Jensen G, Barefoot J. Vital exhaustion as a risk factor for ischaemic heart disease and all-cause mortality in a community sample. A prospective study of 4084 men and 5479 women in the Copenhagen City Heart Study. Int J Epidemiol 2003 Dec;32(6):990-997. [Medline: 14681262]
24. Cornelissen V, Smart N. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc 2013;2(1):e004473 [FREE Full text] [doi: 10.1161/JAHA.112.004473] [Medline: 23525435]
25. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology. 2013 ESH/ESC practice guidelines for the management of arterial hypertension. Blood Press 2014 Feb;23(1):3-16. [doi: 10.3109/08037051.2014.868629] [Medline: 24359485]
26. Leung AA, Nerenberg K, Daskalopoulou SS, McBrien K, Zarnke KB, Dasgupta K, CHEP Guidelines Task Force. Hypertension Canada's 2016 Canadian Hypertension Education Program guidelines for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2016 Dec;32(5):569-588. [doi: 10.1016/j.cjca.2016.02.066] [Medline: 27118291]
27. Whelton P, Carey R, Aronow W, Casey Jr DJ, Collins K, Dennison H, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol 2017 Nov 07 Epub ahead of print(forthcoming). [doi: 10.1016/j.jacc.2017.11.006] [Medline: 29146535]
28. Wen W, Luo R, Tang X, Tang L, Huang HX, Wen X, et al. Age-related progression of arterial stiffness and its elevated positive association with blood pressure in healthy people. Atherosclerosis 2015 Jan;238(1):147-152. [doi: 10.1016/j.atherosclerosis.2014.10.089] [Medline: 25485738]
29. Fransson E, Knutsson A, Westerholm P, Alfredsson L. Indications of recall bias found in a retrospective study of physical activity and myocardial infarction. J Clin Epidemiol 2008 Aug;61(8):840-847. [doi: 10.1016/j.jclinepi.2007.09.004] [Medline: 18359191]
30. Stock SR, Fernandes R, Delisle A, Vézina N. Reproducibility and validity of workers' self-reports of physical work demands. Scand J Work Environ Health 2005 Dec;31(6):409-437 [FREE Full text] [Medline: 16425584]
31. Hansen TW, Thijs L, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K, International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. Hypertension 2010 Apr;55(4):1049-1057 [FREE Full text] [doi: 10.1161/HYPERTENSIONAHA.109.140798] [Medline: 20212270]
32. Hermida RC, Ayala DE, Fernández JR, Mojón A. Sleep-time blood pressure: prognostic value and relevance as a therapeutic target for cardiovascular risk reduction. Chronobiol Int 2013 Mar;30(1-2):68-86. [doi: 10.3109/07420528.2012.702581] [Medline: 23181592]
33. Hannerz H, Holtermann A. Heavy lifting at work and risk of ischemic heart disease: protocol for a register-based prospective cohort study. JMIR Res Protoc 2014 Aug 20;3(3):e45 [FREE Full text] [doi: 10.2196/resprot.3270] [Medline: 25164612]
34. Danish Working Environment Authority. Lift, drag and push URL: https://arbejdstilsynet.dk/da/regler/at-vejledninger/l/d-3-1-loft-traek-og-skub [accessed 2018-03-30] [WebCite Cache ID 6yIYdsqoX]

Abbreviations

BMI: body mass index
BP: blood pressure

DBP: diastolic blood pressure
IHD: ischemic heart disease
OPA: occupational physical activity
OR: odds ratio
SBP: systolic blood pressure

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Review

Comparing the Effects of Combined Oral Contraceptives Containing Progestins With Low Androgenic and Antiandrogenic Activities on the Hypothalamic-Pituitary-Gonadal Axis in Patients With Polycystic Ovary Syndrome: Systematic Review and Meta-Analysis

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Abstract

Background: Different products of combined oral contraceptives (COCs) can improve clinical and biochemical findings in patients with polycystic ovary syndrome (PCOS) through suppression of the hypothalamic-pituitary-gonadal (HPG) axis.

Objective: This systematic review and meta-analysis aimed to compare the effects of COCs containing progestins with low androgenic and antiandrogenic activities on the HPG axis in patients with PCOS.

Methods: We searched PubMed, Scopus, Google Scholar, ScienceDirect, and Web of Science databases (1980-2017) to identify randomized controlled trials or nonrandomized studies investigating the effect of COCs containing progestins with low androgenic and antiandrogenic activities, including the products containing desogestrel, cyproterone acetate, and drospirenone, on the HPG axis in patients with PCOS. In this meta-analysis, fixed and random effect models were used. Outcomes of interest were weighted mean differences (WMD) of hormonal parameters, including the follicle-stimulating hormone (FSH), luteinizing hormone (LH), LH-to-FSH ratio, estradiol, total testosterone, and sex hormone–binding globulin. Potential sources of heterogeneity were investigated using meta-regression and subgroup analyses. Subgroup analyses were performed based on the used progestin compound and treatment duration. We assessed quality of included studies and their risk of bias using Cochrane guidelines. Publication bias was assessed using Egger test and funnel plot.

Results: COC use was significantly associated with a decrease in gonadotropin levels, including FSH and LH. Use of products containing cyproterone acetate was associated with a decrease in FSH levels after 3 months (WMD=−0.48; 95% CI −0.81 to −0.15), 6 months (WMD=−2.33; 95% CI −3.48 to −1.18), and 12 months (WMD=−4.70; 95% CI −4.98 to −4.42) and a decrease in LH levels after 3 months (WMD=−3.57; 95% CI −5.14 to −1.99), 6 months (WMD=−5.68; 95% CI −9.57 to −1.80), and 12 months (WMD=−11.60; 95% CI −17.60 to −5.60). Use of COCs containing drospirenone for 6 months decreased FSH

(WMD=−0.93; 95% CI −1.79 to −0.08) and LH (WMD=−4.59; 95% CI −7.53 to −1.66) levels. Data for products containing desogestrel were few, but this compound generally had no statistically significant influence on gonadotropin levels similar to that observed with COCs containing cyproterone acetate and drospirenone. Use of COCs was not associated with any significant change in LH-to-FSH ratio. COCs containing cyproterone acetate showed maximum effect on gonadotropin suppression. COCs containing cyproterone acetate significantly decreased estradiol concentrations, whereas those containing drospirenone exhibited no such effect. All COCs demonstrated improvement in androgenic profile and had the same effects on total testosterone and sex hormone–binding globulin concentrations. Progestin compound and treatment duration had no statistically significant effects on changing total testosterone and sex hormone–binding globulin levels.

Conclusions: COCs containing cyproterone acetate can effectively suppress gonadotropins, leading to a decrease in androgenic parameters. Although different products of COCs could significantly suppress the androgenic profile, it seems that products containing cyproterone acetate are more effective in suppressing gonadotropin and estradiol levels in patients with PCOS.

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KEYWORDS

meta-analysis; combined oral contraceptives; androgens; gonadotropins; polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder in reproductive age women [1-3], characterized by chronic oligo and/anovulation and hyperandrogenism (HA), which results in infertility, menstrual irregularities, hirsutism, acne, and alopecia [4]. PCOS is associated with an increase in risk of metabolic disorders such as obesity, dyslipidemia, and impaired glucose metabolism, which in turn increase the risk of diabetes mellitus and cardiovascular disease [3,5,6]. This endocrine disorder can have negative effects on the health-related quality of life of these women [7].

Combined oral contraceptives (COCs) are considered as the most common symptomatic treatment of PCOS and contain a combination of estrogen and progestin [8]. COCs are used not only to regulate menstrual cycle but also to suppress the hypothalamic-pituitary-gonadal (HPG) axis and improve clinical and biochemical HA in women with PCOS [9].

The effectiveness of COCs for the treatment of PCOS is well documented [10]. Previous studies show that COCs affect androgen synthesis by inhibiting ovarian androgen production [11-13]. The main potential mechanisms of COC action include inhibition of folliculogenesis as a result of suppression of gonadotropin secretion, suppression of ovarian and adrenal androgen synthesis, inhibition of 5 alpha reductase, and increased sex hormone–binding globulin (SHBG) [14,15]. Hence, COCs can improve the HPG axis function through a decrease in gonadotropin and ovarian androgen levels, which is a major goal of PCOS treatment [16].

Progestin activity of COCs inhibits luteinizing hormone (LH) secretion and results in a decline in ovarian androgen release [17]. Current COC products containing newer progestins with low androgenic or antiandrogenic effects, such as cyproterone acetate (CA), chlormadinone acetate (CMA), desogestrel (DSG), and drospirenone (DRSP), are considered to be effective in decreasing gonadotropin and androgen levels [14,18,19]. In particular, these progestins are better for women with PCOS suffering from HA [17].

Although the effect of COCs on the HPG axis of PCOS women has been introduced before, however, to the best of our knowledge, there is no other meta-analysis comparing this effect among COCs with various progesterone components. In our opinion, this is a valuable piece of knowledge that could provide some clues for a better understanding of the mechanism of effect of various COC compounds, which may be helpful in the decision-making process for treatment options.

This meta-analysis aimed to compare the effects of COCs containing progestins with low androgenic and antiandrogenic activities on the HPG axis in patients with PCOS.

Methods

Overview

This systematic review and meta-analysis was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Multimedia Appendix 1) [20] and the Cochrane Handbook for Systematic Reviews of Interventions [21] to answer the following questions:

1. Do COCs affect the HPG axis of women with PCOS?
2. Is there any difference among the effects of COCs on the HPG axis in women with PCOS?
3. Is there any difference in the effects of these compounds based on the duration of their use?

The study was approved by the ethics committee of Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Registration number: IR.SBMU.RIES.RES.1394.90).

Search Strategy

PubMed, Scopus, Google Scholar, ScienceDirect, and Web of Science were searched for clinical trials investigating the influence of COCs containing progestins with low androgenic and antiandrogenic activities on the HPG axis in patients with PCOS from January 1980 to June 2017. After searching for subheadings of PCOS in MeSH, the following keyword combinations were selected: [“polycystic ovary syndrome” AND “contracept*”] and [“polycystic ovary syndrome” AND “contraceptives, oral hormonal” OR “pill” OR “progestin”].

Search limitations were human, females, clinical trial, and English language.

A hand search of the reference lists of all selected papers was also conducted to prevent missing studies.

Eligibility Criteria

Studies conducted on reproductive age women with PCOS who were treated with monophasic COCs were selected for this meta-analysis; these studies were randomized clinical trials (RCTs) or nonrandomized studies (NRS).

Diagnostic criteria of each study are identified in Multimedia Appendix 2. In all the included studies, nonclassic congenital adrenal hyperplasia, hyperprolactynemia, and other HA etiologies were ruled out. The intervention of interest was COC containing progestins with low androgenic or antiandrogenic activities. Follicle-stimulating hormone (FSH), LH, LH-to-FSH ratio, estradiol (E2), total testosterone (TT), and SHBG levels were considered as main outcomes of the study.

Exclusion criteria were as follows: (1) women with idiopathic hirsutism or other types of HA, (2) women with diabetes or other chronic diseases, (3) use of biphasic or triphasic contraceptives, (4) use of gonadotropin-releasing hormone agonist-antagonist and antiandrogen drugs (eg, ketoconazole and spironolactone), (5) studies with follow-ups of <3 months or >24 months, (6) use of biphasic and triphasic COCs, (7) use of progesterone-only compounds, (8) use of metformin in combination with COC, and (9) treatment groups with inadequate number of participants for performing meta-analysis (<1 study).

Only one study had a follow-up of 24 months and was excluded from the analysis [9]. We also excluded intervention groups that had no adequate number of study participants for performing a meta-analysis, including products containing levonorgestrel (LNG) and gestodene (GSD). In addition, study groups that assessed metformin + COCs were excluded from the analysis.

Study Selection

We included all relevant RCTs or NRS assessing COC effects on the HPG axis in reproductive age women with PCOS. At least one of the following hormonal parameters had to be reported: FSH, LH, LH-to-FSH ratio, E2, TT, or SHBG. We considered COCs containing CPA, DRSP, DSG, and CMA as interventions of interest. Due to inadequate number of studies that assessed products with LNG and DSG, these were excluded from the study.

The results of the searches were screened for meeting the predefined eligibility criteria. All references were entered to the endnote software. Selection was performed based on their titles, followed by using a second selection performed by 1 reviewer (MA), who deleted duplicates and reviewed abstracts of all remaining records. Any disagreement in the selection of abstracts was resolved by consensus or by another reviewer (FRT). Full-text articles for review and data processing were obtained for all selected abstracts.

Data Extraction

For each study, the following information were extracted: authors, year of publication, title, study design, characteristics of study population, type of intervention, outcome measurements—including FSH, milliunits per milliliters (mU/mL); LH, mU/mL; E2, picograms per milliliter; TT, nanograms per milliliter; and SHBG, nanomole per liter—and analytical methods. After data extraction, all the measurement units of hormones were identical. Data were extracted from full-text articles by 2 reviewers (MA and AK) in close consultation with another reviewer (FRT).

Data of studies were extracted by mean and SD [22]. To prevent extraction errors, a control check between the final data used in the meta-analysis and the original publications was performed by all authors.

Quality Assessment

Two reviewers (MA and AK) assessed the quality of the studies separately. They were blinded to study author, institution, and journal name. Disagreement was resolved and adjusted by the senior reviewer (FRT). A validated quality assessment checklist for clinical trial as the modified Consolidated Standards of Reporting Trials (CONSORT) was used to assign a score to each paper. The quality assessment of RCTs was assessed based on the 37-item CONSORT checklist. Each of the 37 items included in CONSORT were scored to compute an overall quality score (range 0-37). For scoring of the quality of items, 1 point was given if the information for each item was stated in the study, and 0 was given if the information was not stated or was unclear. CONSORT was also modified to the NRS, which were not randomized controlled studies. For modification of the checklist, questions related to the blinding and randomization were excluded.

All clinical trial papers were categorized into 4 groups: high, moderate, low, and very low quality. Studies with scores ≥70% of the highest level of the CONSORT checklist were considered as high, 40% to 70% as moderate, 20% to 40% as low, and <20% as very low quality [23].

Risk of Bias Assessment

Two authors (MA and AK) independently assessed risk of bias. The risk of bias in each included study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [21,24,25]. Six domains related to risk of bias were assessed in each included RCTs: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; and (6) selective reporting. Review authors' judgments were categorized as "low risk," "high risk," and "unclear risk" of bias [24].

For NRS, 7 domains were assessed, including (1) confounding, (2) enrollment of participants in the study, (3) classification of interventions, (4) deviations from intended, (5) missing data, (6) measurement of outcomes, and (7) selection of the reported results. Review authors' judgments were categorized as "low risk," "moderate risk," "serious risk," "critical or high risk," and "unclear or no information risk" of bias [25].

We planned to assess outcomes based on the risk of bias in the following subgroups: (1) low risk, (2) moderate risk, (3) serious/high/critical risk, and (4) unclear or no information risk.

Statistical Methods

The studies selected assessed the effects of one or more COCs. Means and SDs of data at baseline and after treatment were collected. For studies reporting median and range, a conversion to mean and SD was performed, when possible [26]. Differences of mean and SD at both baseline and at end of treatment were calculated, as were standard errors of these differences, using the *Cochrane Reviewers' Handbook*. For effect measures, the mean difference [27] and related 95% CIs were calculated based on the means of the pretreatment and those at the end of treatment levels of FSH, LH, LH-to-FSH ratio, E2, TT, and SHBG. Therefore, the primary pooled effect analysis was estimated weighted mean differences (WMD) for the studies comparing treatment groups of studies. For the end-of-treatment time point, the assessment (mean/SD) after a 3-, 6-, or 12-month cycle was used [21].

Heterogeneity tests were assessed by I-squared and chi-squared tests [28]. Both fixed and random effect models were used in the study. The random effect estimation method was applied for significant chi-squared test results (P<.10) or I-squared greater than 50%.

Subgroup analyses were performed based on COC compound and duration of use. In addition to funnel plot, Begg test [27] and Egger test [29] were used to assess publication bias. Publication bias was found to be significant for P values <.10 to indicate significant asymmetry. For significant results or asymmetric funnel plot, the trim and fill method (by metatrim) was used to identify and correct for publication bias. Metatrim is a command used in the STATA version 12 software (StataCorp, College Station, TX, USA) for overcoming publication bias. It simulates studies that have not been published in literature and assesses whether the results would be different when there is or there is no publication bias. Indeed, for significant results or asymmetric funnel plot, the trim and fill method (by metatrim) was used to identify and correct for publication bias by adding some study measures [30,31]. We used meta-regression to evaluate heterogeneity induced by important variables, including diagnostic criteria of PCO (Rotterdam; National Institutes of Health, NIH; Androgen Excess Society, AES]; and others), body mass index (BMI), and method of assay of different hormones (radioimmunoassay, chemical/electrochemical luminescence, enzyme, and unknown). In addition, we used metainf for performing the sensitivity analysis. We also assessed risk of bias for included studies using the Risk of Bias tools as per the Cochrane guidelines, which are tools designed for RCTs and NRS [24,25]. We then performed a subgroup analysis based on the risk of bias. P values <.05 were considered significant for all comparisons, except for heterogeneity, publication bias, and meta-regression, where .10 was set as the significance level. All analyses were performed with STATA software, version 12.

Results

Search Results, Study Selection, Study Characteristics, and Quality Assessment

A total of 1310 studies were retrieved by searching the electronic databases. After removing duplicates and assessing for quality appraisal and eligibility criteria, 34 studies were selected for the final analyses, which had 46 treatment groups (Figure 1 and Multimedia Appendix 2). Among these, 19 studies were RCTs and 15 studies were NRS. In all, 6 studies were classified as high, 20 as moderate, and 8 as low quality; 6 studies were identified as very low quality and were excluded from the meta-analysis. In most of the included studies (n=25), PCOS was diagnosed by Rotterdam criteria. For other studies, NIH (n=4) and AES criteria (n=2) for diagnosing PCOS were used. Only 2 studies did not report their PCOS criteria. Also, for one study, we used the Homburg criteria for diagnosing PCOS. Ethinyl estradiol (EE) was the estrogenic component of COCs in all studies, whereas the progestin components were CA, DSG, DRSP, or CMA. Of 46 study arms, 20 were exposed to EE 35 µg + CA 2 mg [2,4,10,32-47], 17 to EE 30 µg + DRSP 3 mg [1,4,9,10,19,42,45,48-56], 6 to EE 30 µg + DSG 150 µg and 3 to EE 30 µg + CMA 2 mg (Multimedia Appendix 2) [9,53,57].

The study population consisted of 1224 women with PCOS with a mean age of 24.20 (95% CI 23.19-25.30) years and a mean BMI of 24.42 (95% CI 23.83-25.74) kg/m^2 (Multimedia Appendix 2). Sufficient data were collected for treatments of 3, 6, and 12 months but not for treatments of 24 months. All hormonal measurements of the studies were performed during the early follicular phase. Only 2 studies did not report days of hormonal assessment [22,58]. The effects of different COC treatments are summarized in Table 1 and Multimedia Appendices 3 and 4.

Follicle-Stimulating Hormone

A total of 13 studies reported effects of COCs on FSH. No study assessed the effects on FSH of EE + CMA for 3 to 12 months and EE + DSG for 12 months.

The use of EE + CA for 3 months was significantly associated with a decrease in FSH concentrations (WMD=−0.48; 95% CI −0.81 to −0.15), whereas use of EE + DSG or use of EE+ DRSP were not significantly associated. After 6 months of treatment with EE + CA (WMD=−2.33; 95% CI −3.48 to −1.18) and DRSP (WMD=−0.93; 95% CI −1.79 to −0.08), FSH concentrations decreased, but there was no decrease with EE + DSG use. Use of EE + CA for 12 months was associated with a decrease in FSH concentrations (WMD=−4.70; 95% CI −4.98 to −4.42), whereas the use of EE +DRSP was not. A significant heterogeneity was identified among most comparisons made with the FSH concentrations (Table 1 and Multimedia Appendices 3-5).

Luteinizing Hormone

A total of 18 studies reported the effects of COCs on LH. No study assessed the effects on LH of EE + CMA for 3 to 12 months and EE + DSG for 12 months.

LH concentrations significantly decreased after 3 months of treatment with EE + DSG (WMD=−11.68; 95% CI −13.72 to −9.64) and EE + CA (WMD=−3.57; 95% CI −5.14 to −1.99) but not with EE + DRSP. After 6 months of treatment with EE + CA (WMD=−5.68; 95% CI −9.57 to −1.80) and EE + DRSP (WMD=−4.59; 95% CI −7.53 to −1.66), LH concentrations significantly decreased, whereas no significant decrease in concentration was observed with EE + DSG use (Figure 2). The use of EE + CA (WMD=−11.60; 95% CI −17.60 to −5.60) for 12 months also decreased LH concentrations, whereas use of EE + DRSP did not. There was significant heterogeneity among some comparisons (Table 1 and Multimedia Appendices 3-5).

Figure 1. Flow diagram of literature search and study selection. PCOS: polycystic ovary syndrome; GnRH: gonadotropin-releasing hormone; COC: combined oral contraceptives.

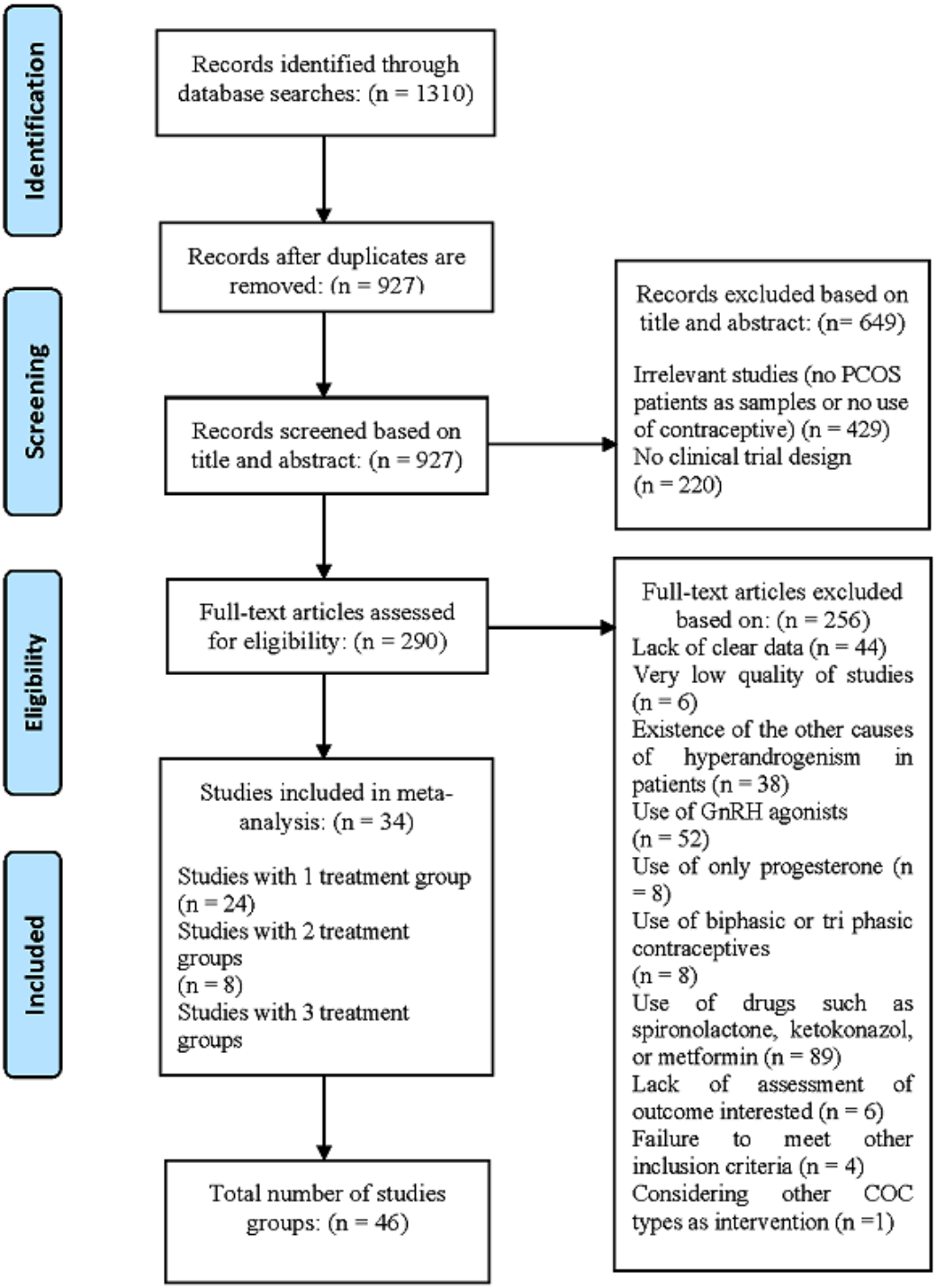
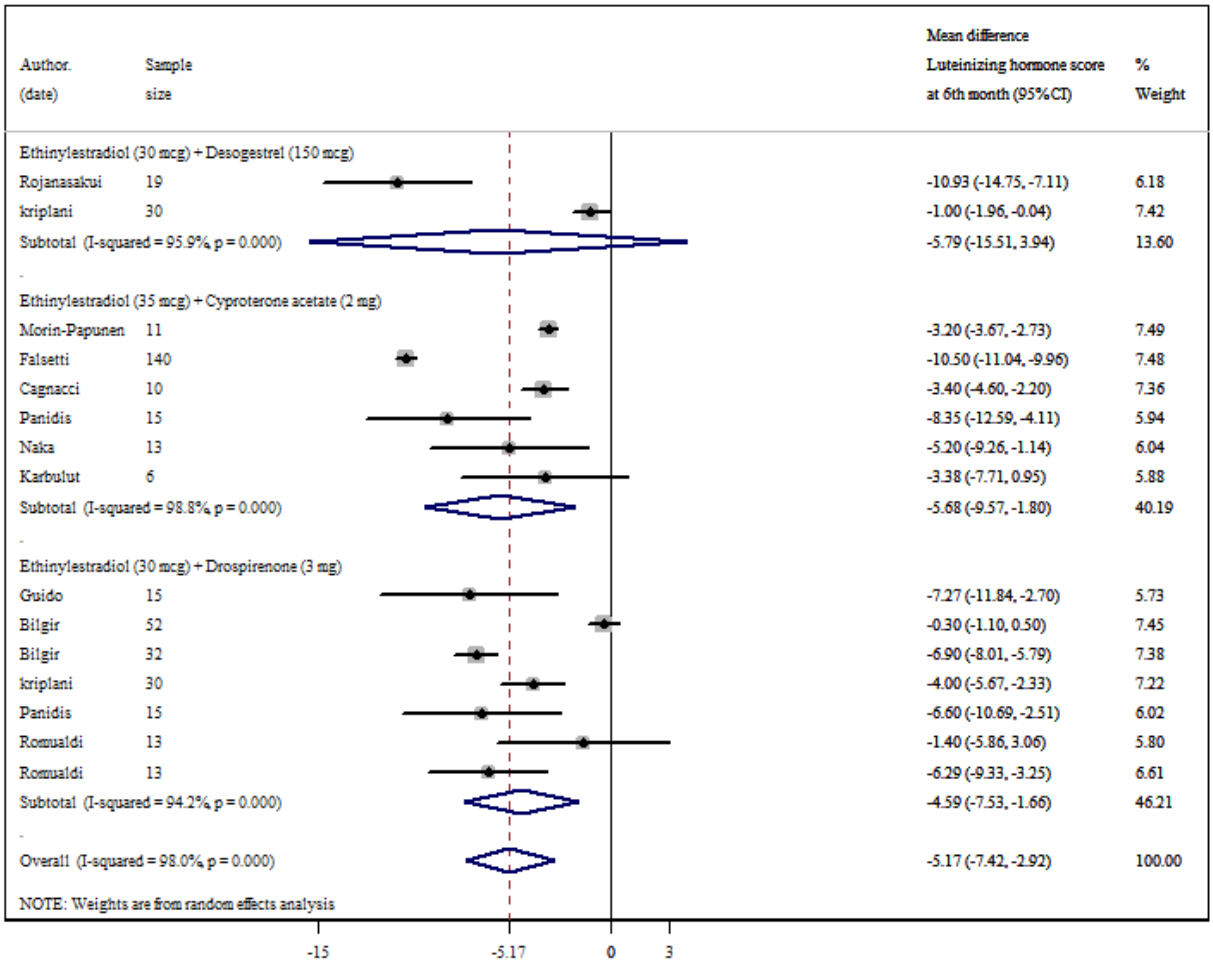


Table 1. Effects of different combined oral contraceptives on hormonal parameters in women with polycystic ovary syndrome. ↑ and ↓ indicate increase and decrease, respectively.

Hormonal parameters	EE[a] + CA[b]	EE + DRSP[c]	EE + CMA[d]	EE + DSG[e]
FSH[f]				
3 months	↓	NO[g]	N/A[h]	NO
6 months	↓	↓	N/A	NO
12 months	↓	NO	N/A	N/A
LH[i]				
3 months	↓	NO	N/A	↓
6 months	↓	↓	N/A	NO
12 months	↓	NO	N/A	N/A
LH-to-FSH ratio				
3 months	NO	NO	N/A	NO
6 months	NO	NO	N/A	NO
12 months	NO	NO	N/A	N/A
E2[j]				
3 months	↓	NO	N/A	N/A
6 months	↓	NO	N/A	N/A
12 months	↓	NO	N/A	N/A
TT[k]				
3 months	↓	↓	↓	↓
6 months	↓	↓	↓	↓
12 months	↓	↓	↓	NO
SHBG[l]				
3 months	↑	↑	↑	↑
6 months	↑	↑	NO	↑
12 months	↑	↑	↑	↑

[a]EE: ethinyl estradiol.
[b]CA: cyproterone acetate.
[c]DRSP: drospirenone.
[d]CMA: chlormadinone acetate.
[e]DSG: desogestrel.
[f]FSH: follicle-stimulating hormone.
[g]NO: no significant effect.
[h]N/A: not assessed.
[i]LH: luteinizing hormone.
[j]E2: estradiol.
[k]TT: total testosterone.
[l]SHBG: sex hormone–binding globulin.

Figure 2. Forest plot of combined oral contraceptives' effects on luteinizing hormone after 6 months of treatment.



Luteinizing Hormone to Follicle-Stimulating Hormone Ratio

A total of 13 studies reported the effects of COCs on LH-to-FSH ratio. No study assessed the effect on LH-to-FSH ratio of EE + CMA for 3 to 12 months and EE + DSG for 12 months.

The use of EE + DSG, EE + CA, and EE + CMA for 3 to 12 months was not associated with any significant change in LH-to-FSH ratio (Table 1 and Multimedia Appendices 3-5).

Estradiol

A total of 7 studies reported the effects of COCs on E2, whereas no study assessed the effect on E2 of EE + CMA and EE + DSG for 3 to 12 months.

The use of EE + CA for 3 to 12 months significantly decreased the E2 concentrations; WMDs (95% CI) in these durations of follow-ups were −5.62 (−10.49 to −0.75), −28.90 (−31.44 to −26.36), and −32.43 (−46.11 to −18.74), respectively. EE + DRSP use was not associated with any significant change in E2 concentrations. No significant heterogeneity was identified among comparisons (Table 1 and Multimedia Appendices 3-5).

Total Testosterone

A total of 30 studies reported the effects of COCs on TT.

The use of various COCs, including EE + DSG (WMD=−0.41; 95% CI −0.73 to −0.08), EE + CA (WMD=−0.25; 95% CI −0.29 to −0.21), and EE + DRSP (WMD=−0.22; 95% CI −0.38 to −0.05), was associated with a significant decrease in TT after 3 months of treatment; however, there was no decrease after EE + CMA use. After 6 months of use, all treatments including EE + DSG (WMD=−0.20; 95% CI −0.36 to −0.04), EE + CA (WMD=−0.30; 95% CI −0.44 to −0.16), EE + DRSP (WMD=−0.17; 95% CI −0.23 to −0.11), and EE + CMA (WMD=−0.24; 95% CI −0.37 to −0.11) decreased TT concentrations. The 12-month use of EE + CA (WMD=−0.29; 95% CI −0.54 to −0.04), EE + DRSP (WMD=−0.12; 95% CI −0.22 to −0.03), and EE + CMA (WMD=−0.10; 95% CI −0.17 to −0.03) also decreased TT concentrations, although EE + DSG use was not associated with any significant change in TT. For all comparisons made with TT concentrations, significant heterogeneity was identified (Table 1 and Multimedia Appendices 3-5).

Sex Hormone–Binding Globulin

A total of 25 studies reported the effects of COCs on SHBG.

Different COCs containing EE + DSG (WMD=99; 95% CI 88.74-109.26), EE + CA (WMD=96.86; 95% CI 47.88-145.84), EE + DRSP (WMD=100.90; 95% CI 12.50-189.30), and EE + CMA (WMD=137.73; 95% CI 89.14-186.32) were associated with increase in SHBG concentrations, following 3 months of

treatment. After 6 months of treatment, EE + DSG (WMD=57.35; 95% CI 19.59-95.11), EE + CA (WMD=102.17; 95% CI 82.72-121.63), EE + DRSP (WMD=93.54; 95% CI 63.63-123.45) increased SHBG concentrations, whereas EE + CMA use was not associated with any significant change in SHBG. SHBG concentrations were also increased after 12 months of treatment with all COCs, including EE + DSG (WMD=181.98; 95% CI 20.25-343.71), EE + CA (WMD=162.10; 95% CI 101.63-222.56), EE + DRSP (WMD=89.33; 95% CI 41.45-137.21), and EE + CMA (WMD=9.24; 95% CI 6.65-11.83). There was significant heterogeneity identified among comparisons (Table 1 and Multimedia Appendices 3-5).

Publication Bias

The results of Egger test showed a significant publication bias for FSH (*P*=.01) and E2 after 6 months (*P*=.07), and corrections were performed on the outcomes. Metatrim showed a change (from mean difference, MD=−1.30; 95% CI −2.14 to −0.46 to MD=−1.33; 95% CI −2.16 to −0. 49) for FSH after 6 months but no change for E2 (MD=−8.96; 95% CI −24.16 to 6.24) in women with PCOS after correcting for publication bias (Multimedia Appendix 6). Other publication biases were not significant.

Meta-Regression Analysis

We used meta-regression to evaluate heterogeneity induced by variables, including diagnostic criteria of PCOS (Rotterdam, NIH, AES, and other), BMI, and method of assay of different hormones (radioimmunoassay, chemical/electrochemical luminescence, enzyme, and unknown). Our univariate meta-regression analysis showed that BMI has a significant effect on FSH difference at 6th month compared with baseline level (beta=.55; *P*=.096). Diagnostic criteria of PCOS were also a significant source of heterogeneity for FSH difference at the 6th month from the baseline level (*P*=.02) and SHBG difference at the 12th month from the baseline level (beta=−4.21; *P*=.002). The method of assay was also a significant source of heterogeneity for TT difference at the 6th month from the baseline level (beta=−.29; *P*=.007) and SHBG difference at the 6th month from the baseline level (beta=44.45; *P*=.085). None of the potential confounders had any effect on LH and E2 levels. As previously mentioned, for meta-regression, a *P* value <.10 was considered statistically significant.

Our multivariate meta-regression was done only for FSH difference at the 6th month from the baseline level, which had more than one source of heterogeneity: BMI and diagnostic criteria of PCOS. It showed that only diagnostic criteria of PCOS is a significant source of heterogeneity (beta=−4.46; *P*=.059). We did not use multivariate meta-regression for other variables because none of them had more than 1 source for their heterogeneity among the 3 variables, including BMI, diagnostic criteria of PCOS, and method of assay.

Sensitivity Analysis

The results of metainf showed that there are few studies that can distort the results. Most of the time the point estimates and 95% CIs are in a specified similar limit with others, which showed homogeneity among the studies. We can hence ignore the risk of introducing bias by BMI, diagnostic criteria of PCOS, or method of assay. Details of the sensitivity analysis are presented in Multimedia Appendix 7.

Risk of Bias Assessment

Multimedia Appendices 8 and 9 show details of risk of bias of published studies. Most RCT studies were at low risk of bias of random sequence generation (52%, 10/19), blinding of participants and personnel (63%, 17/19), and selective outcome reporting (89%, 17/19; in these studies, some biases were more probable such as blinding of outcome assessment and incomplete outcome data (Multimedia Appendix 8). The NRS were not at a high risk of bias. . They had a low risk bias for classification of interventions and selection of reported results (Multimedia Appendix 9).

Generally, most studies had an acceptable validity (low risk of bias), demonstrating high quality of these studies in most aspects. Subgroup analysis based on the risk of bias showed no significant change in outcomes, indicating logical generalizability of these studies.

Discussion

Principal Findings

This meta-analysis compared the effects of COCs with progestins containing low androgenic and antiandrogenic activities on the HPG axis in patients with PCOS. A total of 34 studies involving 1224 women was included in this analysis. Findings showed that the use of COCs containing CA was significantly associated with a decrease in gonadotropins (FSH and LH) and E2 concentrations, whereas COCs containing DRSP did not change these parameters. Data were insufficient to assess the effects of COCs containing CMA and DSG on gonadotropins and E2, but in general these products had no significant effects on these hormonal parameters. COCs were not associated with any significant change in the LH-to-FSH ratio. The use of all COCs was associated with an increase in SHBG and decrease in TT levels, except for DSG at 12 month and CMA at 6 month of treatment.

PCOS has a complex pathogenesis and is believed to be a result of disturbances in gonadotropin secretion. Abnormal secretion of gonadotropins, particularly LH, from the pituitary gland leads to abnormal and excessive ovarian theca cell androgens [59].

Estrogen and progestin components of COCs act together to suppress FSH and LH secretion and the midcycle gonadotropin surge by a feedback mechanism, which results in a decrease in ovarian steroidogenesis [49,60,61]. Indeed, suppression of LH is the major mechanism that mediates the effects of these products in PCOS patients [62].

This study showed that COC use was significantly associated with a suppression of gonadotropin (FSH and LH) levels. Duration of treatment is considered to be an important factor in the suppression of gonadotropins. In fact, the use of products containing CA for 3 to 12 months was associated with a decrease in FSH and LH levels, whereas COCs containing DRSP decreased these hormones only after 6 months of treatment. Thus, products containing DRSP generally require a more

prolonged usage to suppress the gonadotropins. Data for products containing DSG are limited, but this compound generally had no influence on gonadotropin levels similar to that observed with COCs containing CA and DRSP. COCs containing CA are associated with higher gonadotropin suppression compared with that of other COCs.

No studies assessed the effect of EE + DSG, EE + CMA, and EE + GSD on E2 levels. Therefore, data were available only for evaluating the effect of compounds containing EE 35 μg + CA 2 mg and EE 30 μg + DRSP 3 mg on E2 levels. This analysis demonstrated that COCs containing CA significantly decreased E2 concentrations, whereas COCs containing DRSP exhibited no such effect. Duration of treatment with COCs was not significant on E2 concentrations. This review clearly shows that COCs containing CA are more effective compared with COCs containing DRSP on E2 levels; however, these data are not sufficient to assess the effect of other contraceptives on E2.

Testosterone, a major androgen in women, increases in many PCOS patients. Although all COCs can decrease androgen levels by gonadotropin suppression, contraceptives with antiandrogen progestins have additional specific mechanisms in addition to the main mechanisms to improve HA [16,63]. Therefore, it can be suggested that gonadotropins are independent of sex steroid secretion [64]. Similar to all progestins, antiandrogen progestins inhibit LH and increase clearance of testosterone, which leads to a decrease in androgen levels [65,66]. These newer progestins also exert antiandrogenic effects by competing at the receptor sites with androgens and inhibit 5 alpha-reductase activity [16,65]. Five alpha reductase enzyme catalyzes testosterone to dihydrotestosterone [67]. This key enzyme is necessary for biosynthesis and metabolism of androgens [68]. Adipose tissue is an important source of active steroid production and metabolism. It contains the aromatase enzyme that converts circulating androgens to estrogens. As some estrogens in premenopausal women originate from the peripheral conversion of androgens, the plasma concentrations of estrone and E2 may be significantly correlated with the extent of adipose mass. Obesity is associated with several abnormalities in androgen metabolism [69]. Urinary excretion of SHBG is lower in obese women compared with normal-weight women [70]. Kirschner et al found that menopausal women with abdominal obesity had higher testosterone levels than those with peripheral obesity [71]. Obesity is associated with increased androgen production rate and metabolic clearance rate; however, the main differences are higher estrogen and lower SHBG levels, whereas usually no differences are found in androgen and gonadotropin concentrations [69].

Interestingly, this study showed that all COCs containing CA, DRSP, CMA, and DSG can decrease TT concentrations. The type of COC and duration of treatment with COCs had no significant effects on TT concentrations. A meta-analysis assessed the effect of COCs on testosterone concentrations in healthy women and found that the progestin type of COCs does not affect the testosterone levels [66]; their findings are consistent with those of this meta-analysis. However, they did not evaluate the pituitary hormones and other hormones secreted by the ovary in women with PCOS.

This review also strongly demonstrates that SHBG significantly increased during the use of COCs. Progestin compound and duration of treatment had no important effects on the changes in SHBG levels.

Comparative studies are not adequate to assess the effect of COCs on HPG; therefore, this meta-analysis included NRS and individual arms of RCTs. However, it is well known that meta-analysis of NRS can produce equally or more precise findings for a clinical question compared with meta-analysis of RCTs alone [3,72].

Limitations

This study has several limitations that should be mentioned. First, there is no single definition for the diagnosis of PCOS and its components. Second, different studies assessed hormonal measurements by different methods. Third, some studies did not assess all hormonal parameters. Finally, some subgroups in this meta-analysis had limited studies to analyze, which can affect the robustness of the results. Therefore, additional studies are required to provide more concrete data to investigate and confirm the accuracy of this conclusion.

There was significant heterogeneity in most outcomes, which can reflect clinical heterogeneity related to variability in PCOS diagnostic criteria; interpretation of laboratory tests; study population, for example, age; BMI; ethnicity or race; and methods used to measure hormones. To deal with significant heterogeneities, we used the random effect model. A majority of studies included in this analysis used the Rotterdam criteria for diagnosing PCOS and a limited number used other diagnostic criteria, such as AES or NIH. Therefore, this meta-analysis has also included PCOS patients with oligomenorrea and cystic ovaries without clinical or biochemical HA. The results of this study showed that diagnostic criteria of PCOS can also be a source of heterogeneity for FSH concentrations, indicating that variability in diagnostic criteria can be a cause of differences in gonadotropin concentrations. However, a sensitivity analysis showed that most of the time point estimates and 95% CIs are in a specified limit similar to those of others; hence, we can ignore the risk of introducing bias by BMI, diagnostic criteria of PCOS, or method of assay. Some included studies reported the early follicular phase as the timing of hormonal measurement without determining its exact time; however, blood samples for all studies were collected at early follicular phase of the spontaneous menstrual cycle or progesterone-induced menstrual bleeding.

To minimize selection bias, study selection was conducted based on the eligibility criteria, which had been accurately determined just before the study. A hand search of the reference lists of all selected papers was also conducted to prevent missing studies.

The pooled estimate of this meta-analysis provides precise results as it has acceptable risk of bias and publication bias; in addition, it included studies conducted among reproductive age women from various regions of the world. Moreover, a subgroup analysis based on the risk of bias was not associated with any significant differences in outcomes. Hence, we can rely on the pooled estimate and the generalizability of these studies.

In this review, the difference between baseline and posttreatment levels was calculated to assess the effects of COCs on the HPG axis. However, subgroup analyses based on different baseline levels and PCOS phenotypes were not performed because of the limitations of the existing studies.

Conclusions

This meta-analysis indicates that COC use for 3 to 12 months can suppress gonadotropins, leading to a decrease in androgenic profiles in women with PCOS. Although progestin compounds used and duration of treatment were not effective in reducing the circulating levels of androgens and SHBG, they were important in gonadotropin suppression. This study demonstrates that products containing CA have the greatest suppressive effect on gonadotropins and E2, indicating that the use of this compound may be a better alternative for PCOS patients with impaired gonadotropins. However, because of the limitations of the data available for comparison of the effects of all COCs on HPG, the investigators recommend designing further comparative studies.

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Authors' Contributions

MA was involved in the study design, search in databases, study selection, data analysis, manuscript drafting, and critical discussion. FRT was involved in the study design, data analysis, critical discussion, and editing and submission of the manuscript. AK contributed to the study selection, data analysis, and critical discussion. FN and FA contributed to the study design and critical discussion. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

PRISMA (Preferred Reporting Items checklist for Systematic Reviews and Meta-Analyses) 2009 checklist.

[PDF File (Adobe PDF File), 60KB - resprot_v7i4e113_app1.pdf]

Multimedia Appendix 2

Characteristics of eligible studies included in the meta-analysis.

[PDF File (Adobe PDF File), 55KB - resprot_v7i4e113_app2.pdf]

Multimedia Appendix 3

Effects of EE 35 + CA 2 and EE 30 + DRSP 3 on hormonal parameters.

[PDF File (Adobe PDF File), 33KB - resprot_v7i4e113_app3.pdf]

Multimedia Appendix 4

Effects of EE 30 + CMA 2 and EE 30 + DSG 150 on hormonal parameters.

[PDF File (Adobe PDF File), 32KB - resprot_v7i4e113_app4.pdf]

Multimedia Appendix 5

Forest plots of combined oral contraceptives' effects on hormonal parameters, including the follicle-stimulating hormone, luteinizing hormone, estradiol, total testosterone, and sex hormone-binding globulin.

[PDF File (Adobe PDF File), 119KB - resprot_v7i4e113_app5.pdf]

Multimedia Appendix 6

Funnel plots of publication bias and related corrections.

[PDF File (Adobe PDF File), 151KB - resprot_v7i4e113_app6.pdf]

Multimedia Appendix 7

The results of sensitivity analysis.

[PDF File (Adobe PDF File), 86KB - resprot_v7i4e113_app7.pdf]

Multimedia Appendix 8

Risk of bias for randomized controlled trials.

[JPG File, 105KB - resprot_v7i4e113_app8.jpg]

Multimedia Appendix 9

Risk of bias for nonrandomized studies.

[JPG File, 90KB - resprot_v7i4e113_app9.jpg]

References

1. Kriplani A, Periyasamy AJ, Agarwal N, Kulshrestha V, Kumar A, Ammini AC. Effect of oral contraceptive containing ethinyl estradiol combined with drospirenone vs. desogestrel on clinical and biochemical parameters in patients with polycystic ovary syndrome. Contraception 2010 Aug;82(2):139-146. [doi: 10.1016/j.contraception.2010.02.009] [Medline: 20654754]
2. Elter K, Imir G, Durmusoglu F. Clinical, endocrine and metabolic effects of metformin added to ethinyl estradiol-cyproterone acetate in non-obese women with polycystic ovarian syndrome: a randomized controlled study. Hum Reprod 2002 Jul;17(7):1729-1737. [Medline: 12093831]
3. Amiri M, Ramezani Tehrani F, Nahidi F, Kabir A, Azizi F, Carmina E. Effects of oral contraceptives on metabolic profile in women with polycystic ovary syndrome: a meta-analysis comparing products containing cyproterone acetate with third generation progestins. Metabolism 2017 Aug;73:22-35. [doi: 10.1016/j.metabol.2017.05.001] [Medline: 28732568]
4. Kahraman K, Sükür YE, Atabekoğlu CS, Ateş C, Taşkın S, Cetinkaya SE, et al. Comparison of two oral contraceptive forms containing cyproterone acetate and drospirenone in the treatment of patients with polycystic ovary syndrome: a randomized clinical trial. Arch Gynecol Obstet 2014 Aug;290(2):321-328. [doi: 10.1007/s00404-014-3217-5] [Medline: 24676694]
5. Robinson S, Henderson AD, Gelding SV, Kiddy D, Niththyananthan R, Bush A, et al. Dyslipidaemia is associated with insulin resistance in women with polycystic ovaries. Clin Endocrinol (Oxf) 1996 Mar;44(3):277-284. [Medline: 8729522]
6. Amiri M, Mirmiran P, Ramezani Tehrani P, Ramezani Tehrani F. Effect of interventions based on lifestyle modification on clinical, hormonal and metabolic findings in the patients with polycystic ovary syndrome: a systematic review. Iran J Endocrinol Metab 2016 Mar 16;17(6):489-500 [FREE Full text]
7. Hahn S, Janssen OE, Tan S, Pleger K, Mann K, Schedlowski M, et al. Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome. Eur J Endocrinol 2005 Dec;153(6):853-860 [FREE Full text] [doi: 10.1530/eje.1.02024] [Medline: 16322391]
8. Yildiz BO. Approach to the patient: contraception in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2015 Mar;100(3):794-802. [doi: 10.1210/jc.2014-3196] [Medline: 25701301]
9. Yildizhan R, Gokce AI, Yildizhan B, Cim N. Comparison of the effects of chlormadinone acetate versus drospirenone containing oral contraceptives on metabolic and hormonal parameters in women with PCOS for a period of two-year follow-up. Gynecol Endocrinol 2015 May;31(5):396-400. [doi: 10.3109/09513590.2015.1006187] [Medline: 25739031]
10. Bhattacharya SM, Jha A. Comparative study of the therapeutic effects of oral contraceptive pills containing desogestrel, cyproterone acetate, and drospirenone in patients with polycystic ovary syndrome. Fertil Steril 2012 Oct;98(4):1053-1059. [doi: 10.1016/j.fertnstert.2012.06.035] [Medline: 22795636]
11. Helvaci N, Yildiz BO. Oral contraceptives in polycystic ovary syndrome. Minerva Endocrinol 2014 Sep;39(3):175-187. [Medline: 25003228]
12. Breitkopf DM, Rosen MP, Young SL, Nagamani M. Efficacy of second versus third generation oral contraceptives in the treatment of hirsutism. Contraception 2003 May;67(5):349-353. [Medline: 12742556]
13. Rosen MP, Breitkopf DM, Nagamani M. A randomized controlled trial of second- versus third-generation oral contraceptives in the treatment of acne vulgaris. Am J Obstet Gynecol 2003 May;188(5):1158-1160. [Medline: 12748463]
14. Burkman Jr RT. The role of oral contraceptives in the treatment of hyperandrogenic disorders. Am J Med 1995 Jan 16;98(1A):130S-136S. [Medline: 7825633]
15. Raudrant D, Rabe T. Progestogens with antiandrogenic properties. Drugs 2003;63(5):463-492. [Medline: 12600226]
16. Mathur R, Levin O, Azziz R. Use of ethinylestradiol/drospirenone combination in patients with the polycystic ovary syndrome. Ther Clin Risk Manag 2008 Apr;4(2):487-492 [FREE Full text] [Medline: 18728832]

17. Di Carlo C, Gargano V, Sparice S, Tommaselli GA, Bifulco G, Nappi C. Effects of an oral contraceptive containing estradiol valerate and dienogest on circulating androgen levels and acne in young patients with PCOS: an observational preliminary study. Gynecol Endocrinol 2013 Dec;29(12):1048-1050. [doi: 10.3109/09513590.2013.831834] [Medline: 24020909]
18. Sitruk-Ware R. Pharmacological profile of progestins. Maturitas 2008;61(1-2):151-157. [Medline: 19434887]
19. Palep-Singh M, Mook K, Barth J, Balen A. An observational study of Yasmin in the management of women with polycystic ovary syndrome. J Fam Plann Reprod Health Care 2004 Jul;30(3):163-165 [FREE Full text] [Medline: 15222920]
20. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8(5):336-341 [FREE Full text] [doi: 10.1016/j.ijsu.2010.02.007] [Medline: 20171303]
21. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions, Vol 5. UK: Wiley Online Library; 2008.
22. Rojanasakul A, Sirimongkolkasem R, Piromsawasdi S, Sumavong V, Chailurkit L, Chaturachinda K. Effects of combined ethinylestradiol and desogestrel on hormone profiles and sex hormone binding globulin in women with polycystic ovarian disease. Contraception 1987 Dec;36(6):633-640. [Medline: 2965636]
23. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT. Amsterdam, Netherlands: Elsevier; 2010:e1-e37.
24. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J 2011;343:d5928 [FREE Full text] [Medline: 22008217]
25. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. Br Med J 2016 Oct 12;355:i4919 [FREE Full text] [Medline: 27733354]
26. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005 Apr 20;5(1):13. [doi: 10.1186/1471-2288-5-13]
27. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994 Dec;50(4):1088-1101. [Medline: 7786990]
28. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003 Sep 6;327(7414):557-560 [FREE Full text] [doi: 10.1136/bmj.327.7414.557] [Medline: 12958120]
29. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997 Sep 13;315(7109):629-634 [FREE Full text] [Medline: 9310563]
30. Taylor S, Tweedie R. Trim and fill: a simple funnel plot based method of testing and adjusting for publication bias in meta-analyses. Fort Collins, CO: Colorado State University 1998:455-463.
31. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000 Jun;56(2):455-463. [Medline: 10877304]
32. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, Tapanainen JS. Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab 2000 Sep;85(9):3161-3168. [doi: 10.1210/jcem.85.9.6792] [Medline: 10999803]
33. Armstrong VL, Wiggam MI, Ennis CN, Sheridan B, Traub AI, Atkinson AB, et al. Insulin action and insulin secretion in polycystic ovary syndrome treated with ethinyl oestradiol/cyproterone acetate. QJM 2001 Jan;94(1):31-37. [Medline: 11161134]
34. Falsetti L, Gambera A, Tisi G. Efficacy of the combination ethinyl oestradiol and cyproterone acetate on endocrine, clinical and ultrasonographic profile in polycystic ovarian syndrome. Hum Reprod 2001 Jan;16(1):36-42. [Medline: 11139533]
35. Mastorakos G, Koliopoulos C, Creatsas G. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. Fertil Steril 2002 May;77(5):919-927. [Medline: 12009344]
36. Cagnacci A, Paoletti AM, Renzi A, Orrù M, Pilloni M, Melis GB, et al. Glucose metabolism and insulin resistance in women with polycystic ovary syndrome during therapy with oral contraceptives containing cyproterone acetate or desogestrel. J Clin Endocrinol Metab 2003 Aug;88(8):3621-3625. [doi: 10.1210/jc.2003-030328] [Medline: 12915645]
37. Lv L, Liu Y, Sun Y, Tan K. Effects of metformin combined with cyproterone acetate on clinical features, endocrine and metabolism of non-obese women with polycystic ovarian syndrome. J Huazhong Univ Sci Technolog Med Sci 2005;25(2):194-197. [Medline: 16116971]
38. Wu J, Zhu Y, Jiang Y, Cao Y. Effects of metformin and ethinyl estradiol-cyproterone acetate on clinical, endocrine and metabolic factors in women with polycystic ovary syndrome. Gynecol Endocrinol 2008 Jul;24(7):392-398. [doi: 10.1080/09513590802217027] [Medline: 18608522]
39. Gul OB, Somunkiran A, Yucel O, Demirci F, Ozdemir I. The effect of ethinyl estradiol-cyproterone acetate treatment on homocysteine levels in women with polycystic ovary syndrome. Arch Gynecol Obstet 2008 Jan;277(1):25-30. [doi: 10.1007/s00404-007-0401-x] [Medline: 17618446]
40. Bilgir O, Kebapcilar L, Taner C, Bilgir F, Kebapcilar A, Bozkaya G, et al. The effect of ethinylestradiol (EE)/cyproterone acetate (CA) and EE/CA plus metformin treatment on adhesion molecules in cases with polycystic ovary syndrome (PCOS). Intern Med 2009;48(14):1193-1199 [FREE Full text] [Medline: 19602786]

41. Kebapcilar L, Yuksel A, Bozkaya G, Taner CE, Kebapcilar AG, Bilgir O, et al. Effects of an EE/CA compared with EE/CA-metformin on serum ADMA levels in women with polycystic ovary syndrome. Cent Eur J Med 2009 Dec;4(4):423-427 [FREE Full text] [doi: 10.2478/s11536-009-0074-x]
42. Mahmood M, El-Kattan E, El-Aal H, El LA, Ghamry N, Sheta M. Evaluation of the clinical and biochemical effects of medical therapy in women with polycystic ovary syndrome. Med J Cairo Univ 2009 Sep;77(2):59-67.
43. Chen MJ, Yang WS, Chen HF, Kuo JJ, Ho HN, Yang YS, et al. Increased follistatin levels after oral contraceptive treatment in obese and non-obese women with polycystic ovary syndrome. Hum Reprod 2010 Mar;25(3):779-785. [doi: 10.1093/humrep/dep459] [Medline: 20093255]
44. Teede HJ, Meyer C, Hutchison SK, Zoungas S, McGrath BP, Moran LJ. Endothelial function and insulin resistance in polycystic ovary syndrome: the effects of medical therapy. Fertil Steril 2010 Jan;93(1):184-191. [doi: 10.1016/j.fertnstert.2008.09.034] [Medline: 19019358]
45. Panidis D, Georgopoulos NA, Piouka A, Katsikis I, Saltamavros AD, Decavalas G, et al. The impact of oral contraceptives and metformin on anti-Müllerian hormone serum levels in women with polycystic ovary syndrome and biochemical hyperandrogenemia. Gynecol Endocrinol 2011 Aug;27(8):587-592. [doi: 10.3109/09513590.2010.507283] [Medline: 20836726]
46. Naka KK, Kalantaridou SN, Bechlioulis A, Kravariti M, Kazakos N, Katsouras CS, et al. Effect of ethinylestradiol/cyproterone acetate on endothelial function in young non-obese women with polycystic ovary syndrome: a pilot study. Gynecol Endocrinol 2011 Sep;27(9):615-621. [doi: 10.3109/09513590.2010.521265] [Medline: 21329419]
47. Karabulut A, Demirlenk S, Sevket O. Effects of ethinyl estradiol-cyproterone acetate treatment on metabolic syndrome, fat distribution and carotid intima media thickness in polycystic ovary syndrome. Gynecol Endocrinol 2012 Apr;28(4):245-248. [doi: 10.3109/09513590.2011.613971] [Medline: 21961995]
48. Guido M, Romualdi D, Giuliani M, Suriano R, Selvaggi L, Apa R, et al. Drospirenone for the treatment of hirsute women with polycystic ovary syndrome: a clinical, endocrinological, metabolic pilot study. J Clin Endocrinol Metab 2004 Jun;89(6):2817-2823. [doi: 10.1210/jc.2003-031158] [Medline: 15181063]
49. Pehlivanov B, Mitkov M. Efficacy of an oral contraceptive containing drospirenone in the treatment of women with polycystic ovary syndrome. Eur J Contracept Reprod Health Care 2007 Mar;12(1):30-35. [doi: 10.1080/13625180600983082] [Medline: 17455042]
50. Gregoriou O, Papadias K, Konidaris S, Bakalianou K, Salakos N, Vrachnis N, et al. Treatment of hirsutism with combined pill containing drospirenone. Gynecol Endocrinol 2008 Apr;24(4):220-223. [doi: 10.1080/09513590801948309] [Medline: 18382909]
51. Ozdemir S, Görkemli H, Gezginç K, Ozdemir M, Kiyici A. Clinical and metabolic effects of medroxyprogesterone acetate and ethinyl estradiol plus drospirenone in women with polycystic ovary syndrome. Int J Gynaecol Obstet 2008 Oct;103(1):44-49. [doi: 10.1016/j.ijgo.2008.05.017] [Medline: 18635183]
52. Sağsöz N, Orbak Z, Noyan V, Yücel A, Uçar B, Yildiz L. The effects of oral contraceptives including low-dose estrogen and drospirenone on the concentration of leptin and ghrelin in polycystic ovary syndrome. Fertil Steril 2009 Aug;92(2):660-666. [doi: 10.1016/j.fertnstert.2008.07.008] [Medline: 18973889]
53. Colonna L, Pacifico V, Lello S, Sorge R, Raskovic D, Primavera G. Skin improvement with two different oestroprogestins in patients affected by acne and polycystic ovary syndrome: clinical and instrumental evaluation. J Eur Acad Dermatol Venereol 2012 Nov;26(11):1364-1371. [doi: 10.1111/j.1468-3083.2011.04292.x] [Medline: 22011217]
54. Romualdi D, De Cicco S, Busacca M, Gagliano D, Lanzone A, Guido M. Clinical efficacy and metabolic impact of two different dosages of ethinyl-estradiol in association with drospirenone in normal-weight women with polycystic ovary syndrome: a randomized study. J Endocrinol Invest 2013 Sep;36(8):636-641. [doi: 10.1007/BF03346756] [Medline: 24105072]
55. Aydin K, Cinar N, Aksoy DY, Bozdag G, Yildiz BO. Body composition in lean women with polycystic ovary syndrome: effect of ethinyl estradiol and drospirenone combination. Contraception 2013 Mar;87(3):358-362. [doi: 10.1016/j.contraception.2012.07.005] [Medline: 22898361]
56. Macut D, Božić Antić I, Nestorov J, Topalović V, Bjekić Macut J, Panidis D, et al. The influence of combined oral contraceptives containing drospirenone on hypothalamic-pituitary-adrenocortical axis activity and glucocorticoid receptor expression and function in women with polycystic ovary syndrome. Hormones (Athens) 2015;14(1):109-117 [FREE Full text] [doi: 10.14310/horm.2002.1526] [Medline: 25402380]
57. De Leo V, Di Sabatino A, Musacchio MC, Morgante G, Scolaro V, Cianci A, et al. Effect of oral contraceptives on markers of hyperandrogenism and SHBG in women with polycystic ovary syndrome. Contraception 2010 Sep;82(3):276-280. [doi: 10.1016/j.contraception.2010.04.002] [Medline: 20705157]
58. Nader S, Riad-Gabriel MG, Saad MF. The effect of a desogestrel-containing oral contraceptive on glucose tolerance and leptin concentrations in hyperandrogenic women. J Clin Endocrinol Metab 1997 Sep;82(9):3074-3077. [doi: 10.1210/jcem.82.9.4192] [Medline: 9284746]
59. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med 2005 Mar 24;352(12):1223-1236. [doi: 10.1056/NEJMra041536] [Medline: 15788499]

60. Vrbíková J, Cibula D. Combined oral contraceptives in the treatment of polycystic ovary syndrome. Hum Reprod Update 2005;11(3):277-291. [doi: 10.1093/humupd/dmi005] [Medline: 15790599]
61. Uras R, Orrù M, Pani F, Marotto M, Pilloni M, Guerriero S, et al. Endocrinological, metabolic and clinical features of treatment with oral contraceptive formulation containing ethinylestradiol plus chlormadinone acetate in nonobese women with polycystic ovary syndrome. Contraception 2010 Aug;82(2):131-138. [doi: 10.1016/j.contraception.2010.01.022] [Medline: 20654753]
62. Carlström K, Karlsson R, Von Schoultz B. Diurnal rhythm and effects of oral contraceptives on serum dehydroepiandrosterone sulfate (DHEAS) are related to alterations in serum albumin rather than to changes in adrenocortical steroid secretion. Scand J Clin Lab Invest 2002;62(5):361-368. [Medline: 12387582]
63. Nader S, Diamanti-Kandarakis E. Polycystic ovary syndrome, oral contraceptives and metabolic issues: new perspectives and a unifying hypothesis. Hum Reprod 2007 Feb;22(2):317-322. [doi: 10.1093/humrep/del407] [Medline: 17099212]
64. Holte J, Bergh T, Gennarelli G, Wide L. The independent effects of polycystic ovary syndrome and obesity on serum concentrations of gonadotrophins and sex steroids in premenopausal women. Clin Endocrinol (Oxf) 1994 Oct;41(4):473-481. [Medline: 7955458]
65. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. Int J Womens Health 2011 Feb 08;3:25-35 [FREE Full text] [doi: 10.2147/IJWH.S11304] [Medline: 21339935]
66. Zimmerman Y, Eijkemans MJ, Coelingh Bennink HJ, Blankenstein MA, Fauser BC. The effect of combined oral contraception on testosterone levels in healthy women: a systematic review and meta-analysis. Hum Reprod Update 2014;20(1):76-105 [FREE Full text] [doi: 10.1093/humupd/dmt038] [Medline: 24082040]
67. Longcope C. Adrenal and gonadal androgen secretion in normal females. Clin Endocrinol Metab 1986 May;15(2):213-228. [Medline: 3013468]
68. Thiboutot D, Jabara S, McAllister JM, Sivarajah A, Gilliland K, Cong Z, et al. Human skin is a steroidogenic tissue: steroidogenic enzymes and cofactors are expressed in epidermis, normal sebocytes, and an immortalized sebocyte cell line (SEB-1). J Invest Dermatol 2003 Jun;120(6):905-914 [FREE Full text] [doi: 10.1046/j.1523-1747.2003.12244.x] [Medline: 12787114]
69. Pasquali R, Casimirri F. The impact of obesity on hyperandrogenism and polycystic ovary syndrome in premenopausal women. Clin Endocrinol (Oxf) 1993 Jul;39(1):1-16. [Medline: 8348699]
70. Glass AR, Burman KD, Dahms WT, Boehm TM. Endocrine function in human obesity. Metabolism 1981 Jan;30(1):89-104. [Medline: 6780754]
71. Kirschner MA, Samojlik E, Drejka M, Szmal E, Schneider G, Ertel N. Androgen-estrogen metabolism in women with upper body versus lower body obesity. J Clin Endocrinol Metab 1990 Feb;70(2):473-479. [doi: 10.1210/jcem-70-2-473] [Medline: 2298859]
72. Shrier I, Boivin J, Steele RJ, Platt RW, Furlan A, Kakuma R, et al. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. Am J Epidemiol 2007 Nov 15;166(10):1203-1209. [doi: 10.1093/aje/kwm189] [Medline: 17712019]

Abbreviations

AES: Androgen Excess Society
BMI: body mass index
CA: cyproterone acetate
CMA: chlormadinone acetate
COCs: combined oral contraceptives
CONSORT: Consolidated Standards of Reporting Trials
DRSP: drospirenone
DSG: desogestrel
EE: ethinyl estradiol
E2: estradiol
FSH: follicle-stimulating hormone
GSD: gestodene
HA: hyperandrogenism
HPG: hypothalamic-pituitary-gonadal
LH: luteinizing hormone
LNG: levonorgestrel
MD: mean difference
NIH: National Institutes of Health
NO: no significant effect
NRS: nonrandomized studies
N/A: not assessed

PCOS: polycystic ovary syndrome
PRISMA: Preferred Reporting Items checklist for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial
SHBG: sex hormone–binding globulin
TT: total testosterone
WMD: weighted mean differences

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Original Paper

A Website Supporting Sensitive Religious and Cultural Advance Care Planning (ACPTalk): Formative and Summative Evaluation

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Abstract

Background: Advance care planning (ACP) promotes conversations about future health care needs, enacted if a person is incapable of making decisions at end-of-life that may be communicated through written documentation such as advance care directives. To meet the needs of multicultural and multifaith populations in Australia, an advance care planning website, ACP*Talk*, was funded to support health professionals in conducting conversations within diverse religious and cultural populations. ACP*Talk* aimed to provide religion-specific advance care planning content and complement existing resources.

Objective: The purpose of this paper was to utilize the context, input, process, and product (CIPP) framework to conduct a formative and summative evaluation of ACP*Talk*.

Methods: The CIPP framework was used, which revolves around 4 aspects of evaluation: context, input, process, and product. Context: health professionals' solutions for the website were determined through thematic analysis of exploratory key stakeholder interviews. Included religions were determined through an environmental scan, Australian population statistics, and documentary analysis of project steering committee meeting minutes. Input: Project implementation and challenges were examined through documentary analysis of project protocols and meeting minutes. Process: To ensure religion-specific content was accurate and appropriate, a website prototype was built with content review and functionality testing by representatives from religious and cultural organizations and other interested health care organizations who completed a Web-based survey. Product: Website analytics were used to report utilization, and stakeholder perceptions were captured through interviews and a website survey.

Results: Context: A total of 16 key stakeholder health professional (7 general practitioners, 2 primary health nurses, and 7 palliative care nurses) interviews were analyzed. Website solutions included religious and cultural information, communication ideas, legal information, downloadable content, and Web-based accessibility. Christian and non-Christian faiths were to be included in the religion-specific content. Input: Difficulties gaining consensus on religion-specific content were overcome by further state and national religious organizations providing feedback. Process: A total of 37 content reviewers included representatives of religious and cultural organizations (n=29), health care (n=5), and community organizations (n=3). The majority strongly agree or agree that the content used appropriate language and tone (92%, 34/37), would support health professionals (89%, 33/37), and was accurate (83%, 24/29). Product: Resource usage within the first 9 months was 12,957 page views in 4260 sessions; majority were (83.45%, 3555/4260) from Australia. A total of 107 Australian-based users completed the website survey;

most felt information was accurate (77.6%, 83/107), easy to understand (82.2%, 88/107), useful (86.0%, 92/107), and appropriate (86.0%, 92/107). A total of 20 nurses (general practice n=10, palliative care n=8, and both disciplines n=2) participated in stakeholder interviews. Qualitative findings indicated overall positivity in relation to accessibility, functionality, usefulness, design, and increased knowledge of advance care planning. Recommended improvements included shortened content, a comparable website for patients and families, and multilingual translations.

Conclusions: The CIPP framework was effectively applied to evaluate the development and end product of an advance care planning website.Although overall findings were positive, further advance care planning website development should consider the recommendations derived from this study.

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KEYWORDS

advance care planning; ehealth; religion; culture; health personnel

Introduction

Application of Electronic Health in Advance Care Planning

Integration of advance care planning (ACP) is associated with improved quality of life, better adherence to patients' wishes, and reduced hospitalizations [1]. ACP promotes conversations about future health care needs, enacted if a person is incapable of making decisions at end-of-life that may be communicated through written documentation such as advance care directives (ACDs) [2]. Globally, technological advancements have resulted in an abundance of ACP electronic health (eHealth) apps with the emergence of ACD registries, Web-based educational material, commercial and government websites, and decisions aids [3]. Reviews have largely focused on ACP decision aids or Web-based tools for patients or community members [4,5], with demonstrated improvements in patient knowledge, preparation of treatment options, and communication of health care goals [4]. Although studies of ACP websites have shown benefits [6-9], few published studies have evaluated health professionals' experiences and perceptions of ACP websites. Notably, studies of a computer-based ACP decision aid, accessible via a website, was helpful for patients and medical students [10-15].

Promotion of Religious and Cultural Sensitivity and Education

Although national ACP frameworks and guidelines promote inclusion of cultural and religious beliefs in end-of-life decision making [2,16,17], core value assumptions may differ between dominant western and minority cultural worldviews in relation to autonomy, decision making, information disclosure, and control over dying [18]. Within the diverse Australian multicultural [19] and multifaith [20] population, evidence suggests cultural sensitivities and divergent views about death, dying, and end-of-life care (EoLC) among Dutch and Italian migrants [21], people of Sudanese [22], African [23], Chinese [24,25], and Indian [26,27] backgrounds, and Aboriginal and Torres Strait Islander peoples [28-32]. This has implications for health care providers. EoLC, therefore, requires a considered approach, assimilating knowledge and awareness of the importance of culture, religion, spiritual beliefs, and backgrounds [33]. Education of health professionals about cultural differences expressed in ACP, communication training [34], and knowledge acquisition skills are essential to providing culturally appropriate care [35].

The ACP*Talk* Website

To address this gap, an Australian-based website, ACP*Talk* [36], was funded to support health professionals in conducting ACP conversations with people from diverse religious and cultural backgrounds. Goals of the website were to (1) create a Web-based resource that would provide religion-specific information for health professionals conducting ACP conversations with people from diverse religious and cultural backgrounds and (2) complement existing Web-based ACP resources by providing links to religious and cultural information readily available on the Internet. A website was deemed suitable, given the necessity to create a resource that would be freely accessible, in contrast to most ACP decision aids that are proprietary or not publically available [5]. ACP*Talk* was tailored to meet the needs of the Australian-based population, consistent with the goals of the *National Palliative Care Strategy Supporting Australians to Live Well at End of Life* [37] by addressing barriers to uptake of ACP, in this case religious and cultural facets.

Evaluation

Systematic evaluation is required to assess the effectiveness, efficiency, and appropriateness of activities [38], including the development and implementation of new eHealth apps and programs. Key evaluation standards examine the utility, feasibility, propriety, and accuracy of programs [39,40]. Although numerous evaluation approaches exist [41], evaluations should be tailored to examine specific objectives, processes, and outcomes. Program logic models [42] are frequently used in project evaluation to assess planning, implementation, and outcomes [43-46]. However, they are often constrained by the assumption of linear relationships that are presumed within the logic model [47]. The context, input, process, and product (CIPP) model is a comprehensive framework initially developed by Stufflebeam in the 1960s that may be utilized to conduct formative and summative evaluation [48]. The framework is not inhibited by assumptions of logic models [47] and is underpinned by the principles of the Joint Committee on Standards for Educational Evaluation [40]. CIPP has been widely used to evaluate health care services [49-51], educational and training programs [47,52-54], and webinars [55].

The purpose of this paper was to present a formative and summative evaluation of an ACP website, ACP*Talk*, using the CIPP framework.

Methods

Context, Input, Process, and Product Framework

The CIPP framework consists of four evaluation types that are summarized below [48]:

- Context evaluation is used to judge and assess project needs, problems, assets, opportunities, and contextual conditions
- Input evaluation is concerned with program planning through assessing budgets, procedural plans, feasibility, challenges, and targets
- Process evaluation examines implementation of planned and actual processes
- Product is concerned with examining program outcomes, how the program effectively addressed needs, and achieved its goals

The CIPP model enables evaluators to design specific core questions for each evaluation type that are relevant to the intended project to be assessed. On the basis of the ACP*Talk* project, evaluation questions were devised (Table 1). Rationale and methods for each evaluation type are presented; mixed methods consistent with the CIPP framework were employed. Schematic flow of the ACP*Talk* evaluation and presentation of results are described in Figure 1.

Context and Input Evaluation

Project Protocol and Implementation

A project protocol was developed inclusive of three main phases: (1) an exploratory study, (2) religious leader interviews that would be used to derive religion-specific website content, and (3) an evaluation. The study received ethical approval by a human research ethics committee (CHREC 02-05-10-15).

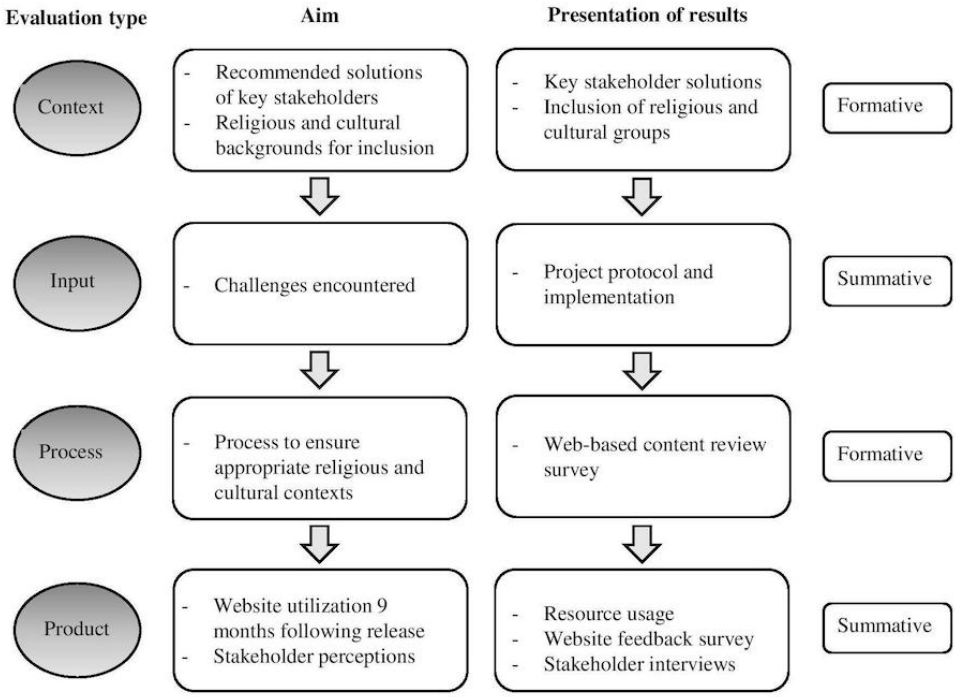
Project governance was established with a project steering committee (PSC) and project working group (PWG) convened. The PWG developed project and research aims, protocol, data collection, and management procedures and reported outcomes to the PSC. The PSC consisted of expert representatives from religious and cultural organizations, universities, palliative care, and nursing researchers and general practitioners (GPs) who were responsible for providing overall project oversight, approving protocols, procedures, recommending linkages for recruitment, and website feedback. Documentation resulting from these committees included PSC meeting minutes, the project protocol, email correspondence, and reports.

Table 1. Overview of context, input, process, and product (CIPP) model for ACP*Talk* (ACP: advance care planning).

Type and questions	Rationale	Evaluation methods
Context		
In developing an Australian-based ACP website for health professionals focusing on religious and cultural appropriateness		
What were the recommended solutions of key stakeholders (Health professionals—general practitioners and nurses)?	It was important to understand the recommendations of potential website users (ie, key stakeholders) to tailor content to the intended audience	Thematic analysis of interviews with health professionals (exploratory study)
What religious or cultural backgrounds were included in website content?	Appropriate consideration should be undertaken to ensure that the website contains religion-specific information representative of Australian-based groups, with integration of cultural information where relevant	Review of Australian cultural diversity data, conduct of an environmental scan of Australian religious and cultural ACP resources, and documentary analysis of meeting minutes
Input		
What challenges were encountered during project implementation?	Creating a website integrating information representative of multiple religious and cultural groups requires an appropriate governance structure, timelines, and procedures	Documentary analysis of project protocol and meeting minutes
Process		
What process was utilized to ensure that the website content supported ACP conversations within appropriate religious and cultural contexts?	It was important to ensure accuracy of different religion-specific content as this was a key project requirement	Development of website prototype, pretesting of functionality and content review by religious and cultural leaders. Analysis of religion-specific Web-based content review survey[a]
Product		
How was the website used within the initial 9 months following release?	Measurement of website utilization is important to assess impact and inform strategies for improvements	Reporting of analytic data integrated in the website
What were stakeholders' (website users and nurses) perceptions of the website?	Obtaining stakeholder perceptions of website benefits, weaknesses, and suggestions for improvements to inform further development	Analysis of website user feedback survey[a] and thematic analysis of stakeholder (nurse) interviews

[a]Reported as per the *Checklist* for Reporting Results of Internet E-Surveys [56] checklist.

Figure 1. ACP*Talk* evaluation schema.



Inclusion of Religious and Cultural Groups

An environmental scan [57] was conducted to examine availability and accessibility of Web-based Australian ACP resources (websites and informational booklets) that contained religious and cultural information. This was intended to assist with identifying needs, determining religious and cultural groups for inclusion in the website, and locating quality resources to be incorporated in the website. Cultural diversity statistics [19,20] were examined to determine potential religions for inclusion in the religion-specific search function of the website.

Stakeholder Solutions

Given that ACP conversations can occur throughout the illness trajectory [2,58], the website was tailored to health professionals; in particular GPs and general practice nurses working in primary health care with applicability to palliative care professionals.

Key stakeholders—GPs and palliative care and general practice nurses (minimum qualification clinical nurse specialists) were invited to participate in the exploratory study. Following consent, semistructured interviews were conducted using a questionnaire based on the cultural awareness framework by Jirwe [59] that outlines four components of cultural competence: awareness of diversity among human beings, an ability to care for individuals, nonjudgmental openness for all individuals, and enhancing cultural competence as a long-term continuous process. Pretesting of the interview guide for clarity and understanding was undertaken with clinical nurse educators. Health professionals were asked about their experiences of conducting ACP with people from diverse religious and cultural backgrounds, what they perceived to be important when facilitating such conversations, difficulties they encountered, and recommendations for improving these. Recommended solutions for improving difficulties are presented in this paper.

Participants completed a demographics form that collected data about age, sex, years working as a health professional, health professional type, country of birth, religion, and perceived importance of religion. Recruitment strategy included purposive sampling, where cultural population demographics [60] were reviewed to target health professionals working among diverse religious and cultural population distributions across Australia. Interviews were voice recorded and transcribed verbatim.

Process and Product Evaluation

Website Content and Functionality

Findings from the environmental scan [57] and health professional exploratory study informed refinement of a semistructured questionnaire guide used to interview religious leaders. Following pretesting with a religious leader of Christian and non-Christian faith, interviews with religious and cultural leaders were voice recorded and transcribed verbatim. Religion-specific content was derived from thematic analysis of interviews with 38 religious and cultural leaders.

A prototype of the website was initially built by website developers, with functional and design specifications determined by the PWG and PSC. This enabled content review and functionality testing of a religion-specific search function embedded in the website, which allowed users to select a religion and denomination (if applicable) from a predetermined drop-down list and view content pertinent to that religion. To ensure accurate and appropriate representation of religious information, content underwent an extensive review process with religious and cultural leader interviewees, representatives from state and national religious and cultural organizations, and health care organizations in specialized end-of-life roles. Reviewers were invited to view the website prototype, in particular information about their religion (if applicable), and

were then invited to participate in a closed, Web-based content review survey.

Web-Based Content Review and Website Feedback Surveys

Although the Web-based content review survey obtained feedback about religion-specific content, a website feedback survey was used to examine stakeholder perceptions of the end product, the ACP*Talk* website. Both surveys will be reported according to the *Checklist* for Reporting Results of Internet E-Surveys [56] checklist.

Both the Web-based content review survey and website feedback survey were based on the core program evaluation standards, utility, feasibility, propriety, and accuracy [40] and elements of the Website Evaluation Questionnaire (relevance, comprehensibility, user friendliness, structure, and layout) [61]. A 5-point Likert scale with statements was developed, and responders were asked to indicate the extent to which they agree or disagree with statements through a Web-based SurveyMonkey [62] survey. Likert questions were reviewed by the PSC and pretested among peers to ensure clarity and understanding before use.

For the Web-based content review survey, questions were about accuracy of content, appropriateness to the intended audience, detail and depth, ease of reading, completeness of information, perceptions of utility, and least and most useful section. Questions were nonrandomized, located on one page, and two out of five total questions were compulsory. Answers to the least and most useful sections and comments were not compulsory.

For the website feedback survey, to examine users' perceptions of the website, an open, voluntary, Web-based feedback survey using SurveyMonkey [62] was available for completion accessible from the website. A campaign was conducted from March 1, 2017 to May 1, 2017, promoting the website and feedback survey via Internet-based newsletters and postal mail with a prize draw offered to encourage participation. The survey asked users to indicate what state they reside in; if they were a health professional, if so what type; how they found out about the website; which parts of the website they explored; and least and most useful section. They were asked to indicate the extent to which they agree or disagree with statements based on a 5-point Likert scale that examined their perceptions of the website design, content, information, and impact on ACP knowledge and awareness. A total of 11 nonrandomized questions, seven of them compulsory, with two questions per page were asked. Responses to questions on explored website sections, most or least useful sections, and comments were not compulsory. For both surveys, consent was implied by participation, and users were only able to respond once, as determined by cookies.

Resource Usage

Google analytics [63] were integrated into the website to track resource usage, users' state and territory location, number of unique visits, total visits, new or returning visitors, bounce rate, as well as time spent on the site [64].

Stakeholder Interviews

General practice and palliative care nurses were invited to participate in the evaluation of ACP*Talk* through national professional association newsletters and ACP-attended training sessions. Interested nurses registered via an online form. Following consent, nurses completed an instructional website exploration guide, demographics form, and a semistructured voice-recorded interview. The instructional website exploration guide was developed to ensure they had used key elements of the website before interview feedback, which included the ACP*Talk* religion-specific search function, discussion scripts, religious and cultural resources section, and the ACP law component. The demographics form requested nurses to indicate sex; age; whether they were a general practice or palliative care nurse; years of nursing experience; country of birth; if born overseas, number of years living in Australia; and religion. Nurses were asked to indicate on a 5-point Likert scale from strongly agree to strongly disagree with the statement, "Religion is important to the way I live my life." A semistructured interview questionnaire was developed for the interviews to examine user perceptions of benefits, weaknesses, and improvements to the website (Textbox 1).

Evaluation Analysis

Qualitative interview data (context and product evaluation) was examined using thematic analysis [65]. This involved an iterative process of data immersion, repeatedly reading transcripts, and with similar content coded into themes, supported by qualitative data management software [66]. Documentary analysis was performed to review cultural diversity data, environmental scan, and meeting minutes (input evaluation). Quantitative data obtained from Web-based surveys (process and product evaluation) were collapsed into three Likert categories for simplicity (strongly agree or agree, neutral, or strongly disagree or disagree) and analyzed as frequency distributions using statistical software. Quantitative participant demographic data (process and product evaluation) were analyzed with descriptive statistics or frequency distributions where appropriate, using statistical software [67].

Textbox 1. Nurse stakeholder interview questionnaire.

1. What are your experiences of having advance care planning (ACP) conversations with people from different religious and cultural backgrounds?
2. What do you think are some of the benefits of the website? [Ask to provide an example of how the website has been useful]
3. What are some of the weaknesses? [Ask to provide an example of any issues or concerns or difficulties]
4. How do you think ACP*Talk* can be improved?
5. How do you feel the website has contributed to your understanding of ACP in a culturally diverse context?
6. Would you recommend the resource to colleagues? If no, why not?
7. Are there any additional comments or questions you have and feel would be important for the evaluation and improvement of this resource?

Results

Context and Input Evaluation

Key Stakeholder Solutions

A total of 16 health professionals (GPs: n=7, primary health nurses: n=2, and palliative care nurses: n=7) were included in the exploratory study analysis (participation rate 26%, 17/65). One participant's interview was inaudible and therefore not included in the analysis. Characteristics are summarized in Table 2.

All interviewed GPs and nurses had ACP experiences with people across the lifespan from different religious and cultural backgrounds; in rural, urban, community, residential, and hospital settings.

In providing a resource to support religiously and culturally appropriate ACP, health professionals stated the following solutions (N indicates nurse; GP indicates general practitioner):

Improved Availability of Content

Although health professionals asserted the importance of nonpresumptive individualized care in facilitating ACP, they expressed solutions for enhanced religious and cultural information provision, which encompassed:

- An understanding of varied religious beliefs and related requirements, N5 stated:

  I think if you had an easy guide to—like 4 or 5 dot points under some of the more common cultural or religious beliefs that would be helpful...

- Religious or cultural information outlining communication ideas to introduce ACP and decision making with different religious groups. This would include generically safe words to use and ideas for how to explain medical and technical ACP-related terms in sensitive ways. N6 exclaimed:

  It would be good to have something to support you and guide you in those conversation.

- Preparatory information for dealing with potential reactions. This could include education with role plays and discussions. GP3 stated:

  ...you could have an education session that involved role playing...just doing examples of various ways in which there may be problems with communication or difficulties getting over certain stumbling blocks.

- Legal information applicable to one's work jurisdiction
- Additional support contacts, for example, interpreter details
- ACP multilingual resources for patients or families

Well-Developed Design and Functionality

- Online, textual, and audio-visual; N7 stated:

  ...a video on iPad or computer that has a person from that culture speaking about how they approached advance care planning.

- Ease of access was mentioned, with GP2 requesting:

  ...online resources available and easily accessible, and if you're not sure, you can just go and have a look at those resources. That would be quite handy.

- Link-in with well-known palliative care websites
- Easy to follow downloadable resources guides

Inclusion of Religious and Cultural Groups

The environmental scan identified seven Australian-based ACP websites and seven ACP informational booklets with cultural and religious information representative of Aboriginal and Torres Strait Islander (n=5), Sikh (n=1), and Italian communities (n=1) [57]. No comprehensive Australian-based ACP website or informational booklet supporting ACP across several cultural and religious contexts was identified. Review of Australian Bureau of Statistics census data [19,20] indicated that the majority of the population were Christian (61%), which was made up of 9 denominations (Catholic, Anglican, Uniting Church, Presbyterian, Eastern Orthodox, Baptist, Lutheran, Pentecostal, other Christian). Non-Christian faiths accounted for 7% (Buddhism, Islam, Hinduism, Judaism, other-non-Christian), with 22% of people not reporting a religion. It was determined by the PWG and PSC that religion-specific website content about ACP would need to be reflective of these faith groups to be relevant to an Australian-based population.

Project Protocol and Implementation

The major project challenge related to difficulties in recruiting GPs to the exploratory study. Further recruitment strategies were employed, including liaison with primary health care networks to assist in recruitment and reimbursing providers operating solely under fee-for-service.

It was determined by the PSC that religion-specific content would need to incorporate heterogeneity within religions. The strategy to minimize conflicting information was attempting to

interview at least two leaders from these groups so that dichotomist views could be investigated. Despite this, there were some issues with differences in beliefs within certain religions. State and national religious and cultural organizations were called upon to review content to ensure accuracy.

Process and Product Evaluation

Website Content and Functionality

ACP*Talk* features a religion-specific search function (Figure 2) that enables review of Christian (Anglican, Baptist, Catholic, Coptic Orthodox, Greek Orthodox, Lutheran, Presbyterian, and Uniting Church denominations) and non-Christian faiths (Bahai, Buddhism, Hinduism, Islam, Sikhism, and Secularism), reflective of population demographics [20]. Selection of religion and denomination (if applicable) functions on the website present content about background and beliefs, disclosure of medical prognosis and language, who should be involved, advice on having the ACP conversation, special considerations, rituals and practices, and festivals and dates (Figure 3).

Table 2. Characteristics of interviewed health professionals.

Characteristics	n (%) or median years (range)
Type of health professional, n (%)	
General practitioner	7 (44)
Primary health nurse	2 (12)
Palliative care nurse	7 (44)
Health professional experience, median years (range)	9.5 (1.5-40)
Sex, n (%)	
Male	8 (50)
Age, median years (range)	51 (38-67)
Country of birth, n (%)	
Australia	11 (69)
Overseas	5 (31)
If born overseas, time living in Australia, median years (range)	29 (9-62)
Religion, n (%)	
Christian	7 (44)
None	8 (50)
Hindu	1 (6)
Religion is important to me, n (%)	
Strongly disagree or disagree	6 (37)
Neutral	3 (19)
Strongly agree or agree	7 (44)

Figure 2. Religion-specific search function.

Figure 3. Religion-specific information.

Quick Navigation features the sections about this website, ACP discussion scripts that have suggestions from interviewed health professionals and religious leaders, ACP law, general information, videos, and religious and cultural events (Figure 4). To complement existing resources, an external ACP resources section features general Australian-based ACP websites, and a religious and cultural resources section features informational booklets and websites identified through the environmental scan. ACP*Talk* features a responsive design to adjust for mobile device use such as tablets and mobile phones.

Web-Based Content Review Survey

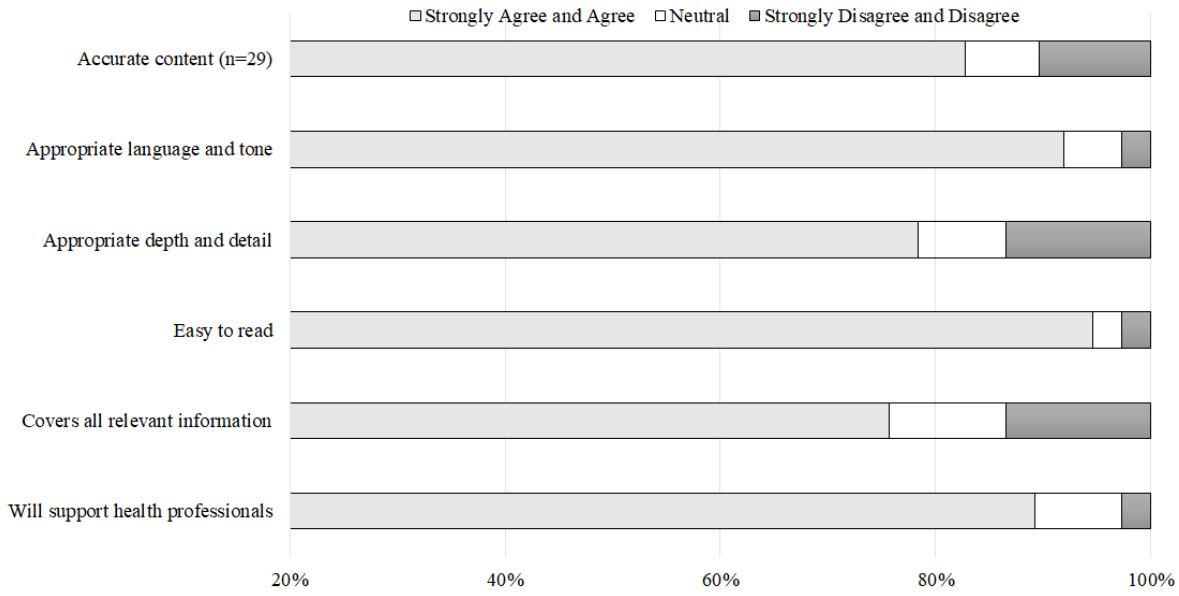
A total of 37 individuals (participation rate 67%, 37/55 [survey responders/invited participants]), representative of religious and cultural organizations (n=29) and members of other interested organizations (health care n=5, community organization n=3), reviewed the website content from February 17, 2016 to April 25, 2016 and completed the Web-based survey (Figure 5). The majority of individuals strongly agree or agree that the website used appropriate language and tone (92%, 34/37), will support health professionals (89%, 33/37), and featured accurate content (83%, 24/29). Equal percentages of reviewers (24% each, 9/37) considered advice on the ACP conversation and backgrounds and beliefs as the most useful section of the religion-specific content. The least useful section indicated was special considerations (30%, 11/37). Where content reviewers felt they strongly disagree or disagree with an item and provided comment, this was addressed with amendment incorporated where relevant.

For example, interviewed religious and cultural leaders spoke about practices and rituals after death; this was not included in

the initial content for inclusion in the website given that the website was focused on ACP discussions. Several reviewers of Christian and non-Christian faiths indicated it was necessary, as people may request postdeath rituals as part of the planning process; hence, this was written, and sections were reviewed. Content refinement was completed within the allocated time frame of 3 months, and no project delays occurred.

Figure 4. Quick Navigation.

Figure 5. Religion-specific content reviewer responses (n=37).



Resource Usage

Data from Google analytics indicated that from September 1, 2016 to May 14, 2017, there were 12,957 page views and 4260 sessions by 2920 users. Of this, 68.33%, (2911/4260) were new sessions and bounce rate, which indicates people visiting a page, and leaving without further exploration was 40.40%, (1721/4260). Most sessions were from Australia (83.45%, 3555/4260), with a bounce rate of 40.84%, 1452/3555). Most Australian users resided in the states of Victoria (46.81%, 1664/3555) and New South Wales (27.99%, 995/3555). Other countries where the website was used included the United States (5.19%, 221/4260, bounce rate 65.16%, 144/221) and Russia (3.71%, 158/4260, bounce rate 6.96%, 11/158). Users spent an average of 3.21 min on ACP*Talk*.

Website Feedback Survey

From March 1, 2017 to May 14, 2017, 107 Australian-based website users completed the website evaluation survey (10% participation rate [participating users/unique site visitors determined by Internet protocol address]), of which the majority (88.8%, 95/107) indicated that they were health professionals. Of those that were health professionals, approximately 57% (49/86) were nurses, 14% (12/86) allied health, 14% (12/86) GPs, 5% (4/86) medical specialists, and 10.5% (9/86) indicated other (ie, practice managers, students, and program coordinators). Table 3 shows survey responder background data.

The majority of responders resided in Victoria (n=53), found out about the website via email (n=35), and explored the home page (n=52) and religious and cultural resources (n=49). Survey responders' perceptions of the information on the website (Figure 6) and experiences with using the website (Figure 7) are presented. The majority of survey responders viewed the

website favorably. In comparison to other questions, a lower percentage, yet still the majority reported that the website increased knowledge (64.5%, 69/107) and awareness of ACP (59.8%, 64/107), with 67.3% (72/107) of responders indicating that the website assisted them in preparation of ACP with people from different religious or cultural backgrounds. Approximately 37.9% (39/103) of survey responders nominated the most useful section of religion-specific content as backgrounds and beliefs, whereas 42.2% (38/90) stated festivals and special dates as the least useful.

Stakeholder Perceptions

Interviews were conducted with 20 registered nurses (NS indicating nurse stakeholder; working in palliative care n=8, general practice n=10, and across both disciplines n=2). Characteristics are summarized in Table 4.

All except NS6 were experienced in offering ACP, and five nurse stakeholders (NS11, NS12, NS9, NS14, and NS26) also described ACP education roles in health care teams.

Thematic findings follow.

Accessibility, Functionality, and Design

Participants were complimentary about the ACP*Talk* website. Many praised its online accessibility, easy and quick navigational properties, user friendliness, clear font, and attractive format. In terms of usability, participant NS17 commented the following:

> *...it took me a little bit of time and I'm talking minutes rather than hours to actually work out how the website worked.*

Specific appealing design features mentioned included no login required, responsive design for tablet and mobile phone use enabling access on homecare visits, (religion-specific) search function that avoided the need for scrolling, and downloadable information. Comments included the following:

> *For a lot of us in primary care we're doing home visits so you're out there with a laptop and you can flag stuff and print it off and send it out to people and that kind of stuff* [NS9]

> *I think it's set out...clear enough that you don't get lost within it...* [NS14]

Table 3. Web-based survey responders' background data (ACP: advance care planning).

Survey questions	n
State of residence	
New South Wales	13
Queensland	10
South Australia	18
Tasmania	5
Victoria	53
Western Australia	8
How users found out about the website[a]	
Search engine (ie, Google)	4
Other website	7
Email	35
General practitioner office or staff	4
Hospital	10
Place of worship	1
Electronic newsletter	7
Printed media	22
Professional association	14
Other	18
Parts of the website explored[a]	
Home page	52
Religion-specific content	20
About this website	26
ACP discussion scripts	29
ACP law	28
General information	40
External ACP resources	20
ACP videos	16
Religious and cultural resources	49
Religious and cultural events	12

[a]Able to indicate more than one answer for the question.

Figure 6. Web-based survey respondents' perceptions of website information (n=107).

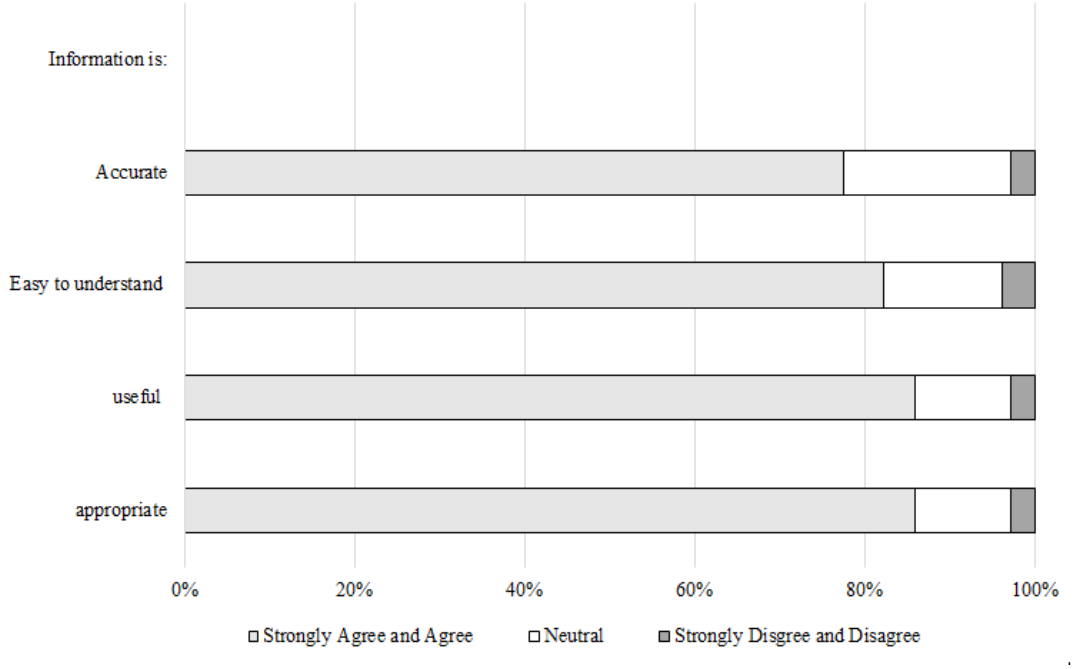


Figure 7. Web-based survey respondents' experiences with using the website (n=107). ACP: advance care planning.

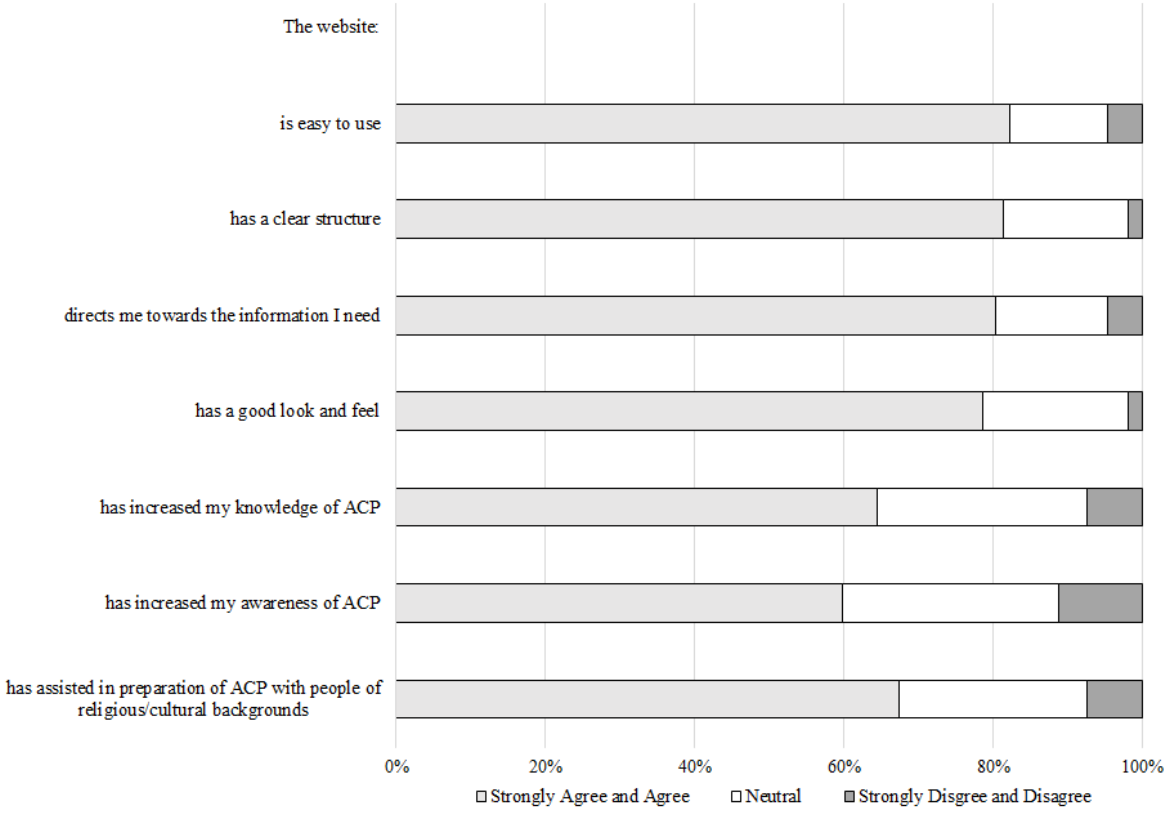


Table 4. Characteristics of interviewed nurses.

Characteristics	n (%) or median years (range)
Area of nursing, n (%)	
Palliative care	8 (40)
General practice	10 (50)
Both	2 (10)
Nursing experience, median years (range)	29 (5-44)
Sex, n (%)	
Female	18 (90)
Age, median years (range)	52 (32-63)
Country of birth, n (%)	
Australia	12 (60)
Overseas	8 (40)
If born overseas, time living in Australia, median years (range)	19 (5-38)
Religion, n (%)	
Christian	12 (60)
None	6 (30)
Mixed religions	2(10)[a]
Religion is important to me, n (%)	
Strongly disagree or disagree	5 (25)
Neutral	3 (15)
Strongly agree or agree	12 (60)

[a]More than one religion stated by individuals.

Usefulness of Content

Participants commented on the comprehendible, concise, sufficient, and manageable information; and links to relevant sites. NS25 stated the following:

> *If I had someone culturally diverse and I could just click on that (home page) and get into the link straight away without wasting hours and searching. I could get the accurate information for whatever I needed. I really liked that.*

Individuals added that it addressed a knowledge gap or was a good addition to existing cultural care resources. Especially agreeable were consistent informational headers across religions; multimedia (textual and video) and multilingual (video) learning options.

Many commended specific information provided, including different EoLC procedures associated with varied traditions, acknowledgment of two main Buddhism streams, description of Ramadan, links to state-specific legal information, interpreter contact details, religious festival dates, scripts on guiding ACP conversations, suggestions for approaching difficult situations, and advice that ACP*Talk* information is only a guideline, whereas ACP should remain individualized.

Improved Advance Care Planning (ACP) Knowledge, Confidence, and Cultural Awareness

Although some participants had not viewed the entire ACP*Talk* website because of time constraints or technical problems, most stated that the content examined had extended their competence and confidence in conducting or educating about ACP with people from multicultural and religious backgrounds. Comments included the following:

> *I think it's assisting me in understanding the sensitivities that come with different groups and that we need to be respectful and sensitive in our conversations.* [NS19]

> *My intention is for us to use the information to frame our initial contact a little bit differently. At the moment, we tend to pretty much say the same script to everybody, which in light to this kind of information may not be the best way to go.* [NS9]

Many found ACP*Talk* interesting and were pleased to know of its availability if needed to increase or "refresh" ACP knowledge and competency. NS16 stated:

> *I would use it at the drop of a hat for any sort of unfamiliar territory.*

All had already used and/or recommended ACP*Talk*, or anticipated using and recommending it to others. Although three highly ACP-experienced participants did not learn new

information from ACP*Talk*, two of those welcomed using it for their ACP education. NS12 stated:

> *I have used it for educational purposes for myself and directed people towards it as a resource...in that way it has helped me.*

Many also expected that the website would enable improved staff-client relationships through extending health professionals' cultural ACP competency. Furthermore, occasional participants considered the website could potentially assist volunteers, patients, and families.

Website Challenges and Suggestions

Four participants could not think of ways to improve the website, and some offered minor design critiques, for example, on menu visuals. Some also commented on omission of materials beyond the website's remit, for example, advance directive forms, or content which were already included, for example, an educational video on ACP with indigenous Australians. A number also described technical issues related to Web-based links or Web-enabled personal devices.

Suggested technical website improvements included increased search and home page button visibility and reduced steps (clicks) to reach Christian pages. Two participants also believed that information presented on Aboriginal and Torres Strait Islander peoples could be more prominent.

Almost all the participants thought that the website had enough information; however, individuals suggested additional information was needed on minority religions such as scientology and how to approach multicultural families before commencing ACP conversations. One who lived in an area with "huge" Chinese and Vietnamese populations queried whether information on these groups was also needed. Additionally, individuals recommended an advanced directive example, interpretations of complex legal-based ACP information, comparable websites for patients and families, and a related online chat service. Also suggested was further clarity on ACP terms through a larger glossary and acknowledging that different terms in different Australian states can refer to the same thing, as illustrated in the following quote:

> *Quite often when somebody is talking to you about power of attorney they'll also talk to you about power of enduring guardianship...The medical power of attorney and some of those languages cross over.* [NS9]

Further recommendations included increasing content to include a "frequently asked questions" page and further condensing each religion's information into dot points. Extending comprehension of website content to health professionals without English as a first language was also recommended through presenting more information visually and multilingual translations. NS7 stated the following:

> *I certainly know Doctors who are practicing in this country who speak English well enough to practice the mechanics of medicine but don't speak English well and confidently enough to have sensitive conversations with people about advance care planning...Medical practitioners might actually benefit from...having it written in their own language.*

Discussion

Principal Findings

This study demonstrates that the CIPP evaluation model can be applied to conduct a formative and summative evaluation of an ACP website development and end product. In terms of website development, health professionals provided the following solutions: religious or cultural information guides, communication examples, education featuring role-plays, legal information, additional support contact details (ie, interpreters), and multilingual ACP resources. Recommended design and functionality included online accessibility, audio-visuals, linkages with existing websites, and downloadable content. Most of the requested content elements and design features were integrated into the ACP*Talk* website with the exception of education featuring role-plays and multilingual ACP resources that were not within the scope of the project. The external ACP resources and religious and cultural resources sections, however, contained links to several websites that link with similar products.

Online resources identified through the environmental scan were linked to ACP*Talk*, thus meeting the project objective of complementing existing available resources and health professionals' solutions specified in the exploratory study. Utilization of statistics from the Australian Bureau of Statistics and PSC expert opinion ensured that religion-specific content was in accordance with Australian-based faith populations, although inclusion of minority religions, that is, scientology, and further cultural information was recommended during the product evaluation.

Utilization of both state and national religious and cultural organizations ensured accuracy of religion-specific content and resolved ambiguities. Importantly, process evaluation determined that an overwhelming majority of religious leaders felt content was easy to read, used appropriate language and tone, featured accurate content, and would support health professionals in ACP. Refinements were made to content where appropriate, that is, inclusion of end-of-life rituals and practices based on feedback that this was important.

Google analytics data revealed the majority of users were new, with a bounce rate of 40%. The bounce rate is reflective of people visiting the landing page and leaving without further exploration, which may be suggestive of people either finding what they are searching for and then leaving the website or leaving the website after unintentional visitation. Australia had the highest usage, which was to be expected; interestingly Russia accounted for approximately 4% of users with a bounce rate of about 7%, indicating that residents in Russia were exploring the website.

Overall, website feedback was favorable, and the majority of survey responders were health professionals, predominantly nurses, followed by GPs and allied health and medical specialists, indicative of the target audience. The remaining survey responders may have been members of the general

community, which illustrates reach of website users broader than the targeted audience and the need for such a resource within the community. Most survey responders were positive about information accuracy, ease of understanding, usefulness, appropriateness, and website design. A lower proportion of survey responders (though still a majority) felt that the website increased their knowledge and awareness of ACP and assisted in preparation of ACP with people from different religious and cultural backgrounds. This may be explained by users having existing knowledge and expertise in ACP, with experience in discussions already among diverse religious and cultural communities.

Interviewed nurse stakeholders commented on the benefits of online accessibility; user friendliness; appealing design features and functionality, including the religion-specific search function; and absence of log-in requirements. Some nurses, however, suggested that menu visuals could be improved by increasing search function and home page button visibility. Many felt that the content was useful in addressing knowledge gaps, adding to existing religious and cultural resources, and would recommend the website to others. A comprehensive list of recommendations for consideration of further Web-based development included a glossary for varying state-based legal terms, condensing religion-specific content, comparable website for patients and families, an online chat service, and multilingual translations. Though multilingual translations were mentioned in the exploratory study and end-product evaluation, this was beyond the scope of the project resources and timelines.

Limitations

Participation rate for the exploratory health professional study was low (26%), and health professionals were not from the most culturally diverse Australian-based communities as initially intended. Although difficulties in recruitment of GPs are consistent with the literature [68,69], health professionals' views reflected diverse involvement in ACP with people from a range of religious and cultural backgrounds. Hence, though data saturation was not reached, useful and sufficient recommendations were derived from interviews to inform website development. Due to the recruitment strategy (convenience sampling through professional newsletters and member associations), a participation rate could not be obtained for the nurse stakeholder evaluation interviews. Included nurses were reflective of palliative care and general practice disciplines, and data saturation was reached among this group with interviews ceased when no new information was emerging. Due to the interest-based nature of participation, nurse stakeholder interviews and website survey responses may be limited by responder bias. A more in-depth analysis of the website with other health professionals may have provided further recommendations.

Comparison With Prior Work

Multiple ACP eHealth apps are available, such as governmental and commercial websites, Web-based ACD registries, and educational material [3], and published reviews have predominantly examined ACP decision aids or Web-based tools [4,5]. Broadly, evaluation of decision aids [4,5] and ACP websites [6,8-10] indicates development and acceptability of Web-based material predominantly among patients or community-based audiences. Evaluation of two community-based ACD websites revealed ACP information was increasingly sourced from the Internet; the majority of users reporting ease of use as the main reason for completing a Web-based ACD [6]. Ease of use was also reported among individuals who used *PREPARE*, a website that prepares older adults for decision making [8] and by nurses in our study. More recent evidence indicates increased ACP documentation and higher self-reported engagement in ACP by participants who used the PREPARE website [7].

In contrast to these studies, ACP*Talk* was custom-built to support health professionals in conducting ACP conversations with a particular focus on the needs of people from diverse religious and cultural backgrounds. There is limited published literature evaluating ACP websites designed for health professionals for comparison with our study. Of note, the *Making Your Wishes Known (MYWK)* computer-based decision aid is accessible via a website, developed to guide individuals through ACP with tailored education, and a tool that translates preferences and values into a medical plan for access by the treatment team [10,14]. Further studies, however, indicate usefulness of MYWK in educating medical students with reports of improved knowledge, confidence in helping patients with ACP, and greater satisfaction in learning [11,13]. Similarly, in our study, the majority of interviewed nurse stakeholders reported improved ACP knowledge, confidence, and cultural awareness, whereas most website survey responders' felt ACP*Talk* assisted in preparation or participation of ACP with people of different religious and cultural backgrounds.

Conclusions

This study demonstrates that all facets of the CIPP framework can be effectively applied for evaluation of eHealth technologies, specifically ACP websites, with assessment of ACP*Talk*. Results show that most users viewed the website positively in terms of design, content, and functionality and found it useful to increase knowledge and preparation for ACP with people of different religious and cultural backgrounds. Further ACP website development should consider the recommendations derived from this study, including multilingual translations and the development of comparable culturally sensitive websites tailored for patients and families, which may assist in strengthening understanding and cognizance of ACP among these populations.

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Authors' Contributions

APS designed and led the research program. APS, PM, and LB carried out the research program. APS and PM developed the content of the website. COC led qualitative data analysis with interrater reliability from PM and APS. APS analyzed quantitative data. All authors contributed to the writing and/or critical revision of the paper.

Conflicts of Interest

None declared.

References

1. Brinkman-Stoppelenburg A, Rietjens JA, van der Heide A. The effects of advance care planning on end-of-life care: a systematic review. Palliat Med 2014 Sep;28(8):1000-1025. [doi: 10.1177/0269216314526272] [Medline: 24651708]
2. The Clinical Technical Ethical Principal Committee of the Australian Health Ministers' Advisory Council. COAG Health Council. 2011. A national framework for advance care directives URL: http://www.coaghealthcouncil.gov.au/Publications/Reports/ArtMID/514/ArticleID/63/National-Framework-for-Advance-Care-Directives [accessed 2017-05-31] [WebCite Cache ID 6qrcFCQSg]
3. Green MJ, Levi BH. The era of "e": the use of new technologies in advance care planning. Nurs Outlook 2012;60(6):376-83.e2 [FREE Full text] [doi: 10.1016/j.outlook.2012.08.005] [Medline: 23141197]
4. Austin CA, Mohottige D, Sudore RL, Smith AK, Hanson LC. Tools to promote shared decision making in serious illness: a systematic review. JAMA Intern Med 2015 Jul;175(7):1213-1221 [FREE Full text] [doi: 10.1001/jamainternmed.2015.1679] [Medline: 25985438]
5. Butler M, Ratner E, McCreedy E, Shippee N, Kane RL. Decision aids for advance care planning: an overview of the state of the science. Ann Intern Med 2014 Sep 16;161(6):408-418. [doi: 10.7326/M14-0644] [Medline: 25069709]
6. Klugman CM, Usatine RP. An evaluation of 2 online advance directive programs. Am J Hosp Palliat Med 2013 Nov;30(7):657-663. [doi: 10.1177/1049909112463116] [Medline: 23087248]
7. Sudore RL, Boscardin J, Feuz MA, McMahan RD, Katen MT, Barnes DE. Effect of the PREPARE website vs an easy-to-read advance directive on advance care planning documentation and engagement among veterans: a randomized clinical trial. JAMA Intern Med 2017;177(8):1102-1109. [doi: 10.1001/jamainternmed.2017.1607] [Medline: 28520838]
8. Sudore RL, Knight SJ, McMahan RD, Feuz M, Farrell D, Miao Y, et al. A novel website to prepare diverse older adults for decision making and advance care planning: a pilot study. J Pain Symptom Manage 2014 Apr;47(4):674-686 [FREE Full text] [doi: 10.1016/j.jpainsymman.2013.05.023] [Medline: 23972574]
9. Vogel RI, Petzel SV, Cragg J, McClellan M, Chan D, Dickson E, et al. Development and pilot of an advance care planning website for women with ovarian cancer: a randomized controlled trial. Gynecol Oncol 2013 Nov;131(2):430-436 [FREE Full text] [doi: 10.1016/j.ygyno.2013.08.017] [Medline: 23988413]
10. Green MJ, Levi BH. Development of an interactive computer program for advance care planning. Health Expect 2009 Mar;12(1):60-69 [FREE Full text] [doi: 10.1111/j.1369-7625.2008.00517.x] [Medline: 18823445]
11. Green MJ, Levi BH. Teaching advance care planning to medical students with a computer-based decision aid. J Cancer Educ 2011 Mar;26(1):82-91 [FREE Full text] [doi: 10.1007/s13187-010-0146-2] [Medline: 20632222]
12. Levi BH, Heverley SR, Green MJ. Accuracy of a decision aid for advance care planning: simulated end-of-life decision making. J Clin Ethics 2011;22(3):223-238 [FREE Full text] [Medline: 22167985]
13. Levi BH, Wilkes M, Der-Martirosian C, Latow P, Robinson M, Green MJ. An interactive exercise in advance care planning for medical students. J Palliat Med 2013 Dec;16(12):1523-1527. [doi: 10.1089/jpm.2013.0039] [Medline: 24175635]
14. Schubart JR, Levi BH, Camacho F, Whitehead M, Farace E, Green MJ. Reliability of an interactive computer program for advance care planning. J Palliat Med 2012 Jun;15(6):637-642 [FREE Full text] [doi: 10.1089/jpm.2011.0489] [Medline: 22512830]
15. Green MJ, Schubart JR, Whitehead MM, Farace E, Lehman E, Levi BH. Advance care planning does not adversely affect hope or anxiety among patients with advanced cancer. J Pain Symptom Manage 2015 Jun;49(6):1088-1096. [doi: 10.1016/j.jpainsymman.2014.11.293] [Medline: 25542552]
16. Speak Up. 2010. Advance care planning in Canada: national framework URL: http://www.advancecareplanning.ca/wp-content/uploads/2015/09/acp_framework_nov2010_dec16_final_en.pdf [accessed 2017-05-31] [WebCite Cache ID 6qrbsqlJH]
17. General Medicine Council. 2010. Treatment and care towards the end of life: decision making URL: http://www.gmc-uk.org/guidance/ethical_guidance/end_of_life_care.asp [accessed 2017-05-31] [WebCite Cache ID 6qrc0daP4]
18. Johnstone MJ, Kanitsaki O. Ethics and advance care planning in a culturally diverse society. J Transcult Nurs 2009 Oct;20(4):405-416. [doi: 10.1177/1043659609340803] [Medline: 19597187]

19. Australian Bureau of Statistics. 2012. Cultural diversity in Australia URL: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/2071.0main+features902012-2013 [accessed 2017-05-31] [WebCite Cache ID 6qrcIzwYw]
20. Australian Bureau of Statistics. 2011. B14 religious affiliation by sex URL: http://stat.data.abs.gov.au/Index.aspx?DataSetCode=ABS_CENSUS2011_B14 [accessed 2017-05-31] [WebCite Cache ID 6qrceY86A]
21. Sinclair C, Smith J, Toussaint Y, Auret K. Discussing dying in the diaspora: attitudes towards advance care planning among first generation Dutch and Italian migrants in rural Australia. Soc Sci Med 2014 Jan;101:86-93. [doi: 10.1016/j.socscimed.2013.11.032] [Medline: 24560228]
22. Sneesby L, Satchell R, Good P, van der Riet P. Death and dying in Australia: perceptions of a Sudanese community. J Adv Nurs 2011 Dec;67(12):2696-2702. [doi: 10.1111/j.1365-2648.2011.05775.x] [Medline: 21831110]
23. Hiruy K, Mwanri L. End-of-life experiences and expectations of Africans in Australia: cultural implications for palliative and hospice care. Nurs Ethics 2014 Mar;21(2):187-197. [doi: 10.1177/0969733012475252] [Medline: 23462503]
24. Hsu CY, Lee S, O'Connor M. Issues affecting access to palliative care services for older Chinese people in Australia. J Community Nurses 2005;10(3):9-11.
25. Waddell C, Mcnamara B. The stereotypical fallacy: a comparison of Anglo and Chinese Australians' thoughts about facing death. Mortality (Abingdon) 2010;2(2):149-161. [doi: 10.1080/713685861]
26. McGrath P, Holewa H, Koilparampil T, Koshy C, George S. Learning from each other: cross-cultural insights on palliative care in Indian and Australian regions. Int J Palliat Nurs 2009 Oct;15(10):499-509. [doi: 10.12968/ijpn.2009.15.10.44887] [Medline: 20081722]
27. Shanmugasundaram S, O'Connor M. Palliative care services for Indian migrants in australia: experiences of the family of terminally ill patients. Indian J Palliat Care 2009 Jan;15(1):76-83 [FREE Full text] [doi: 10.4103/0973-1075.53589] [Medline: 20606861]
28. Dembinsky M. Exploring Yamatji perceptions and use of palliative care: an ethnographic study. Int J Palliat Nurs 2014 Aug;20(8):387-393. [doi: 10.12968/ijpn.2014.20.8.387] [Medline: 25151866]
29. McGrath P. 'I don't want to be in that big city; this is my country here': research findings on Aboriginal peoples' preference to die at home. Aust J Rural Health 2007 Aug;15(4):264-268. [doi: 10.1111/j.1440-1584.2007.00904.x] [Medline: 17617091]
30. McGrath P, Patton M. Indigenous understanding of hospice and palliative care: findings from an Australian study. J Hosp Palliat Nurs 2007;9(4):189-197. [doi: 10.1097/01.NJH.0000280230.59214.c5] [Medline: 129191]
31. Sinclair C, Williams G, Knight A, Auret K. A public health approach to promoting advance care planning to Aboriginal people in regional communities. Aust J Rural Health 2014 Feb;22(1):23-28. [doi: 10.1111/ajr.12079] [Medline: 24460996]
32. Willis J. Dying in country: Implications of culture in the delivery of palliative care in Indigenous Australian communities. Anthropol Med 1999;6(3):423-435.
33. Mitchell BL, Mitchell LC. Review of the literature on cultural competence and end-of-life treatment decisions: the role of the hospitalist. J Natl Med Assoc 2009 Sep;101(9):920-926 [FREE Full text] [Medline: 19806850]
34. Zager BS, Yancy M. A call to improve practice concerning cultural sensitivity in advance directives: a review of the literature. Worldviews Evid Based Nurs 2011 Dec;8(4):202-211. [doi: 10.1111/j.1741-6787.2011.00222.x] [Medline: 21668736]
35. Ohr S, Jeong S, Saul P. Cultural and religious beliefs and values, and their impact on preferences for end-of-life care among four ethnic groups of community-dwelling older persons. J Clin Nurs 2017 Jun;26(11-12):1681-1689. [doi: 10.1111/jocn.13572] [Medline: 27603557]
36. Cabrini Health. ACPtalk. 2016. ACPTalk - for sensitive religious and cultural advance care planning URL: http://www.acptalk.com.au [accessed 2017-05-31] [WebCite Cache ID 6qrX2ofqf]
37. Australian Government: Department of Health. 2010. Supporting Australians to live well at the end of life. National Palliative Care Strategy 2010 URL: http://www.health.gov.au/internet/main/Publishing.nsf/Content/EF57056BDB047E2FCA257BF000206168/%24File/NationalPalliativeCareStrategy.pdf [accessed 2017-05-31] [WebCite Cache ID 6qsu5CsgZ]
38. Australasian Evaluation Society. 2013. Guidelines for the ethical conduct of evaluations URL: https://www.aes.asn.au/images/stories/files/About/Documents%20-%20ongoing/AES%20Guidlines10.pdf [accessed 2017-05-31] [WebCite Cache ID 6qrcoCEOM]
39. Centers for Disease Control and Prevention. Framework for program evaluation in public health. MMWR 1999 Sep 17;48(RR-11):1-40 [FREE Full text] [Medline: 10499397]
40. Yarbrough DB, Shulha LM, Hopson RK, Caruthers FA. The Program Evaluation Standards: A Guide for Evaluators and Evaluation Users. Thousand Oaks, CA: SAGE publications, Inc; 2011.
41. Stufflebeam DL, Shinkfield AJ. Evaluation Theory, Models, and Applications. 1st edition. San Francisco: Jossey-Bass; 2007.
42. Taylor-Powell E, Steele S, Douglah M. Fyi.uwex.edu.: Program Development and Evaluation University of Wisconsin-Extension; 1996. Planning a program evaluation URL: http://fyi.uwex.edu/programdevelopment/logic-models/ [accessed 2017-05-31] [WebCite Cache ID 6qrd4hodu]

43. Pereira-Salgado A, Boyd L, Johnson M. Developing online accreditation education resources for health care services: an Australian Case Study. Int J Qual Health Care 2017 Feb 01;29(1):124-129 [FREE Full text] [doi: 10.1093/intqhc/mzw146] [Medline: 27979963]
44. Serowoky ML, George N, Yarandi H. Using the program logic model to evaluate ¡Cuídate!: a sexual health program for Latino adolescents in a school-based health center. Worldviews Evid Based Nurs 2015 Oct;12(5):297-305. [doi: 10.1111/wvn.12110] [Medline: 26422189]
45. Lawless A, Freeman T, Bentley M, Baum F, Jolley G. Developing a good practice model to evaluate the effectiveness of comprehensive primary health care in local communities. BMC Fam Pract 2014 May 15;15:99 [FREE Full text] [doi: 10.1186/1471-2296-15-99] [Medline: 24885812]
46. Butler MM, Brosnan MC, Drennan J, Feeney P, Gavigan O, Kington M, et al. Evaluating midwifery-led antenatal care: using a programme logic model to identify relevant outcomes. Midwifery 2014 Jan;30(1):e34-e41. [doi: 10.1016/j.midw.2013.10.003] [Medline: 24246971]
47. Frye AW, Hemmer PA. Program evaluation models and related theories: AMEE guide no. 67. Med Teach 2012;34(5):e288-e299. [doi: 10.3109/0142159X.2012.668637] [Medline: 22515309]
48. Stufflebeam DL, Coryn CL. Daniel Stufflebeam's CIPP model for evaluation: an improvement-and accountability-orientated approach. In: Evaluation Theory, Models, and Applications. 2nd edition. San Francisco: Jossey-Bass and Pfeiffer Imprints, Wiley; 2014.
49. Jones B, Hopkins G, Wherry SA, Lueck CJ, Das CP, Dugdale P. Evaluation of a regional Australian nurse-led parkinson's service using the context, input, process, and product evaluation model. Clin Nurse Spec 2016;30(5):264-270. [doi: 10.1097/NUR.0000000000000232] [Medline: 27509562]
50. Parfitt BA, Cornish F. Implementing family health nursing in Tajikistan: from policy to practice in primary health care reform. Soc Sci Med 2007 Oct;65(8):1720-1729. [doi: 10.1016/j.socscimed.2007.06.007] [Medline: 17651876]
51. Farley DO, Battles JB. Evaluation of the AHRQ patient safety initiative: framework and approach. Health Serv Res 2009 Apr;44(2 Pt 2):628-645 [FREE Full text] [Medline: 21456107]
52. Al-Khathami AD. Evaluation of Saudi family medicine training program: the application of CIPP evaluation format. Med Teach 2012;34 Suppl 1:S81-S89. [doi: 10.3109/0142159X.2012.656752] [Medline: 22409197]
53. Lippe M, Volker D, Jones T, Carter P. Evaluating end-of-life care education within nursing programs. J Hosp Palliat Nurs 2017;19(3):266-274. [doi: 10.1097/NJH.0000000000000341]
54. Vollmer Dahlke D, Fair K, Hong YA, Kellstedt D, Ory MG. Adolescent and young adult cancer survivorship educational programming: a qualitative evaluation. JMIR Cancer 2017 Feb 10;3(1):e3 [FREE Full text] [doi: 10.2196/cancer.5821] [Medline: 28410172]
55. Marcelo PG, Evangelista AL, Orjalo CS. Webinars as a knowledge sharing platform for ehealth in South and Southeast Asia. J Int Soc Telemed eHealth 2016;4:e25.
56. Eysenbach G. Improving the quality of web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res 2004;6(3):e34 [FREE Full text] [doi: 10.2196/jmir.6.3.e34] [Medline: 15471760]
57. Pereira-Salgado A, Mader P, Boyd LM. Advance care planning, culture and religion: an environmental scan of Australian-based online resources. Aust Health Rev 2017 Apr 20. [doi: 10.1071/AH16182] [Medline: 28424142]
58. The Victorian Department of Health. Melbourne: Victorian Government; 2014. Advance care planning strategy URL: https://www2.health.vic.gov.au/hospitals-and-health-services/patient-care/end-of-life-care/advance-care-planning/acp-strategy [accessed 2017-05-31] [WebCite Cache ID 6qrdB38lh]
59. Jirwe M, Gerrish K, Emami A. The theoretical framework of cultural competence. J Multicult Nurs Health 2006;12(2):6-16 [FREE Full text]
60. Australian Bureau of Statistics. Where do migrants live? URL: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4102.0main+features102014 [accessed 2017-05-31] [WebCite Cache ID 6qrcSuCRq]
61. Elling S, Lentz LR, De Jong M. Website Evaluation Questionnaire: development of a research-based tool for evaluating informational websites. Berlin Heidelberg: Springer; 2007 Presented at: 6th International Conference on Electronic Government, EGOV 2007; September 3-7, 2007; Regensburg, Germancy p. 293-304. [doi: 10.1007/978-3-540-74444-3]
62. SurveyMonkey Inc. SurveyMonkey. San Mateo, California, USA; 2017. URL: https://www.surveymonkey.com [accessed 2017-06-15] [WebCite Cache ID 6rEDRwAXE]
63. Analytics.google. 2017. URL: https://analytics.google.com [accessed 2017-05-31] [WebCite Cache ID 6qremdwRV]
64. Google. 2017. URL: https://www.google.com.au/analytics/analytics/# [accessed 2017-05-31] [WebCite Cache ID 6qreWqMbX]
65. Hansen EC. Successful Qualitative Health Research : A Practical Introduction. Crows Nest, N.S.W: A&U Academic; 2006.
66. Scientific Software Development GmbH. Atlas. Ti v7: Qualitative Data Analysis. v7 for Windows 7 ed. Berlin, Germany: ATLAS.ti Scientific Software Development GmbH; 2016.
67. StataCorp. Stata Statistical Software: Release 14. TX: StataCorp LP; 2015.
68. Bonevski B, Magin P, Horton G, Foster M, Girgis A. Response rates in GP surveys - trialling two recruitment strategies. Aust Fam Physician 2011 Jun;40(6):427-430 [FREE Full text] [Medline: 21655493]

69. VanGeest JB, Johnson TP, Welch VL. Methodologies for improving response rates in surveys of physicians: a systematic review. Eval Health Prof 2007 Dec;30(4):303-321. [doi: 10.1177/0163278707307899] [Medline: 17986667]

Abbreviations

ACD: advance care directive
ACP: advance care planning
CIPP: context, input, process, and product
eHealth: electronic health
EoLC: end-of-life care
GP: general practitioner
MYWK: Making Your Wishes Known
PSC: project steering committee
PWG: project working group

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Original Paper

Perceptions About Disseminating Health Information Among Mommy Bloggers: Quantitative Study

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Abstract

Background: Social media are potentially powerful channels for communicating relevant health information in culturally sensitive and influential ways to key audiences. Moreover, these channels hold promise for promoting awareness and knowledge of health risks, prevention, and treatment by utilizing opinion leaders for message dissemination. Despite limited empirical evidence to-date, early promising results suggest that blogs are a form of social media that should be examined as worthy channels for health communication.

Objectives: This formative study explored mommy bloggers' perceptions about sharing health-related information on their blogs with their readers. It also sought to analyze which topics would be of most interest to mommy bloggers, what motivates them to write about health issues, and how they perceive interest in these topics among their readers.

Methods: This study employed survey methodology, including the use of open-ended questions, the responses to which were coded for analysis. Specifically, a 14-item survey was fielded with mommy bloggers between October 1 and October 28, 2016. Bloggers were recruited through The Motherhood network. A total of 461 mommy bloggers responded to the survey; 163 were removed for low quality responses and incomplete data. As a result, 298 eligible participants completed the survey. For open-ended questions in the survey, a sample of responses were coded and analyzed.

Results: The majority of the respondents (87.2%, 260/298) reported that they have written about health issues in the past; 97.3% (290/298) of the respondents reported that they would consider writing about health issues sometime in the future, and 96.3% (287/298) of the respondents reported that their readers like to read about health issues on their blogs. In terms of content priorities for this sample of bloggers, Nutrition and Physical Activity dominate the current conversation and similarly, Physical Activity and Nutrition remain top content priorities for these bloggers for the future. Moreover, 21.3% of the respondents reported that their readers would be interested in these topics. Finally, having a personal connection with a health issue was found to be positively associated with likeliness to write about health issues on their blog ($P<.001$).

Conclusions: This study illustrates that there are potentially rich opportunities for working with mommy bloggers to communicate with key health decision makers (moms) on important health issues. There is a great support among mommy bloggers for health information dissemination as well as interest for accessing relevant health information from their readers. This presents an opportunity for public health research and communication campaigns to more broadly promote their messages, thereby contributing to their behavior change objectives. Limitations included overrepresentation of white, higher-educated, and younger women. It suggests a need for more targeted engagement of a diverse sample for future work.

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KEYWORDS

mommy bloggers; social media; health messages; health information dissemination

Introduction

Health is nothing if not complex [1], and health communication is the "crucial social process for enabling health care consumers and providers to manage the complex information demands of health care and health promotion, especially in times of high uncertainty" [2]. Health communication has been a primary strategy to improve people's health [3]. Historically, health communication has focused on disseminating evidence-based messages from experts to the public in the hope of motivating them to adopt healthy behaviors and use health care effectively [3,4]; however, these top-down communication approaches have not been particularly effective in engaging key audiences and increasing their understanding and adoption of key health recommendations [5-7]. Problems associated with these traditional communication methods include limited message exposure, failure to target and tailor messages to consumers' literacy levels and cultural orientations, and limited audience access to and use of the communication channels employed [8,9].

Recent studies have shown that Americans are increasingly using the Internet as a primary health information source, with 8 in 10 Internet users in the United States now using the Internet to find health information [10]. Moreover, increasing importance is being placed on the Internet than on interacting directly with providers as an information source [11]. Compounding this is the fact that social media use has vastly increased in the last 10 years, with 65% of American adults now using social networking sites [12]. Much of this use is focused on health-related information dissemination and engagement [12], as social media contribute to "facilitating, sharing, and obtaining health messages" [13].

For over a decade, consumers have been increasingly seeking active channels such as the Internet as a primary source of health information—particularly for the most health conscious [14]. In terms of health information, 86% of women report that they make the decisions about health care treatments for their entire family [15]; and Bailey posits that health communicators should go where women spend time, which increasingly means online social network and blogging sites [16].

The dialogic nature of social media allows senders to reach broad audiences to participate in Web-based conversations about health issues. A few studies have examined health promotion through social media [17-22], the findings from which indicate great potential for using blogs, Facebook, Twitter, and other Web-based communication channels not only for increasing awareness but also to influence decision making concerning health issues. Specifically, blogs represent one powerful channel for potential exploration of health communication messaging and strategies. Blogs are rich communication channels, with different types of information that are shared interactively via bloggers' posts and exchanges of comments from blog readers [23]. The activity on these blogs—both by bloggers and blog readers—create and share information at an unprecedented level, resulting in the broad dissemination of text-based, photo, and video content [23]. Imbued "with a strong sense of the author's personality, passions, and point of view" [24], blogs result in opinions and ideas being shared online [23]. This community therefore has a virtual finger on the pulse of the needs and beliefs of Web-based audiences [23]. In this way, blogs, and their authors, or bloggers, act as opinion leaders for their readers. Yet, as Sundar et al contend [25], "Relatively little media and scholarly attention has been paid to personal blogs that discuss topics other than politics. For example, the burgeoning number of health blogs has gone virtually unnoticed in mainstream media and the academic discourse about blogs."

A subgroup of blogs called mommy blogs has become popularized in recent years. There are about 3.9 million moms in the United States who identify as bloggers [26]. A mommy blogger is defined as, "A mother who blogs about her children, motherhood, parenting or related topics" [27]. The average mommy blogger is 37 years old, and almost 90% of mommy bloggers have kids between the ages of 2 and 11 [26] (It is worth noting that there are also daddy bloggers, and these comprise approximately 3% of all bloggers [28]). Mommy bloggers have traditionally been white, middle to upper class, educated mothers with the average mommy blogger's household income ranging between US $14,000 and US $84,000, which is higher than the average income level for nonblogging moms [26]. In addition, moms who read or contribute to blogs are also 52% more likely to have college degrees than moms who do not blog [26]. This suggests that, "mommy bloggers belong to a pretty elite social set" [26]; however, increasingly, mommy bloggers are becoming more diverse [29].

Ultimately, with 14% of all American mothers with at least 1 child in their household turning to blogs for advice [26], these kinds of blogs can be important sources of information about a variety of topics. Parenting websites are the top source moms use to learn about products and services [30], but these blogs can also serve as sources of social support, connection, and validation for women navigating important health decisions for themselves and their family [31-33]. As a one-stop shop for entertainment, creative ideas, and useful information (including health), it is no surprise that mommy blogs have become so popular. Some of the most successful mommy bloggers tout thousands of followers and readers and earn their living through blogging [34]. Seen as a trusted member of this virtual community, their readers rely upon them for news and information [35]. This presents an opportunity for public health research and communication campaigns to more broadly promote their messages, thereby contributing to their behavior change objectives. The value of these mommy blogs should not be overlooked by public health communicators and should be further explored as sources of interpersonal influence concerning important health issues.

Despite mommy bloggers wielding strong influence with their readers, little research has focused on these bloggers as channels for communication concerning health promotion initiatives. Research by Burke-Garcia et al included formative interviews with mommy bloggers, followed by an intervention to get these bloggers to post health information on their blogs [36]. Data from the study revealed that bloggers can drive health behavior consideration among their readers, but there are also barriers among bloggers concerning sharing of certain kinds of health information [36]. Additionally, Horn et al conducted a pilot

study using mommy bloggers to reach communities of color with health information, which found that the collaboration between health professionals and social media leaders in communities of color has the ability to influence content and dialogue and thus can help reduce health disparities [37].

This paper reports a formative research study that aimed to explore the full complexity of mommy bloggers' perceptions about writing about health-related topics on their blogs in order to help inform future public health initiatives that may seek to use these layperson Web-based opinion leaders. It builds on prior research that looks at the use of Web-based sources as being influential to health information dissemination [33] and expands the limited body of work on mommy bloggers as powerful communication channels for health that exists currently. Findings include an overall willingness to write about health topics among this audience and that mommy bloggers' personal history of having health issues is positively linked with increased likelihood to write about health issues on their blog. This paper reviews the study design and methods as well as the findings and future research opportunities. Finally, it acknowledges the limitations of this study, which were a lack of opportunity to gain additional insight through interviews with the bloggers themselves and the use of a convenience sample, which resulted in the respondents skewing white, female, educated, and younger and which may have influenced the results.

Methods

Research Questions

This pilot study attempted to capture the complexity of mommy bloggers' perceptions about writing about health-related topics on their blogs. This study utilized an inductive approach and purposive sampling whereby, a nonprobability sample was obtained based on the characteristics of the population studied and the objective of the study [38] to explore bloggers' perceptions about writing about health-related topics on their blogs. Specifically, the researcher hoped to better understand mommy blogger perspectives about which issues are more likely to be written about and their motivations for doing so, as well as the perceived interest among their readers for consuming health-related content. In pursuit of these goals, the following research questions were posited:

> RQ1. How willing are mommy bloggers to write about health issues on their blogs?
>
> RQ2. How do bloggers perceive the interest of their readers to read about health issues on blogs?
>
> RQ3. Which topics are mommy bloggers most interested in writing about?
>
> RQ4. How do bloggers perceive the health topic preferences of their readers?
>
> RQ5. What motivates mommy bloggers to write about health issues?
>
> RQ6. What factors contribute to mommy bloggers writing about health issues?

While this is a highly formative study, the researchers hoped to glean some insights that may serve to expand research in this area and inform a larger study and possibly future health communication campaigns.

Recruitment

Institutional Review Board (IRB) approval was obtained through George Mason University's Office of Research Integrity and Assurance. Following IRB approval, participant recruitment commenced. Respondents were recruited via an online mommy blogger network, The Motherhood. To invite the sample of users to be part of this study, messages promoting the survey and inviting members of the network of mommy bloggers to participate were sent via the network manager via email. Three messages were posted including the original announcement and 2 follow-up messages to remind members to take the survey.

Sample

The study analyzed survey responses by members of the online mommy blogger network, The Motherhood. The Motherhood is a leading online influencer network of more than 3000 members comprising moms as well as numerous other demographic groups that support campaign message dissemination for various initiatives such as health, consumer products, and entertainment [39]. The network taps into the need for human connection and focuses on building authentic relationships that benefit all involved [39]. The demographics of the network shift constantly but the following describe the composition of the network as provided by The Motherhood at the time of this study. Geographically, most members of the network are from the United States, with 1.18% in Canada. Across the United States, membership is fairly evenly distributed, with 20.9% in the Southeast; 7.42% in the Southwest; 12.58% in the West; 27.5% in the Northeast and East; 21.72% in the Midwest; and 8.7% in the Plains (personal communication by Erin Olson, August 23, 2016). The network is primarily female, with about 97% being women (personal communication by Erin Olson, August 23, 2016). This reflects the greater number of mom blogs in existence than dad blogs generally (personal communication by Erin Olson, August 23, 2016). The network also asserts that approximately 3% of the network is comprised of men (personal communication by Erin Olson, August 23, 2016). Again, ethnic breakdown continuously changes but recent data show 80% of the network is white, 8% Hispanic/Latino, 2.5% African American, 6% Asian, and 3.5% Other (personal communication by Erin Olson, August 23, 2016). Anyone with a blog and a following of at least 50,000 readers can request to join the network [39]. For this study, four hundred and sixty-one participants of the network initiated the online survey. 163 were removed for low quality responses and incomplete data. As a result, 298 eligible participants completed the survey.

Measures

To collect data and evaluate the outcomes of this study, a 14-item survey was developed. All recruitment materials and messages included the link to the Web-based survey via Qualtrics. The first page of the survey contained informed consent materials. Participants clicked agree to provide consent.

Participants answered sociodemographic questions as well as questions about key variables: Likelihood to share information; Topics of Conversations; and Motivations for sharing.

Likelihood to Share Information

Blogger likelihood to share health information was assessed by asking the question, "Would you consider writing about health topics in the future?" and a dichotomous two-point (Yes or No) scale.

Topics of Conversations

Blogger health topic preferences was assessed by asking the questions, "Which health issues did you write about on your blog?" and "Which health issues would you consider writing about on your blog?," and providing a list of answer choices that included items such as Nutrition, Cancer, Vaccination, and Mental Health. These were selected from prior research [36]. Respondents could choose multiple responses.

Motivations for Sharing

To assess blogger motivations for sharing health information on their blog, the open-ended question, "What would motivate you to consider writing about health issues on your blog?," was asked and respondents could provide a response in their own words. Responses were coded, analyzed, and then grouped into categories based on similarity of response.

The survey can be found in Multimedia Appendix 1.

Analytical Process

The survey was developed and fielded using Qualtrics software. It was conducted from October 1 to October 28, 2016. Frequencies and chi-square tests were run using SPSS Statistical Software Version 20 to answer research questions 1, 2, and 6. A number of questions had open-ended responses, which is why themes were identified through both inductive and deductive processes [40,41], with themes and patterns from prior research with this community used [37,42] and additional themes that emerged from the interview data captured and added to the code frame throughout the data analysis process. Open-coding of the content was conducted on a random sample of 20% of the total number of responses [43]. Content coding was used to answer questions 3, 4, and 5. Two independent coders used this code frame to code responses to the open-ended questions; results were compared and interrater reliability was 90%.

Results

The final sample size recruited for this study was 298 respondents. Among the respondent sample (N=298), the average age was 38 years. While 84.2% of the respondents (251/298) were under the age of 45 years, there were no respondents over the age of 65. In addition, 99.0% of the respondents reported being female (295/298), with males representing only 1% (3/298) of the respondent sample. Similarly, 99.0% of the respondents (295/298) reported having children while 1% (3/298) reported not having children. Additionally, 80.9% of the respondents (241/298) reported that they have histories of health issues while 19.1% (57/298) reported that they do not.

In terms of race, 81.2% (242/298) respondents were white. African Americans represented 5% (16/298) of the respondents; Hispanic/Latinos represented 9% (26/298) of the respondents; Asians represented 1% (4/298) of the respondents; and 3% (10/298) of the respondents chose to identify themselves as Other. Because of the low representation of non-white respondents, all other ethnicities were grouped into an Other category and whites and non-whites were compared for this analysis.

In terms of education, 50.3% of the respondents were college graduates (150/298) and 20% reported having a graduate degree (60/298). These 2 groups comprised 70.5% (210/298) of the sample. The remainder of the respondent sample was comprised as follows: 23% reported having some college education (68/298), 6% reported having a high school degree or GED (18/298), and 1% reported having some high school or less education (2/298). Because of the low representation from less well-educated bloggers, College Degree and Graduate Degree were combined and Some College, High School Degree, and High School or Less were combined. Table 1 includes frequency distributions for these variables.

The primary research question for this study explored how willing mommy bloggers are to discuss health issues on their blogs. In order to assess this question, basic frequencies tests were run on 2 questions in the survey—first, whether respondents have written about health information on their blogs in the past and whether they would consider reporting about health again in the future. Overall, 87.2% of the respondents (260/298) reported having written about health issues in the past. As well, 97.3% of the respondents (290/298) reported that they would consider writing about health issues sometime in the future. This is despite approximately 13% of the respondents (38/298) reporting that they had not written about health issues in the past. Table 2 details these frequencies.

The study's second research question explored bloggers' perceptions of their readers' willingness to read about health issues on their blogs. In order to assess this question, a frequencies test was run on the question in the survey that asked the bloggers to assess their readers' interest in reading about health information on their blogs. The majority of the respondents (96.3%) reported that their readers like to read about health issues on their blogs (287/298). Table 2 details these frequencies.

The third research question explored the topics bloggers had written about and what topics would be of interest to them in the future. In order to assess this question, a sample of responses (chosen from a list of topics selected from prior research [36]) to the question about which topics bloggers have written about were coded and analyzed. Respondents could choose multiple answers. Less than one-fourth (23.9%, 38/159) of the respondents reported having written about the topic of Physical Activity. In addition, 21.4% (34/159) of the respondents reported having written about the topic of Nutrition. Finally, 13.8% (22/159) of the respondents reported having written about the topic of Mental Health. Table 3 provides details on the topics.

In terms of what topics would be of interest to bloggers in the future, a sample of responses (chosen from a list of topics

selected from prior research [36]) to the question about which topics bloggers would like to write about in the future were coded and analyzed. Respondents could choose multiple answers. Similarly, Physical Activity and Nutrition remain top content priorities for these bloggers for the future with 18.9% (54/286) reporting wanting to write about Physical Activity in the future and 17.8% (51/286) reporting wanting to write about Nutrition in the future. Mental Health is also a future interest for these bloggers with 14.3% (41/286) reporting wanting to write about this topic in the future. Finally, Heart Disease is also a topic of interest for these bloggers in the future, with 12.2% (35/286) reporting wanting to write about Heart Disease in the future. Table 3 provides details on the topics.

The fourth research question this study explored blogger perceptions about was which topics their readers would be interested in. In order to assess this question, a sample of responses (chosen from a list of topics selected from prior research [36]) to the question about which topics bloggers perceive their readers to be interested in were coded and analyzed. Respondents could choose multiple answers. Fifty-one respondents (21.3%, 51/239) reported that their readers would be interested in the topic of Nutrition; 21.3% (51/239) of the respondents reported that their readers would be interested in the topic of Physical Activity; and 16.7% (40/239) of the respondents reported that their readers would be interested in the topic of Mental Health. Finally, 10.9% (26/239) of the respondents reported that their readers would be interested in the topic of Vaccination. Table 3 details these data.

The fifth research question this study aimed to explore was about what motivates bloggers to write about health issues. To assess this question, a sample of responses to the open-ended question about what motivates bloggers to write about health topics was coded and analyzed. The main motivation bloggers reported for supporting dissemination of health information is having a personal connection to the issue. Forty-one respondents (45%, 41/92) said that they would write about an issue if they had a connection to it, and 20 (22%, 20/92) reported that making a difference was a motivating factor. Finally, 15% (14/92) of the respondents reported that the desire to help educate or make people aware of an issue was a motivating factor. Only 7% (6/92) reported that compensation was a motivating factor. Figure 1 depicts these data.

The sixth, and final, research question this study aimed to explore focused on what factors contribute to bloggers writing about health issues. Using a chi-square test, the relationship between history of health issues and whether a blogger has written about a health issue in the past was assessed and found to be statistically significant, with χ^2_1 (n=298)=18.47, P<.001. This indicates that having a personal connection with a health issue is positively associated with likeliness to write about health issues on their blog.

Table 1. Frequency distributions for key variables in sample (N=298).

Variable	n (%)
Age in years[a]	
18-44	251 (84.2)
45+	47 (15.8)
Gender	
Male	3 (1.0)
Female	295 (99.0)
Have children	
Yes	295 (99.0)
No	3 (1.0)
Have history of health issues	
Yes	241 (80.9)
No	57 (19.1)
Race/Ethnicity	
White	242 (81.2)
Nonwhite	56 (18.8)
Education	
Less than college	88 (29.5)
College/graduate degree	210 (70.5)

[a]Individual ages were grouped in this chart based on US Census age groups (US Census, 2010)

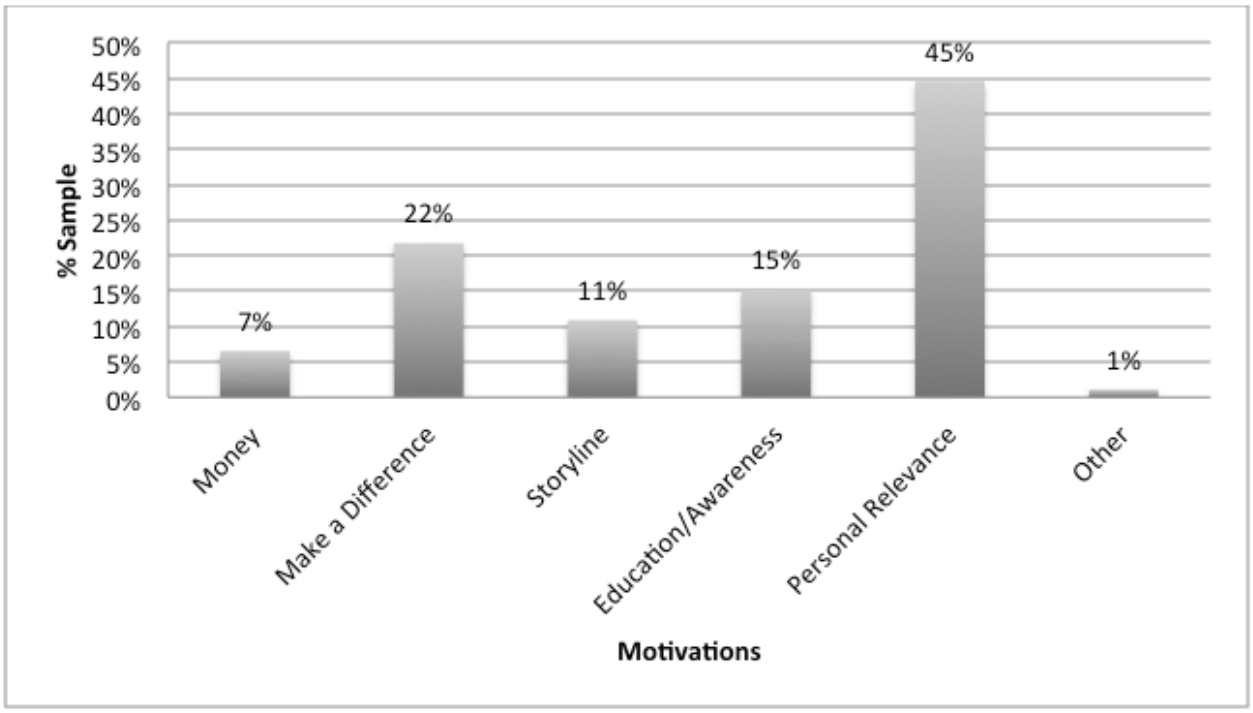
Table 2. Health issue perspectives (N=298).

Variable	n (%)
Written about health issues	
Yes	260 (87.2)
No	38 (12.8)
Willingness to write about health issues	
Yes	290 (97.3)
No	8 (2.7)
Blog reader interest in health issues	
Yes	287 (96.3)
No	11 (3.7)

Table 3. Blog topic analysis in sample.

Variable	n (%)
Topics written about	
Cancer	19 (11.9)
Nutrition	34 (21.4)
Physical Activity	38 (23.9)
Diabetes	10 (6.3)
Heart Disease	10 (6.3)
Mental Health	22 (13.8)
Vaccination	10 (6.3)
Other	16 (10.1)
Possible future topics	
Cancer	34 (11.9)
Nutrition	51 (17.8)
Physical Activity	54 (18.9)
Diabetes	34 (11.9)
Heart Disease	35 (12.2)
Mental Health	41 (14.3)
Vaccination	27 (9.4)
Other	10 (3.5)
Topics blog readers are interested in	
Cancer	24 (10.0)
Nutrition	51 (21.3)
Physical Activity	51 (21.3)
Diabetes	19 (7.9)
Heart Disease	22 (9.2)
Mental Health	40 (16.7)
Vaccination	26 (10.9)
Other	6 (2.5)

Figure 1. Motivations for blogger sample to write about a health issue.



Discussion

Overall Findings

This formative study attempted to capture the complexity of mommy bloggers' perceptions about writing about health-related topics on their blogs, specifically, mommy blogger perspectives about which health issues are more likely to be written about and their motivations for doing so, as well as the perceived interest among their readers for consuming health-related content. In doing so, this study presents data that can inform future public health research and communication campaigns to more broadly promote their messages, thereby contributing to their behavior change objectives. The findings from the analysis of the sample for this study are worthy of discussion and hold several implications for future work in this area. The following in-depth discussion of the study's results begins an exploration of how this work contributes theoretical and translational insights to the social science literature.

In terms of the sample, in this study, the sample was relatively homogenous. It was both a younger group as well as a well-educated one. It skewed white, with less than 20% of the respondents being non-white. Most of these bloggers have children and have dealt with health issues themselves. This study's findings showed that 87% of the respondents reported that they have written about health issues in the past and that 97% of the respondents reported that they would consider writing about health issues sometime in the future. Additionally, 96% of the respondents reported that their readers like to read about health issues on their blogs with the topics of Nutrition and Physical Activity being most commonly cited as having been written about by the respondent sample. Moreover, a significant interaction was found between having a history of health issues and likeliness to write about health issues (P<.001). Having a family history of health issues was found to be positively associated with likeliness to write about health issues on a blog (P<.001).

Theoretical Implications

Theoretically, this study contributes to the literature in a number of ways. First, as noted earlier, there is limited work in the area of mommy bloggers as communication channels for health information to-date. As Lee et al [44] contend, "This popularity has not been fully reflected in empirical academic research yet. Broader publications have considered the influence of blog(ger)s on politics and mass communications [45], tourism [46], journalism [47], and public relations [48]."

In addition, Sundar et al [25] suggest, "Relatively little media and scholarly attention has been paid to personal blogs that discuss topics other than politics. For example, the burgeoning number of health blogs has gone virtually unnoticed in mainstream media and the academic discourse about blogs."

Specific prior research in this area has included work conducted by Burke-Garcia et al where mommy bloggers participated in formative research, followed by an intervention, in order to understand motivations and barriers as well as reader reactions to sharing vaccination information on their blogs [36]. Findings revealed key barriers that bloggers face in sharing vaccination information but that despite these barriers, bloggers who do share this information can drive health behavior consideration among their readers [36]. As well, Horn et al's pilot study on use of mommy bloggers to reach communities of color with health information found that the collaboration between health professionals and social media leaders in communities of color has the ability to influence content and dialogue and thus may be able to help reduce health disparities [37].

This study's findings expand on this current knowledge base by conducting research with a larger sample of this population, looking at perceptions of writing about health topics more broadly (not specifically vaccination), and providing updated data on Web-based health information consumption and dissemination patterns by mommy bloggers to their readers. The findings that mommy bloggers are willing to share health information and their perceptions of their readers' interests in consuming this kind of information via blogs are substantial because as text-based, photo, or video content is being created and shared at an unprecedented level on these blogs—which includes individuals' opinions and ideas—this community has grown to have a virtual finger on the pulse of the needs and beliefs of their Web-based audiences [23]. Therefore, they can provide a window into the needs and wants for their readers and act as trusted communication channels for evidence-based health information on a wide variety of health topics to be communicated to them in ways that work for them. This is worthy of more exploration and comprehension as public health professionals and other scholars seek to understand how to engage with this audience to achieve their program goals.

Finally, while understanding the point of view of bloggers may be theoretically interesting, it also may have implications for real life. Blogs are imbued "with a strong sense of the author's personality, passions, and point of view" [24], and provide the writers' own points of view [49,50]. This may lead them to write about health issues in ways that are problematic for their readers. Risk and Petersen [51] posit, "A plethora of inaccurate and even potentially life-threatening content readily accessible to anyone with a modem and an Internet browser supports the validity of that concern. For instance, Crocco, Villasis-Keever and Jadad reported that inaccurate Internet information contributed to harm in a 1-year-old boy with diarrhea."

Translational Implications

Thus these results also hold promise for future translational health communication efforts. First, there is the potential to work in collaboration with bloggers to promote dissemination of relevant health information. Given the data that suggest the influence these bloggers have with other moms, parents, and caregivers, these should be considered as part of any future health communication campaign seeking to reach and engage these audiences. Additionally, since the data suggest that a primary motivation for bloggers to write about health issues is having a personal connection with the health issues, it indicates that it will be important for public health communicators to get to know bloggers so they can pitch blogging interventions concerning health issues that are most salient to specific bloggers. It also means that the health topic is a critical consideration for bloggers when deciding whether or not to support a campaign. The storyline for the health issue will also impact blogger engagement. Ultimately, the topic of the issue and how it is communicated to bloggers is paramount to bloggers' decisions about whether or not to write about the issue.

This study illustrates that there are potentially rich opportunities for working with mommy bloggers to communicate with key health decision makers (moms) about important health issues. Mommy bloggers are interested in writing about these important health issues and their audiences of moms are interested in reading about these issues. Moreover, the blogs can provide new interactive Web-based communication channels for bloggers and their audiences to communicate about health issues, answer questions, and provide needed support for making health decisions. By working with bloggers to disseminate health information, health communicators can leverage the established powerful, well-utilized, and trusting online social networks established on mommy blogs, while also providing bloggers with relevant, accurate, and up-to-date health information to share with their audiences. This Web-based communication strategy can build upon the established relational strength and influence of communication between bloggers, while also helping to ensure that the health information provided via the blogs is of high accuracy and quality. Ultimately, the value of these mommy blogs should not be overlooked by public health communicators and should be further explored as sources of interpersonal influence concerning important health issues.

Limitations and Future Research

A constraint of this study was the time frame for study design, data collection, and analysis. In addition, there was not an opportunity to gain additional insight by surveying readers of blogs and through interviews with the bloggers themselves. Additionally, this study made use of cross-sectional, self-reported data, among an opt-in sample with the possibility of self-selection bias. This may have skewed how respondents responded to the questions and therefore the data gathered. Finally, the sample skewed white, educated, female, and younger, which may have influenced the results.

Future research should aim to explore this topic with a more diverse sample including men, more representatives from different race or ethnicities, less well-educated bloggers, as well as readers of blogs themselves. There is clearly a need to identify and work with a more diverse sample of mommy bloggers to more broadly and thoroughly disseminate tailored and targeted health information via these trusted networks. Finally, future research should build in interviews or focus groups to gather insights directly from the bloggers in order to better understand their attitudes and motivators and how communication initiatives can work with them in the future.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Survey Instrument.

[PDF File (Adobe PDF File), 15KB - resprot_v7i4e116_app1.pdf]

References

1. Maibach EW, Abroms LC, Marosits M. Communication and marketing as tools to cultivate the public's health: a proposed "people and places" framework. BMC Public Health 2007 May 22;7:88 [FREE Full text] [doi: 10.1186/1471-2458-7-88] [Medline: 17519027]
2. Kreps GL. Applying Weick's model of organizing to health care and health promotion: highlighting the central role of health communication. Patient Educ Couns 2009 Mar;74(3):347-355. [doi: 10.1016/j.pec.2008.12.002] [Medline: 19150591]
3. Neuhauser L, Kreps GL. Participatory Design and Artificial Intelligence: Strategies to Improve Health Communication for Diverse Audiences. 2011 Presented at: AI and Health Communication, Papers from the 2011 AAAI Spring Symposium, Technical Report SS-11-01; March 21-23, 2011; Stanford, California, USA.
4. Kreps GL. Using targeted social media to communicate culturally sensitive and interactive environmental risk information about breast cancer. Proposal to National Institutes of Health (NIH) National Institute of Environmental Health Sciences (NIEHS) 2016 [FREE Full text]
5. Brewer NT, Richman AR, DeFrank JT, Reyna VF, Carey LA. Improving communication of breast cancer recurrence risk. Breast Cancer Res Treat 2012 Jun;133(2):553-561 [FREE Full text] [doi: 10.1007/s10549-011-1791-9] [Medline: 21964579]
6. Mahoney MC, Bevers T, Linos E, Willett WC. Opportunities and strategies for breast cancer prevention through risk reduction. CA Cancer J Clin 2008;58(6):347-371 [FREE Full text] [doi: 10.3322/CA.2008.0016] [Medline: 18981297]
7. Silk KJ, Perrault EK, Neuberger L, Rogers A, Atkin C, Barlow J, et al. Translating and testing breast cancer risk reduction messages for mothers of adolescent girls. J Health Commun 2014;19(2):226-243. [doi: 10.1080/10810730.2013.811322] [Medline: 24111511]
8. Kreps GL. Strategic communication for cancer prevention and control: reaching and influencing vulnerable audiences. In: Georgakilas AG, editor. Cancer Prevention-From Mechanisms to Translational Benefits. University Campus STeP Ri: InTechOpen; 2012.
9. Kreps GL, Sivaram R. Strategic health communication across the continuum of breast cancer care in limited-resource countries. Cancer 2008 Oct 15;113(8 Suppl):2331-2337 [FREE Full text] [doi: 10.1002/cncr.23832] [Medline: 18837025]
10. Fox S, Duggan M. Pew Research Center. 2013. Health online 2013 URL: http://www.pewinternet.org/2013/01/15/health-online-2013/ [WebCite Cache ID 6pHPmiRk6]
11. Kreps GL, Neuhauser L. New directions in eHealth communication: opportunities and challenges. Patient Educ Couns 2010 Mar;78(3):329-336. [doi: 10.1016/j.pec.2010.01.013] [Medline: 20202779]
12. Perrin A. Pew Research Center. 2015. Social Media Usage 2015 URL: http://www.pewinternet.org/2015/10/08/social-networking-usage-2005-2015/ [WebCite Cache ID 6pHPt19t2]
13. Moorhead SA, Hazlett DE, Harrison L, Carroll JK, Irwin A, Hoving C. A new dimension of health care: systematic review of the uses, benefits, and limitations of social media for health communication. J Med Internet Res 2013 Apr 23;15(4):e85 [FREE Full text] [doi: 10.2196/jmir.1933] [Medline: 23615206]
14. Dutta-Bergman MJ. Primary sources of health information: comparisons in the domain of health attitudes, health cognitions, and health behaviors. Health Commun 2004;16(3):273-288. [doi: 10.1207/S15327027HC1603_1] [Medline: 15265751]
15. eMarketer. 2013. What Health Info Do Consumers Seek Online? URL: https://www.emarketer.com/Article/What-Health-Info-Do-Consumers-Seek-Online/1009698 [accessed 2017-03-27] [WebCite Cache ID 6pHPySojt]
16. Bailey M. New survey reveals moms' media habits. Marketing to Moms Coalition and Current Lifestyle Marketing 2008.
17. Gustafson DL, Woodworth CF. Methodological and ethical issues in research using social media: a metamethod of Human Papillomavirus vaccine studies. BMC Med Res Methodol 2014 Dec 02;14:127 [FREE Full text] [doi: 10.1186/1471-2288-14-127] [Medline: 25468265]
18. Zhang C, Gotsis M, Jordan-Marsh M. Social media microblogs as an HPV vaccination forum. Hum Vaccin Immunother 2013 Nov;9(11):2483-2489 [FREE Full text] [Medline: 23842072]
19. Valente TW. Social Networks and Health: Models, Methods, and Applications. Oxford, UK: Oxford University Press; 2010.
20. Berkman LF, Glass T. Social integration, social networks, social support, and health. In: Berkman LF, Kawachi I, editors. Social epidemiology, 1. Oxford, UK: Oxford University Press; 2000:137-173.
21. Vilpponen A, Winter S, Sundqvist S. Electronic word-of-mouth in online environments. J Interact Advert 2006 Mar;6(2):8-77. [doi: 10.1080/15252019.2006.10722120]
22. Huffaker D. Dimensions of leadership and social influence in online communities. Hum Commun Res 2010;36(4):593-617. [doi: 10.1111/j.1468-2958.2010.01390.x]
23. Nardi BA, Schiano DJ, Gumbrecht M, Swartz L. Why we blog. Commun ACM 2004 Dec 01;47(12):41. [doi: 10.1145/1035134.1035163]
24. Sundar SS, Edwards HH, Hu Y, Stavrositu C. Blogging for better health: putting the "public" back in public health. In: Tremayne M, editor. Blogging, Citizenship and the Future of Media. Abingdon, UK: Routledge; 2007:83-102.
25. Scarborough Research. Mashable. 2017. The Rise of the Mommy Blogger INFOGRAPHIC URL: http://mashable.com/2012/05/08/mommy-blogger-infographic/ [accessed 2017-03-27] [WebCite Cache ID 6pHQ6Gr00]

26. Yourdictionary. 2017. Mommy blogger URL: http://www.yourdictionary.com/mommy-blogger [accessed 2017-03-27] [WebCite Cache ID 6pHQC2Ksj]
27. A. The Motherhood. Personal conversation 2016 Oct 18.
28. Chatman E. Collective Bias. 2015. Diversity with Bloggers Brands URL: http://collectivebias.com/blog/2015/01/diversity-bloggers-brands-part-1/ [WebCite Cache ID 6pHQRXkn8]
29. eMarketer. 2010. Understanding How New Moms Share URL: https://www.emarketer.com/Article/Understanding-How-New-Moms-Share/1008056 [WebCite Cache ID 6pHQZ4YLi]
30. Heisler JM, Ellis JB. Motherhood and the construction of "mommy identity": messages about motherhood and face negotiation. Commun Q 2008 Nov 19;56(4):445-467. [doi: 10.1080/01463370802448246]
31. Mitchell W, Green E. 'I don't know what I'd do without our mam' motherhood, identity and support networks. Sociol Rev 2017 Jan 25;50(1):1-22. [doi: 10.1111/1467-954X.00352]
32. Smith JA. Identity development during the transition to motherhood: an interpretative phenomenological analysis. J Reprod Infant Psychol 2007 Dec 11;17(3):281-299. [doi: 10.1080/02646839908404595]
33. Faw L. Forbes. 2012. Is Blogging Really a Way for Women to Earn a Living? URL: http://www.forbes.com/sites/larissafaw/2012/04/25/is-blogging-really-a-way-for-women-to-earn-a-living-2/ [accessed 2017-03-27] [WebCite Cache ID 6pHQhEVdp]
34. Amaral C. Punchbowl. Why Mom Bloggers Are So Valuable to Brands URL: http://www.punchbowl.com/trends/blog/post/why-mom-bloggers-are-so-valuable-to-brands [accessed 2017-03-27] [WebCite Cache ID 6pHQpM71E]
35. Burke-Garcia A, Berry CN, Kreps GL, Wright KB. The Power and Perspective of Mommy Bloggers: Formative Research with Social Media Opinion Leaders about HPV Vaccination. 2017 Presented at: Proceedings of the 50th Hawaii International Conference on System Sciences; January 2017; Hawaii.
36. Horn IB, Burke-Garcia A, Millner D. Use of Social Media for Engaging Communities of Color in Child Health Dialogue. 2012 Sep 16 Presented at: Medicine 2.0 Conference; September 16, 2016; Boston, MA, USA URL: https://cdc.confex.com/cdc/nphic12/webprogram/Paper31650.html
37. Creswell JW. Editorial: Mapping the Field of Mixed Methods Research. J Mix Methods Res 2008 Nov 15;3(2):95-108. [doi: 10.1177/1558689808330883]
38. The Motherhood. The Motherhood Network. URL: http://www.themotherhood.com/network/ [accessed 2018-01-11] [WebCite Cache ID 6wOX1rGq0]
39. Reissman CK. Narrative Methods for the Human Sciences. Thousand Oaks, CA: Sage Publications; 2008.
40. Livescience. 2017. Deductive Reasoning vs. Inductive Reasoning URL: https://www.livescience.com/21569-deduction-vs-induction.html [accessed 2017-11-17] [WebCite Cache ID 6v2lmOZbm]
41. Keyton J. Communication Research: Asking Questions, Finding Answers. London, UK: McGraw-Hill Higher Education; 2006.
42. Tracy SJ. Qualitative Research Methods: Collecting Evidence, Crafting Analysis, Communicating Impact. Hoboken, NJ, USA: Wiley-Blackwell; 2013.
43. Lee HM, Van Dolen W, Kolk A. On the role of social media in the 'responsible' food business: blogger buzz on health and obesity issues. J Bus Ethics 2013;118(4):695.
44. Porter LV, Sweetser Trammell KD, Chung D, Kim E. Blog power: examining the effects of practitioner blog use on power in public relations. Public Relat Rev 2007 Mar;33(1):92-95. [doi: 10.1016/j.pubrev.2006.11.018]
45. Lin Y, Huang J. Internet blogs as a tourism marketing medium: a case study. J Bus Res 2006 Oct;59(10-11):1201-1205. [doi: 10.1016/j.jbusres.2005.11.005]
46. Kaye B. It's a blog, blog, blog world: users and uses of weblogs. Atlantic J Comm 2005 Jun 1;13(2):73-95. [doi: 10.1207/s15456889ajc1302_2]
47. Terilli SA, Arnorsdottir LI. The CEO as celebrity blogger: is there a ghost or ghostwriter in the machine. Public Relat J 2008;2(4):-.
48. Lenhart A, Fox S. Pew Research Center. 2006. Bloggers URL: http://www.pewinternet.org/2006/07/19/bloggers/ [WebCite Cache ID 6yeL5XN1C]
49. Lopez LK. The radical act of 'mommy blogging': redefining motherhood through the blogosphere. New Media Soc 2009 Jul 21;11(5):729-747. [doi: 10.1177/1461444809105349]
50. Risk A, Petersen C. Health information on the Internet: quality issues and international initiatives. J Am Med Assoc 2002 May 22;287(20):2713. [doi: 10.1001/jama.287.20.2713]
51. Crocco AG, Villasis-Keever M, Jadad AR. Two wrongs don't make a right: harm aggravated by inaccurate information on the Internet. Pediatrics 2002 Mar;109(3):522-523. [Medline: 11875153]

Abbreviations

IRB: institutional review board

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Protocol

Comparing the Diagnostic Accuracy of Simple Tests to Screen for Diabetic Peripheral Neuropathy: Protocol for a Cross-Sectional Study

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Abstract

Background: Various tests are used to detect diabetic peripheral neuropathy by assessing sense perception in the feet. Tests vary in terms of time and resources required. Simple tests are those that can be conducted quickly and easily in primary care without laboratory equipment. There are some limitations to these simple tests, an example being the variable amplitude of the 128 Hz tuning fork. A new test, VibraTip (McCallan Medical, UK), might be a valuable alternative as it emits a consistent amplitude and may offer improved diagnostic accuracy.

Objective: The aims of this study are to estimate the diagnostic accuracy of the VibraTip device for diabetic peripheral neuropathy against the reference standard of sural nerve conduction velocity measurement, and to assess whether the VibraTip offers superior diagnostic accuracy to other routine tests based on vibration or touch.

Methods: The study will prospectively recruit adults with type 2 diabetes who are due to attend a routine follow-up clinic. A cross-sectional study design will be employed to assess the diagnostic accuracy of 5 standard index tests for peripheral neuropathy, including VibraTip. The reference test will be sural nerve conduction velocity measurement.

Results: Funding is being sought to conduct this research. The outcomes assessed will be the diagnostic accuracy of the 5 index tests against sural nerve conduction velocity measurement, including sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio. Receiver operating characteristic curves will be constructed and compared for each test.

Conclusions: This study will be the first within-study comparison of 5 simple tests for screening diabetic peripheral neuropathy and will address uncertainties in the potential benefits of using VibraTip in comparison with the other tests.

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KEYWORDS

peripheral nervous system diseases; diabetes mellitus; diabetic foot; diabetic neuropathies; predictive value of tests; sensory thresholds; sensitivity and specificity

Introduction

Background

Diabetic peripheral neuropathy (DPN), nerve damage caused by poorly controlled high blood sugar levels, is the most common complication of diabetes, affecting as many as 50% of people with the disease [1]. DPN can lead to loss of protective sensation in the feet, which is associated with an increased risk of ulceration. Diabetic foot ulcers can become infected and gangrenous and this, ultimately, leads to major (above or below

the knee) or minor (toe or foot) lower limb amputations; indeed, a nonhealing ulcer precedes 85% of such amputations [2]. Diabetes UK has calculated that the number of diabetes-related amputations in England has now reached an all-time record high of 140 per week, equating to approximately 7400 per year [3].

The National Institute for Health and Care Excellence (NICE) Medical Technologies Guidance (MTG) 22 [4] notes that detection, diagnosis, and management of DPN is an important clinical area which has the potential to affect millions of people in the UK. Specifically, foot ulcers cause substantial emotional, physical, and financial losses. Total National Health Service (NHS) spending on ulceration in people with diabetes in England in 2014–15 was estimated at £650 million, equivalent to 0.6%–0.7% of NHS expenditure [5]. Every individual amputation costs the NHS between £8011 and £16,136, depending on whether the patient has comorbidities or develops complications [6].

The prevention of foot ulceration and amputation serves as an effective cost-saving strategy by avoiding the need for expensive interventions such as treatment of foot ulcers and infections, leg amputations, and lower extremity revascularisation procedures [7]. Moreover, beyond the direct costs to the health care sector, there are a number of costs directly incurred by individuals, employers and society in general such as costs for drugs, those indirectly incurred costs due to lost productivity and personal /carer distress. Therefore, even small improvements in the timing and characterisation of DPN detection may have the potential for substantial impact.

Prospective studies have demonstrated that screening for DPN can successfully predict people at risk of ulceration [8]. Vas et al [9] provide a review of the current techniques that may be used for diagnosing DPN. Various simple tests are used to detect DPN by assessing sense perception (either vibration or touch) in the feet. More complex tests, with nerve conduction studies (NCS) only accessible in neurophysiology laboratories, are typically used as the gold standard for diagnosis (noting, however, that there is no universally agreed gold standard). There are often restrictions in time and resource for carrying out in-depth screening in primary care settings where expertise and equipment is unavailable and in busy diabetic clinics when time is constrained and the focus is on fast, simple methods and technologies. The more complex methods tend to be used when clinical presentation is atypical.

In the UK, there is no standardized method of assessing DPN; however, it is typically assessed by a touch test using simpler methods such as 10 gram monofilament, or a vibration test using a 128 Hz tuning fork (NICE MTG 22). The widely-used monofilament [10] has limitations. For example, it needs to be rested for 24 hours after 10 applications and replaced after 100 applications. Furthermore, not all monofilaments available commercially apply 10 g of force and enforcing quality control has been difficult. The tuning fork has one major disadvantage; it constantly decreases in amplitude during its application. Other common tests involve using a neurothesiometer (vibration), which is expensive and not widely used in primary care, or the Ipswich Touch Test (IpTT; touch), which has been validated only in a hospital setting for foot risk prediction. Newer, simple techniques are being developed to help accurately screen for DPN outside of the neurophysiology clinic. One such device, the VibraTip (McCallan Medical, UK; Conformité Européene [CE] marked in 2010) resembles a small keyring fob that provides a near-silent vibration at a frequency similar to that of a calibrated tuning fork, but with a consistent amplitude.

The VibraTip device has been the subject of previous NICE guidance reports. NICE MTG 22 states that VibraTip shows potential to improve the detection of DPN and to provide cost savings to the NHS. The guidance states that VibraTip appears to be easy to use, portable, and reliable in its functionality, but that current evidence is insufficient to support the case for its routine adoption by the NHS. Population size in the studies outlined in the literature review in NICE MTG22 varied between 42 and 496 participants. Studies compared 2-5 index tests against 0-2 reference standards. Bracewell et al [11] was deemed the best quality study in the MTG22 summary of the clinical evidence. MTG22 questioned whether the sample size was adequate (n=141) to assess 4 index tests against 1 reference standard (neurothesiometer). The MTG22 guidance suggests that previous studies [11-16] were of insufficient methodological quality to provide conclusive evidence (eg, sample sizes tended to be small, and inappropriate reference standards were used) and had a high risk of bias. Therefore, research is recommended to address uncertainties in the potential benefits of using VibraTip to patients and the NHS.

As far as the authors are aware, this proposed research would also provide the only within-study comparison of the accuracy of 5 simple and (relatively) commonly used tests for DPN. There are no other published, completed or ongoing studies that compare typically-used methods of assessing DPN with a reference standard of SNCV or neurophysiology, and also address potential biases in previous studies.

Objectives

This study has two aims: (1) to estimate the diagnostic accuracy of VibraTip in detecting DPN against the reference standard of SNCV measurement, and (2) to assess whether the VibraTip device offers superior accuracy compared with 4 other routine tests for peripheral neuropathy (see Table 1 for a description of the tests; these include both touch and vibration tests).

Table 1. Index and reference test schedule. SNCV: sural nerve conduction velocity.

Test	Test type	Is the test typically given to participants as part of care outside research?	Average time per test procedure	Who will conduct the test and where	Description of test procedure[a]
VibraTip	Vibration	Yes	5 min	Clinician; diabetic follow-up clinic	Ten sites on each foot will be tested. The VibraTip is applied to the patient's foot twice: once while not vibrating and once while vibrating. The patient is asked to indicate when they feel vibration. The VibraTip should be applied for 1 second in each instance.
Monofilament (10 g)	Touch	Yes	5 min	Clinician; diabetic follow-up clinic	Ten sites on each food will be tested. The monofilament is lightly pressed to the skin so that it buckles into a C-shape. The patient is asked to indicate whether they feel the touch. The monofilament should be applied for 1 second in each instance.
Tuning fork (128 Hz)	Vibration	Yes	5 min	Clinician; diabetic follow-up clinic	Per typical practice, 3 sites will be tested: tip of hallux on each foot, medial malleolus on each ankle, and each knee (6 sites in total). The 128 Hz tuning fork is struck before being applied to the feet at each site for 1 second.
Neurothesiometer set at ≥25 V	Vibration	Yes	10 min	Clinical scientist; diabetic follow-up clinic	The neurothesiometer will be set at 25 V (vibration perception threshold, VPT) and failure to detect vibration at this VPT indicates neuropathy. In Bracewell et al [11], detection of ≥25 V using the neurothesiometer was assessed at the pulp of the hallux (great toe) only. This will be assessed on each foot.
Ipswich Touch Test (IpTT)	Touch	Yes	5 min	Clinician; diabetic follow-up clinic	The IpTT involves very lightly touching 6 toes, 3 on each foot to find out how many of the touches are felt. Touch will last for 1 second. Each touch will not be repeated (ie, no toes much be touched more than once). Normal sensation is indicated if touch was felt in at least 5 of 6 toes; fewer than this indicates neuropathy.
SNCV measurement (reference test)	SNCV	No	5-15 min	Clinician or clinical technician; neurology department	This involves 2 electrodes being applied to the patient's skin: one at the knee and one at the ankle. The first electrode sends a small painless electrical impulse through the nerve. The second electrode records the impulse. The time difference between the impulse being sent by the first electrode and being received by the second electrode indicates how quickly the sural nerve is transmitting electrical impulses. If the speed at which the impulse is transmitted is abnormal, this is an indication of diabetic peripheral neuropathy. Additionally, bilateral sural nerve amplitude and superficial peroneal amplitude measurements may also be considered within the same session to increase the accuracy of the reference standard. Skin temperature will be kept at a standard level, verified by a skin thermometer, and measurement will be bilateral.

[a]Tests are described in detail by Papanas and Ziegler (2014) [17].

Methods

Type of Study

The study population will be recruited prospectively. A cross-sectional study design will be used to assess the diagnostic accuracy of 5 simple methods of identifying peripheral neuropathy against SNCV measurement as reference standard. This study design will provide a like-for-like comparison of the tests within the same participants. Ideally, patients will only be participating in the study for one day at the time of their routine follow-up appointment.

Setting

For a UK study, settings should include centers that carry out routine screening for diabetic complications. This may be at a general practitioner clinic or, more typically, a diabetes clinic. The researchers will require access to a neurology department within which NCS testing can be carried out by qualified staff. Ideally, this will be within the same center to minimize the time between the carrying out of standard tests and the SNCV assessment.

Inclusion and Exclusion Criteria

The only inclusion criterion is that study participants must be adults with type 2 diabetes mellitus who have no history of foot ulcers.

The following exclusion criteria will be used:

- Patients who already have ulcerations (or a history of ulcers) or amputations
- Patients under 18 years of age
- Those unable to provide consent or a satisfactory response because of cognitive impairment (eg, people with dementia are considered high risk)

Study Procedure

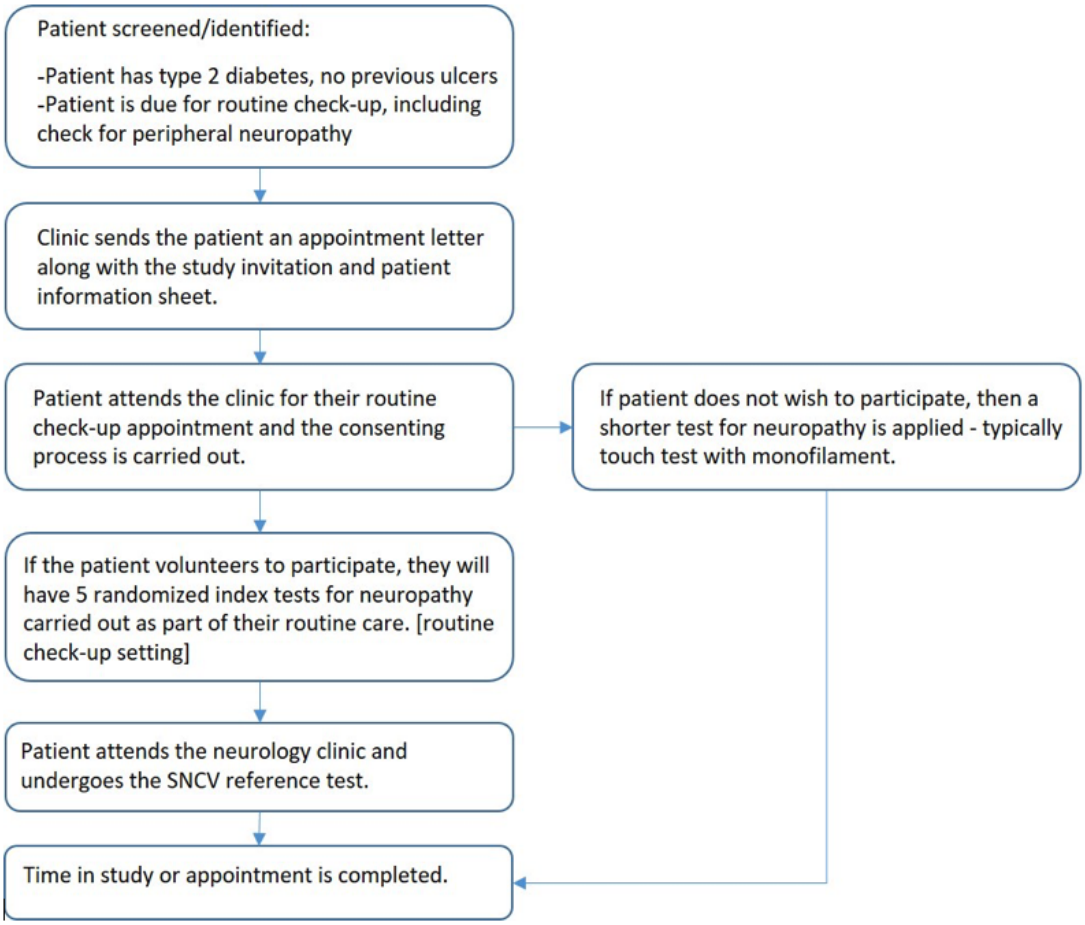
Diabetic patients, who are due to attend routine follow-up clinic, will be screened for eligibility according to the inclusion and exclusion criteria outlined above. Screening may be undertaken by an investigator with permission to access the organization's patient administration system for the diabetes service. Patients will be aware of test results during the testing procedures, but will be asked to close their eyes while the procedures are carried out.

Due to the comparative complexity of setting up the SNCV measurements, this will occur independently of the index tests. Patients will arrive at the neurology department to undergo SNCV measurement, which will take approximately 5-15 min. This may be carried out on the same day (ideally, if the neurology department is close to or within the recruiting clinic), or on a different day if this is not possible. To minimize interexaminer variation, the nerve tests should ideally be carried out by the same examiner, or by a controlled number of neurology staff working based on agreed protocols. The process for the patient is illustrated by Figure 1.

Outcome Measures

For the vibration- and touch-based tests, the outcome measure will be the number of sensate and the number of insensate sites per patient. For the SNCV test, the outcome measure will be the speed of sural nerve conduction in meters per second.

Figure 1. Study process per patient. SNCV: sural nerve conduction velocity.



Number of Test Sites

There is no agreed standard on the number or location of sites on each foot that should be examined [4]; published literature describes different approaches varying from 1 testing site to 10 testing sites per foot [1]. Bracewell et al [11] assessed the optimal number of sites on the feet that should be tested to detect peripheral neuropathy using VibraTip, 10 g monofilament and 128 Hz tuning fork by testing 5 sites on each foot. Their analysis suggested that finding ≥2 insensate sites across the 10 sites (5 on each foot) may be indicative of peripheral neuropathy for VibraTip and monofilament, whereas ≥1 insensate sites across 10 sites in 2 feet may be indicative of peripheral neuropathy for the 128 Hz tuning fork.

To perform tests thoroughly and be able to assess the accuracy of testing at different thresholds for the VibraTip and monofilament, this study will test 10 sites per foot (20 overall per participant). The 128 Hz tuning fork will be tested in 6 sites as per typical practice. The IpTT and neurothesiometer also have more standardized procedures (testing 6 and 2 sites across 2 feet, respectively), which will be followed for this study. The data from this will be used to perform receiver operating characteristic (ROC) analyses for each of the vibration and touch tests compared with SNCV, to assess the optimum number of insensate sites that give the best diagnostic accuracy.

Test Randomization

Repeated touch of the same area on the patient's foot may affect sensitivity to subsequent tests. As a mitigating measure, breaks of at least 5 minutes will occur between each test. The order of the index tests will also be randomized.

Data Collection

A specific proforma has been created to collect data for this study (see Multimedia Appendix 1). This proforma will be used in parallel with the routine case notes for the follow-up appointment. The clinician carrying out the routine follow-up will also be responsible for completing the proforma.

Each proforma (1 per participant) will have 7 pages with the following diagrams/guidance and space to record results:

1. Cover sheet: unique study number, order of tests (prerandomized), record of age, gender, and visit date
2. Index test A for VibraTip: simple illustration of 2 feet with areas marked for 10 sites to be tested on each foot
3. Index test B for 10 g monofilament: simple illustration of 2 feet with areas marked for 10 sites to be tested on each foot
4. Index test C for 128 Hz tuning fork: simple illustration of 2 feet, 2 ankles and 2 knees with areas marked for 6 sites per patient to be tested
5. Index test D for neurothesiometer: simple illustration of 2 feet with areas marked for 1 site to be tested on each toe
6. Index test E for IpTT: simple illustration of 2 feet with areas marked for 3 toe sites to be tested on each foot
7. Space for recording the result of the SNCV test

Sample Size

Peripheral neuropathy can affect up to 50% of the population with type 2 diabetes [18]. The reported 0.79 sensitivity and 0.82 specificity from Bracewell et al [11] can be used as the estimated sensitivity and specificity for VibraTip. These are conservative estimates compared with those described by Bowling et al [12] and Nizar et al [15]. Using the Confidence Interval Analysis software package, a sample size of 102 and a sensitivity of 0.79 will give an acceptable 95% confidence lower limit for sensitivity of 0.7. Assuming half the population will be positive for neuropathy (true cases) and half will be negative for neuropathy, a total sample size of 204 patients will be required.

Statistical Analysis

All analyses will be performed using the latest versions of SPSS, and the following outcomes will be assessed:

1. Primary outcomes: The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios will be measured for each test, using established thresholds, and presented with 95% confidence intervals.
2. Secondary outcomes: The sensitivity and specificity of the five index tests will be compared using McNemar's test for paired proportions. ROC curves will be constructed for each index test, using the full range of possible thresholds per test. Statistical significance of the difference between the areas under ROC curves (derived from the same cases) will be tested with the method of DeLong et al [19].

Ethics and Governance

Patients due for a routine follow-up will be sent a patient information sheet and invitation to take part in the study along with their appointment letter. The date that the letter was sent will be recorded. The patient will receive this at least 48 hours before they attend clinic.

On attending their follow-up appointment, the patient will be asked whether they have read the invitation and patient information sheet. If they respond affirmatively and favorably to this, the investigator will explain the aims, methods, anticipated benefits, and any potential risks of the study. The patient will be able to ask any questions or highlight any concerns about the study. The investigator will explain to the potential participant that they are free to refuse any involvement in the study or withdraw their consent at any point during the study. Individual patient consent will be requested at entry by the recruiting clinician.

The study protocol has been given a favorable ethical opinion from an NHS Research Ethics Service by proportionate review.

Results

Funding has been sought to carry out this proposed research. This study is expected to be completed in 2018.

Discussion

Study Rationale

This study aims to address the uncertainties identified in NICE MTG 22 by carrying out a prospective diagnostic accuracy study with a more robust reference standard than used in previous studies. There is no universally acknowledged reference method

for diagnosing DPN, especially advanced DPN, which increases the risk of developing foot ulceration. The use of nerve NCS is typically viewed as the most acceptable option for confirming DPN. However, DPN is a length-dependent, axonal neuropathy, and therefore, assessment of the sural nerve (as proposed in this study)—the longest sensory nerve—may have the greatest face validity as a single parameter for its identification [18]. There is a paucity of studies comparing methods of diagnosis to the reference standard of NCS such as SNCV. This study should help provide a robust indication of the performance of commonly, and less commonly used methods of routinely testing for DPN.

Recommendations from NICE MTG22 prompted the development of this protocol. NICE may update its guidance if substantive evidence is generated on the superior accuracy of VibraTip in testing for DPN, thus addressing the evidence gaps identified in MTG 22. If the research outcome is favorable, updated NICE guidance would have a very strong influence on adoption nationally and internationally.

DPN is a serious condition that can lead to ulcers and amputation. These preventable outcomes are distressing to patients and costly to the health care system. Early identification and foot risk stratification will allow an increased window of opportunity to ensure at-risk patients are enrolled in an appropriate foot protection program. The evaluation of simple assessment methods may also provide more information for carrying out clinical and cost effectiveness analyses.

Challenges

There are multiple potential methods of assessing DPN. The methods outlined in this protocol are, to the authors' knowledge, the most typical of simple methods carried out in routine practice. This may not, however, be exhaustive. One device that has not been incorporated into this protocol, but may warrant consideration, is the handheld DPN-Check (Neurometrix, USA). The device is able to provide a point-of-care estimate SNCV and sural nerve conduction amplitude, and may be an acceptable proxy to standard NCS for screening and identification. The adoption of this device into routine clinical practice may, however, be limited by device complexity and precision [19].

Many other electrophysiological parameters exist and may be used in the assessment of DPN. However, though a combination of multiple tests may elicit an incrementally more accurate reference standard, research must also remain within the boundaries of practicality. For this reason, and to minimize the inconvenience to the patients who are attending clinic for routine assessment and will already be undergoing multiple index tests, SNCV is an appropriate choice. Additionally, bilateral sural nerve and superficial peroneal amplitude measurements may also be taken.

Future Directions

The proposed study will be undertaken in an environment where the accuracy of different tests with the same patient can be assessed using more complex comparators as the reference standard compared with previous studies. These comparators require technical equipment and trained operators (not readily available in primary or community care). Should the VibraTip reliably demonstrate equivalent or superior accuracy to other index measures for DPN, the device may prove particularly useful in the primary or community care setting, and this may therefore be a key aim of further research.

Another potential factor for testing is the effect of the training and experience of the tester. Tests in the primary care and community settings may be performed by several different examiners (of unspecified levels of training and experience), and therefore, the issue of interrater variability should be investigated.

Acknowledgments

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Authors' Contributions

KG led the development of the protocol design, drafted the initial manuscript and wrote the final manuscript. All authors participated in critical review of the methods and read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Data collection proforma.

[PDF File (Adobe PDF File), 174KB - resprot_v7i4e72_app1.pdf]

References

1. Dros J, Wewerinke A, Bindels PJ, van WHC. Accuracy of monofilament testing to diagnose peripheral neuropathy: a systematic review. Ann Fam Med 2009;7(6):555-558 [FREE Full text] [doi: 10.1370/afm.1016] [Medline: 19901316]
2. Clayton W, Elasy TA. A Review of the Pathophysiology, Classification, and Treatment of Foot Ulcers in Diabetic Patients. Clinical Diabetes 2009 May 18;27(2):52-58 [FREE Full text] [doi: 10.2337/diaclin.27.2.52]
3. Diabetes UK Facts and Stats. 2016 Oct. URL: https://diabetes-resources-production.s3-eu-west-1.amazonaws.com/diabetes-storage/migration/pdf/DiabetesUK_Facts_Stats_Oct16.pdf [accessed 2018-02-27] [WebCite Cache ID 6xXqgwC2I]
4. National Institute for Health and Care Excellence. Medical technologies guidance 22: VibraTip for testing vibration perception to detect diabetic peripheral neuropathy. 2014. URL: https://www.nice.org.uk/guidance/mtg22%20 [accessed 2018-02-27] [WebCite Cache ID 6xXqnXfPb]
5. NHS Digital. National Diabetes Foot Care Audit Report England and Wales 2014-2015. URL: http://digital.nhs.uk/catalogue/PUB20343 [accessed 2018-02-27] [WebCite Cache ID 6xXqqNczg]
6. National Institute for Health and Care Excellence. Lower limb peripheral arterial disease costing report: Implementing NICE guidance. 2012. URL: https://www.nice.org.uk/guidance/cg147/resources/costing-report-186857245 [accessed 2018-02-27] [WebCite Cache ID 6xXquhyAk]
7. Barshes N, Saedi S, Wrobel J, Kougias P, Kundakcioglu O, Armstrong D. A model to estimate cost-savings in diabetic foot ulcer prevention efforts. Journal of Diabetes and its Complications 2017 Apr;31(4):700-707. [doi: 10.1016/j.jdiacomp.2016.12.017] [Medline: 17049917]
8. Crawford F, Cezard G, Chappell FM, Murray GD, Price JF, Sheikh A, et al. A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). Health Technol Assess 2015 Jul;19(57):1-210 [FREE Full text] [doi: 10.3310/hta19570] [Medline: 26211920]
9. Vas PRJ, Sharma S, Rayman G. Distal Sensorimotor Neuropathy: Improvements in Diagnosis. Rev Diabet Stud 2015 Dec;12(1-2):29-47 [FREE Full text] [doi: 10.1900/RDS.2015.12.29] [Medline: 26676660]
10. National Institute for Health and Care Excellence. Diabetic foot problems: prevention and management. 2015. URL: https://www.nice.org.uk/guidance/ng19 [accessed 2018-02-27] [WebCite Cache ID 6xXr6ovrU]
11. Bracewell N, Game F, Jeffcoate W, Scammell BE. Clinical evaluation of a new device in the assessment of peripheral sensory neuropathy in diabetes. Diabet Med 2012 Dec;29(12):1553-1555. [doi: 10.1111/j.1464-5491.2012.03729.x] [Medline: 22672257]
12. Bowling FL, Abbott CA, Harris WE, Atanasov S, Malik RA, Boulton AJM. A pocket-sized disposable device for testing the integrity of sensation in the outpatient setting. Diabet Med 2012 Dec;29(12):1550-1552. [doi: 10.1111/j.1464-5491.2012.03730.x] [Medline: 22672290]
13. Garbas M, Urbancic-Rovan V, Slak M, Hohnjec M. P5 Can we replace 128-Hz tuning fork testing by Vibratip? In: Meeting of the Diabetic Foot Study Group. 2013 Presented at: Can we replace 128-Hz tuning fork testing by Vibratip? Poster abstract from the Meeting of the Diabetic Foot Study Group; 2013; Sitges URL: http://dfsg.org/fileadmin/user_upload/files/DFSG/2013/Abstract_2013/P5.pdf
14. Levy A. Preliminary data on VibraTip(R), a new source of standardised vibration for bedside assessment of peripheral neuropathy. The British Journal of Diabetes & Vascular Disease 2010 Dec 21;10(6):284-286. [doi: 10.1177/1474651410390741]
15. Nizar H, Munro N, Nightingale P, Feher M. Diagnostic accuracy of the VibraTip in detection of diabetic peripheral neuropathy. British Journal of Diabetes and Vascular Disease 2014;14(1):26. [doi: 10.15277/bjdvd.2014.005]
16. Urbancic-Rovan V, Slak M, Hohnjec M. Screening for neuropathy – do additional testing methods make sense? 2012 Presented at: Meeting of the Diabetic Foot Study Group; 2012; Berlin-Potsdam.
17. Lee JA, Halpern EM, Lovblom LE, Yeung E, Bril V, Perkins BA. Reliability and validity of a point-of-care sural nerve conduction device for identification of diabetic neuropathy. PLoS One 2014;9(1):e86515 [FREE Full text] [doi: 10.1371/journal.pone.0086515] [Medline: 24466129]
18. Boulton AJ. Management of Diabetic Peripheral Neuropathy. Clinical Diabetes 2005 Jan 01;23(1):9-15 [FREE Full text] [doi: 10.2337/diaclin.23.1.9]
19. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988 Sep;44(3):837-845. [Medline: 3203132]

Abbreviations

CE: Conformité Européene
DPN: diabetic peripheral neuropathy
IpTT: Ipswich Touch Test
MTG: Medical Technologies Guidance
NCS: nerve conduction studies
NHS: National Health Service
NICE: National Institute for Health and Care Excellence

ROC: receiver operating curve
SNCV: sural nerve conduction velocity
VPT: vibration perception threshold

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Protocol

Impact of Oral Side Effects from Conditioning Therapy Before Hematopoietic Stem Cell Transplantation: Protocol for a Multicenter Study

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Abstract

Background: The oral cavity is a common site of complications related to the cytotoxic effect of high-dose chemotherapy and radiation therapy. Considering our limited understanding of the burden of illness in the oral cavity from various cytotoxic therapies, it is difficult to produce evidence-based, preventive and management protocols. A prospective multicenter study is necessary to collect data on the burden of illness from various cytotoxic regimens.

Objective: The objectives of this prospective international observational multicenter study in hematopoietic stem cell transplant (HSCT) patients are to establish the nature, incidence and temporal relationship of oral complications related to conditioning regimens (chemotherapy with or without total body irradiation), stem cell transplantation and the immunologic reactions (mainly graft-vs-host-disease) that may follow, and to determine what subjective and objective oral complications related to treatment can predict negative clinical and economic outcomes and reduced quality of life.

Methods: Adult patients at six study sites receiving full intensity conditioning, reduced intensity conditioning or nonmyeloablative conditioning, followed by autologous or allogeneic hematopoietic stem cell infusion, are included. A pre-treatment assessment includes medical conditions, planned chemo- and radiation therapy regimen, medications, allergies, social history, patient report of oral problems, dental history, subjective oral complaints, objective measures of oral conditions, current laboratory values, dental treatment recommended and untreated dental disease. Starting 1-3 days after hematopoietic stem cell infusion, a bedside assessment is completed 3 days per week until resolution of neutropenia. A patient questionnaire is also completed during hospitalization. Beyond this time, patients with continued oral mucositis or other oral problems are followed 1 day per week in an inpatient or outpatient setting. Additional visits for urgent care for acute oral problems after hospitalization are documented.

Autologous transplant patients are being followed up at 100 days (SD 30 days) and at 1 year (SD 30 days) post-transplantation to identify any long-term side effects. Patients treated with allogeneic transplantation are being followed at 100 days (SD 30 days), 6 months (SD 30 days), and 12 months (SD 30 days). The follow-up assessments include cancer response to therapy, current medical conditions, medications, subjective and objective oral findings, quality of life measures and laboratory values. The targeted enrollment is 254 patients who have received HSCT.

Results: A total of 260 participants have been enrolled, with 233 (91%) who have received HSCT. We anticipate enrollment of 20-30 additional participants to obtain the sample size of 254 enrolled participants who have received HSCT.

Conclusions: The results of the ongoing prospective study will provide a unique dataset to understand the impact of oral complications on patients undergoing HSCT and provide needed evidence for guidelines regarding the management of this patient cohort.

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KEYWORDS

mucositis; hematopoietic stem cell transplantation; chemotherapy; xerostomia; cohort studies; graft vs host disease; dental disease; multicenter study; oral cavity; costs and cost analysis

Introduction

The annual incidence of cancer is 11 million cases worldwide [1]. Early cancer detection and advances in cancer therapies have provided important management advances to improve survival, and quality of life (QOL) in later years. Common cancer treatment strategies include surgical resection, chemotherapy (CT), radiotherapy (RT), and hematopoietic stem cell transplantations (HSCT). The goal of such treatments is to eliminate all cancer cells. However, side effects from these therapies can limit the effectiveness of treatment and have a marked impact on the patient's QOL. The oral cavity is a common site of complications related to cytotoxic therapies. The Surgeon General's report on Oral Health in America estimates that more than 400,000 patients in the US undergoing cancer treatment will develop oral complications annually [2]. The report calls for more science and the effective translation of science to improve oral health and establish clinical practice guidelines based on a higher quality science base. Recommendations are needed to effectively transfer research findings in the field of oncology, including oral complications seen with cancer therapies, and oral management prior to the start of cancer therapy, to public and health professionals. Well developed, evidence-based management recommendations have the potential to enhance the appropriateness of clinical practice, improve the quality of oral health care, lead to better patient outcomes, and identify areas of further research needs. To effectively change perceptions of the burden of illness of oral complications from cancer therapies, a complete understanding of the impact of these complications is vital. Underestimating the impact of oral complications may result in avoidance or delay in appropriate care for cancer patients.

Numerous preventive care protocols have been proposed to minimize oral complications from cancer therapies. Unfortunately, these protocols are rarely evidence-based and often rely on "expert opinion" or anecdotes. The lack of well-controlled, prospective studies is the primary reason for the limitation in preventive and management protocols. The Institute of Medicine (IOM) report determined that insufficient systematic research is available to assess the prevention and management of the oral problems associated with head and neck cancer, leukemia, and lymphoma [3].

Considering our limited understanding of the burden of illness in the oral cavity from various cancer therapies, it is difficult to produce evidence-based, preventive and management protocols. Therefore, a prospective multicenter study is necessary to collect data on the burden of illness from various cancer regimens.

The literature reports a wide range of oral complications with varying incidences. Oral mucositis, or inflammation of the mucosal surfaces, sometimes also called mucosal barrier injury (MBI), is a major dose-limiting side effect of chemo- and radiation therapy, specifically conditioning therapy before HSCT. Severe mucositis has been associated with pain, infection, poor nutrition, increased hospitalization and a major impact on QOL and economic outcomes. Other reported complications are bleeding, dysphagia (difficulty swallowing), dysgeusia (altered sensation of taste), infection (bacterial, viral, and fungal), pain, trismus, medication-related osteonecrosis of the jaw, osteoradionecrosis, xerostomia/salivary gland dysfunction, caries, periodontal disease, and graft-vs-host-disease (GVHD) [4]. Recent systematic reviews of these oral complications have confirmed the limitations in knowledge of the incidence and severity of the various additive oral complications [5]. Additionally, based on these systematic reviews, prevention and management protocols are very limited in quality and design such that it is difficult to produce evidence-based protocols leading to a significant gap in treatment protocols for this patient population. Furthermore, how these common oral complications impact clinical and economic outcomes and affect (QOL) is poorly understood [6]. The goal of the present study is to bridge these research gaps by way of a well-designed, prospective, multicenter observational study.

The objectives of this prospective international observational multicenter study in HSCT patients is to determine the relevant factors that may predict negative clinical and economic outcomes through the following methods and approaches. We will establish the nature, incidence and temporal relationship of oral complications related to conditioning regimens

(chemotherapy with or without total body irradiation, HSCT and the immunologic reactions (mainly chronic GVHD) that may follow, and to determine what subjective and objective oral complications related to treatment can predict negative clinical and economic outcomes and reduced QOL.

The purpose of this manuscript is to describe the study protocol for this important ongoing multi-center study and to report the current sites and enrollment.

Methods

Study Design

The present study aims to address research gaps regarding the impact of oral complications in HSCT patients by way of a well-designed prospective, longitudinal, international, observational, multicenter cohort study of patients receiving conditioning regimens followed by HSCT (autologous or allogeneic). Data collected from this study will allow a comprehensive understanding of the burden of illness of oral complications related to type of conditioning therapy and provide a clearer understanding of prevention and management protocols for oral complications in HSCT patients.

Outcome Measures

To address the primary aim of determining the incidence, severity and temporal relationship of oral complications related to type of conditioning regimen, we register demographics (age, sex), diagnosis, cytotoxic therapy and assess the following outcomes (details are provided in Multimedia Appendix 1):

- Subjective oral complications: Oral pain, xerostomia (dry mouth), dysgeusia (taste changes) and dysphagia (swallowing difficulties);
- Objective oral complications: Oral mucositis, hyposalivation, oral infections (viral, fungal, bacterial), submucosal hemorrhage, dental and periodontal diseases and complications, osteonecrosis, and GVHD.

To address the secondary aims of determining what factors can predict negative clinical and economic outcomes and reduced QOL, we assess the following:

- Antimicrobial prophylaxis or Keratinocyte Growth Factor medication and ongoing immunosuppression for GVHD
- Institutional standard of care preventative and management protocols
- Nausea or vomiting, diarrhea, fever, weight and blood values
- Additional hospital visits, prolonged hospital stays, systemic infection, increased medication/treatment (eg antibiotics, opioids), poor nutrition or parenteral nutrition and death.
- Subjective measures of oral pain, xerostomia, dysgeusia and dysphagia, and a feeling of well-being. To minimize the length of time needed to participate in the present study, generic oral health-related quality of life measures (eg, OHIP-14) were not used and instead QOL questions were focused on subjective areas related to oral complications from cancer therapy.
- Genomic factors (Multimedia Appendix 2).

Study Organization

Subjects are enrolled at six clinical study sites: Sahlgrenska University Hospital, Gothenburg, Sweden; Karolinska University Hospital Huddinge, Stockholm, Sweden; Carolinas Medical Center, Charlotte, NC, USA; BC Cancer, Vancouver, BC, Canada; Academic Medical Center, Amsterdam, The Netherlands; Radboud University Medical Center, Nijmegen, The Netherlands. Study personnel at each site include the site principal investigator, study coordinator(s), and clinical examiner(s). The Data Coordinating Center for the study is located at the Carolinas HealthCare Systems, Charlotte, NC, USA.

Safety of Human Subjects and Data Integrity

Approval from the research ethics board at each clinical study site was obtained prior to enrollment. Sites were approved to start enrollment after a site visit was completed by the study principal investigators (IVB, MTB) to ensure appropriate infrastructure, patient population, research staffing, calibration of research personnel of the study design, data management and study outcomes. Informed consent is obtained from each study participant prior to inclusionStudy data is entered into MedView, which is a computer program that is based on formalized input and registration of all clinical information. MedView provides a suite of tools for formalizing, gathering, and analyzing data. MedView is aimed at clinical research and is well suited for multicenter studies [7]. MedView program is accessible on the Internet. Each participating center is provided with a unique username and password. Data sent over the internet are encrypted. No personal identifiers are included. Study data is loaded into a secure database at University of Gothenburg, Sweden. Staff from the Data Coordinating Center monitors validation of the study data to identify missing data or forms or incorrect registrations and communicates this information with each enrollment site to resolve any problems.

Training and Calibration

All study personnel receive training on the parameters needed to conduct this study which includes training on clinical assessments; training on completing study forms, data entry and all non-clinical procedures. In addition, annual calibration on objective clinical measures is conducted for all clinical examiners.

Subject Selection Criteria

Inclusion Criteria

Adult patients receiving full intensity conditioning, reduced intensity conditioning or nonmyeloablative conditioning, followed by hematopoietic stem cell infusion (autologous or allogeneic) are eligible for inclusion. For diagnoses, see Textbox 1.

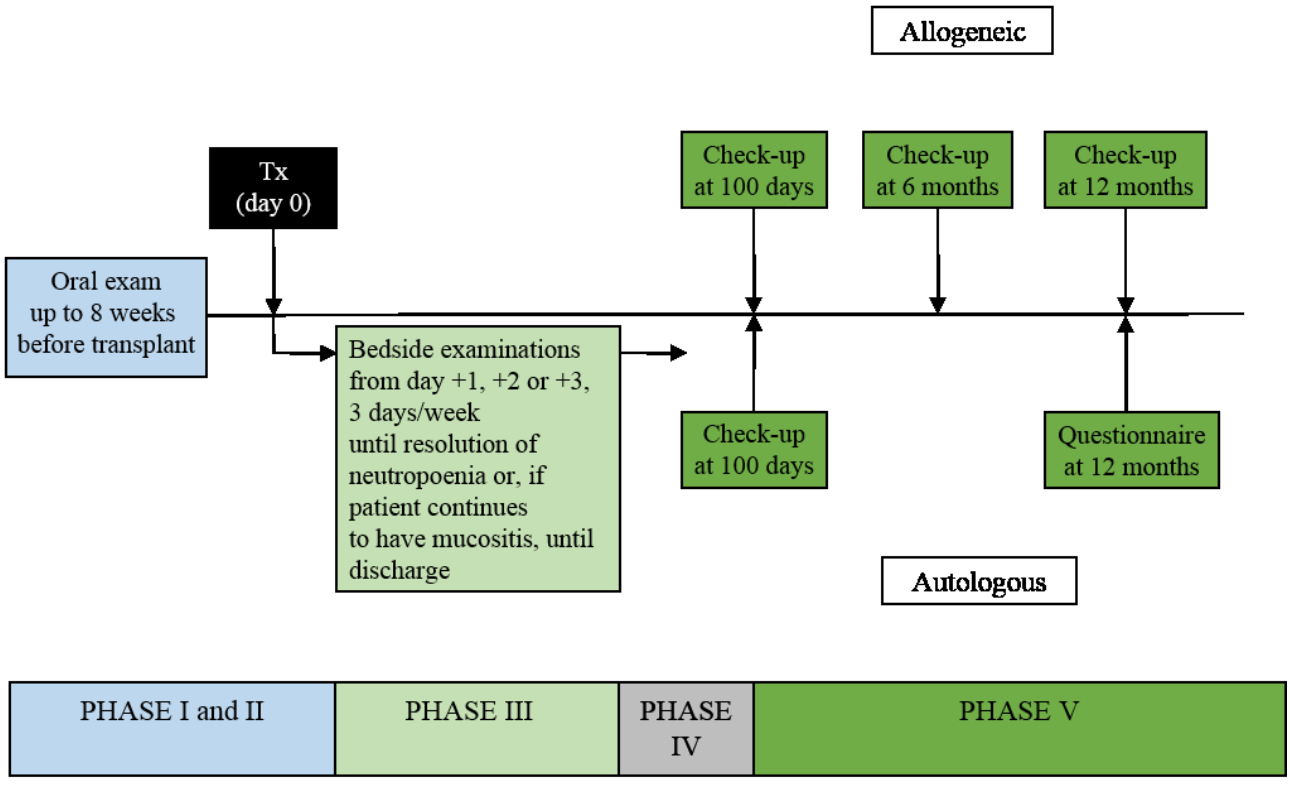
Exclusion Criteria

Patients unable to give consent are not eligible for inclusion.

Textbox 1. Patients with the following diagnoses to go through hematopoietic stem cell transplantations (HSCT) are eligible for inclusion.

For allogeneic transplant:
Acute leukemia
Myelodysplastic syndrome
Aplastic anemia
Lymphoma including chronic lymphocytic leukemia
Chronic myeloid leukemia
Myelofibrosis
Other conditions being managed with HSCT
For autologous transplant:
Multiple myeloma
Lymphoma including chronic lymphocytic leukemia
Testicular cancer
Autoimmune diseases (scleroderma; systemic sclerosis)
Other conditions being managed with HSCT

Figure 1. Study flow diagram.



Study Assessments

Patients who meet the enrollment criteria are approached and consent is reviewed and obtained. A pretreatment assessment (Phase I and II) is completed to include the following: medical conditions, planned chemo- and radiation conditioning therapy regimen, medications, allergies, social history, patient report of oral problems, dental history, subjective oral complaints, objective measures of oral conditions, current laboratory values, dental treatment recommended and untreated dental disease. This pretreatment assessment will occur up to 8 weeks prior to stem cell transplantation (Figure 1).

Study Flow Diagram

A bedside assessment (Phase III) will be completed 3 days per week (Monday, Wednesday, Friday) starting day +1, +2 or +3 after transplantation (day 0) depending on which day of the week the transplantation occurs, until resolution of neutropenia

(ie, absolute granulocyte count > 0.5 x 10^9/l). For patients with continued mucositis or other oral problems requiring hospitalization after resolution of neutropenia, an oral examination will be completed for up to 6 weeks duration. A patient questionnaire will be completed for each study visit to the patient (Monday, Wednesday, Friday) during the patient hospitalization. Beyond this time, patients with continued oral mucositis or other oral problems will be followed 1 day per week (Phase IV) in an inpatient or outpatient setting.

Additional visits for urgent care for acute oral problems will be documented regarding the nature of the oral problem and treatment provided (Phase IV). This will be documented for up to 6 months for the autologous stem cell transplantation patients and 12 months for the allogeneic transplant patients.

For long-term follow-up, patients with autologous transplantation will be followed-up as part of standard of care visits. The first follow-up visit (Phase V) in an outpatient setting will occur 100 days (SD 30 days). The patients will also complete the patient questionnaire at 100 days (SD 30 days). These patients will also receive a questionnaire (Phase VI) by mail at 1 year (SD 30 days) posttransplantation to identify any long-term side effects **.** Patients with allogeneic transplantation will also be followed up as part of standard of care visits (Phase V) in an outpatient setting at 100 days (SD 30 days), as well as after 6 months (SD 30 days), and 12 months (SD 30 days), at which time the patient questionnaire is also completed. The follow-up assessments will include cancer response to therapy, current medical conditions, medications, subjective and objective oral findings, QOL measures and laboratory values. For the study outline of the standardized examination process, see Figure 1. If a patient is deceased, it will be noted (Phase VII).

Statistical Considerations

Analyses for establishing the nature of oral complications will be primarily descriptive in nature using percentages and rates with corresponding confidence intervals. Analyses to determine what oral complications related to treatment can predict negative outcomes will use inferential statistics comparing those with oral complications to those without. For each outcome, univariate analysis will use Student's *t*-test (or Wilcoxon Rank Sum) for continuous measures and chi-square or Fisher's exact tests for dichotomous variables with a critical value of 0.05. Additional potential risk factors that are thought to have prognostic value will first be analyzed by univariate analysis and appropriate variables (P<0.1) will be considered as confounders in multivariable modeling (either linear or logistic regression depending on the outcome distribution).

Table 1. Expected incidence of oral complications after HSCT and estimated sample size required to reach a statistical significance level of 95%. GVHD: graft-vs-host-disease.

Oral complication	Estimate source	Expected incidence (%)	Sample size	Precision (%)
Mucositis	Preliminary study	65	237	+/– 6
			133	+/– 8
			83	+/– 10
Xerostomia	[8]	40	244	+/– 6
			140	+/– 8
			86	+/– 10
Oral pain	[9]	45	251	+/– 6
			148	+/– 8
			91	+/– 10
Dysphagia	Preliminary literature review	54	252	+/– 6
			139	+/– 8
			93	+/– 10
Chronic GVHD	[10]	7-54	62-252	+/– 6
Dysgeusia	Preliminary study	38	246	+/– 6
			133	+/– 8
			88	+/– 10
Oral viral	[11]	43	254	+/– 6
			148	+/– 8
			93	+/– 10
Oral fungal	[12]	38	252	+/– 6
			142	+/– 8
			91	+/– 10

Adjusted differences in means or adjusted odds ratios and corresponding confidence intervals will be calculated to represent measures of association. Analyses will be performed with the SAS Enterprise Guide version 6.1 (SAS Institute Inc, Cary, North Carolina, USA).

Sample Size

The primary aim of the study is to establish the nature, incidence and temporal relationship of oral complications related to conditioning regimen. The source of the expected incidences is included in Table 1. These samples sizes were determined with alpha of .05 and differing levels of acceptable absolute precision. The range of sample size estimates for the various oral complications ranged from 62-254 depending on the incidence estimate and precision level. Using the most conservative estimate, a total of 254 patients will need to be assessed for oral complications during stem cell transplantation to obtain 6% precision for the main oral complications listed in Table 1. Thus, to account for participants that do not make it to stem cell transplant (approximately 10%) and to ensure sufficient patients are assessed to allow for differences in enrollment sites, we will enroll up to 320 patients. The present study is a prospective, observational registry, with no interventional component. We anticipate that there will be differences in approach to oral prevention and management protocols per treatment center. This will provide an opportunity to describe the impact of different management regimens on Ora-Stem outcomes. The study was not originally powered for these differences; thus, this data may be more preliminary in nature, but still provide a robust dataset to explore differences in enrollment sites.

Results

To date, 91% of a targeted number of participants have been enrolled with 233 participants receiving an HSCT. We anticipate enrollment of at least 20-30 additional participants to ensure 254 enrolled patients receive a HSCT, which will be completed by June 2018.

A preliminary analysis completed October 30, 2017 of 222 enrolled participants demonstrated the most common medical diagnoses managed with HSCT included: multiple myeloma=34%; acute myelogenous leukemia=22%; lymphoma=15%, and acute lymphocytic leukemia=6% with 53% managed by allogeneic transplantation. Preliminary assessment of oral complications demonstrated approximately 32% of all participants experienced a grade 2 or higher mucositis during hospitalization and at least 39% of allogeneic HSCT patients have developed oral GVHD (this is an underestimation as not all patients have completed a follow-up visit).

Discussion

Rationale

Numerous oral complications have been associated with cytotoxic therapies. To establish recommendations for pre-, interim-, and postcancer therapy management of oral problems in patients receiving high dose conditioning regimen and HSCT (autologous or allogeneic), an understanding of the scope of oral complications from HSCT must be established and be related to time after treatment and treatment regimen. The lack of clarity in this field is reflected in a lack of comprehensive and effective oral management regimens in the clinical arena. With a deeper understanding of oral complications, oral care regimens to minimize such complications can be appropriately formulated and evaluated. There is thus a pressing need to establish the nature, incidence and temporal relationship of oral complications related to conditioning therapies, as well as other types of chemo- and radiation therapies.

Limitations

To optimize the data quality and generalizability of the present study, a prospective, multicenter design was planned. Due to limitations in research infrastructure, it was not possible to consecutively enroll patients at every site. Although patients are not consecutively enrolled due to logistical limitations of enrollment of all possible patients; deliberate efforts to ensure high data quality from patients who were enrolled will allow for a robust dataset. We have also tracked and will report on all patients that could have been enrolled and the reason they were not enrolled. Additionally, the current study is observational in nature only and thus relies on institutional standard of care preventative and management protocols. This will allow for comparisons of the different treatment protocols between the enrollment sites. The design of this study is purposefully not an interventional study to allow for this comparison of standard of care protocols, thus definitive data on effectiveness of protocols will not be possible with this study design but will be instrumental in the design of future interventional studies.

Conclusions

The results of the ongoing prospective study will provide a unique dataset to understand the impact of oral complications on patients undergoing HSCT and provide needed information with forming more evidence-based guidelines regarding the management of this patient cohort.

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Authors' Contributions

MB and IvB conceived of the study, created its design, coordinated the study, and drafted the manuscript. BH, KGL and JEJ participated in the design of the study. All authors participated in study coordination and inclusion of patients per site. CM designed the data monitoring and statistical analyses. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Outcomes: Oral findings (complications) to be included in the study.

[PDF File (Adobe PDF File), 109KB - resprot_v7i4e103_app1.pdf]

Multimedia Appendix 2

Saliva samples for functional genomic studies.

[PDF File (Adobe PDF File), 20KB - resprot_v7i4e103_app2.pdf]

References

1. World Health Organization. 2005 URL: http://www.who.int/cancer/en/ [WebCite Cache ID 6qNlgNgeo]
2. Oral health in America: A report of the Surgeon General-Executive Summary. Rockville, MD: US Department of Health and Human Services, National Institute of Dental and Craniofacial Research, National Institutes of Health; 2000.
3. Institute of Medicine, Committee on Medicare Coverage Extensions. Future Directions. In: Field MJ , Lawrence RL , Zwanziger L , editors. Extending Medicare Coverage for Preventative Other Services. Washington, D.C: National Academy Press; 2000:127-140.
4. Dreizen S. Oral complications of cancer therapies. Description and incidence of oral complications. NCI Monogr 1990(9):11-15. [Medline: 2188148]
5. Brennan MT, Elting LS, Spijkervet FKL. Systematic reviews of oral complications from cancer therapies, Oral Care Study Group, MASCC/ISOO: methodology and quality of the literature. Support Care Cancer 2010 Aug;18(8):979-984. [doi: 10.1007/s00520-010-0856-3] [Medline: 20306090]
6. Brennan MT, Spijkervet FKL, Elting LS. Systematic reviews and guidelines for oral complications of cancer therapies: current challenges and future opportunities. Support Care Cancer 2010 Aug;18(8):977-978. [doi: 10.1007/s00520-010-0855-4] [Medline: 20217147]
7. Jontell M, Mattsson U, Torgersson O. MedView: an instrument for clinical research and education in oral medicine. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005 Jan;99(1):55-63. [doi: 10.1016/j.tripleo.2004.01.009] [Medline: 15599349]
8. Jensen SB, Pedersen AML, Vissink A, Andersen E, Brown CG, Davies AN, Salivary Gland Hypofunction/Xerostomia Section, Oral Care Study Group, Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. Support Care Cancer 2010 Aug;18(8):1039-1060. [doi: 10.1007/s00520-010-0827-8] [Medline: 20237805]
9. Epstein JB, Hong C, Logan RM, Barasch A, Gordon SM, Oberlee-Edwards L, et al. A systematic review of orofacial pain in patients receiving cancer therapy. Support Care Cancer 2010 Aug;18(8):1023-1031. [doi: 10.1007/s00520-010-0897-7] [Medline: 20544225]
10. Schubert MM, Correa MEP. Oral graft-versus-host disease. Dent Clin North Am 2008 Jan;52(1):79-109, viii. [doi: 10.1016/j.cden.2007.10.004] [Medline: 18154866]
11. Elad S, Zadik Y, Hewson I, Hovan A, Correa MEP, Logan R, Viral Infections Section, Oral Care Study Group, Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). A systematic review of viral infections associated with oral involvement in cancer patients: a spotlight on Herpesviridea. Support Care Cancer 2010 Aug;18(8):993-1006. [doi: 10.1007/s00520-010-0900-3] [Medline: 20544224]
12. Lalla RV, Latortue MC, Hong CH, Ariyawardana A, D'Amato-Palumbo S, Fischer DJ, Fungal Infections Section, Oral Care Study Group, Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). A systematic review of oral fungal infections in patients receiving cancer therapy. Support Care Cancer 2010 Aug;18(8):985-992 [FREE Full text] [doi: 10.1007/s00520-010-0892-z] [Medline: 20449755]
13. National Cancer Institute. Common terminology criteria for adverse events (CTCAE). Version 3.0 ed. Bethesda, MD: Cancer Therapy Evaluation Program; 2003.

14. WHO Expert Committee on Cancer Pain Relief and Active Supportive Care. Cancer pain relief and palliative care: report of a WHO expert committee [meeting held in Geneva from 3 to 10 July 1989]. In: Report No. 804. Geneva: World Health Organization; 1990.
15. Colevas AD, Setser A. The NCI Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 is the new standard for oncology clinical trials. JCO 2004 Jul 15;22(14_suppl):6098-6098. [doi: 10.1200/jco.2004.22.90140.6098]
16. Epstein JB, Phillips N, Parry J, Epstein MS, Nevill T, Stevenson-Moore P. Quality of life, taste, olfactory and oral function following high-dose chemotherapy and allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2002 Dec;30(11):785-792 [FREE Full text] [doi: 10.1038/sj.bmt.1703716] [Medline: 12439702]
17. World Health Organization. WHO handbook for reporting results for cancer treatment. In: Report No. 48. Geneva: World Health Organization; 1979.
18. Sonis ST, Oster G, Fuchs H, Bellm L, Bradford WZ, Edelsberg J, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol 2001 Apr 15;19(8):2201-2205. [doi: 10.1200/JCO.2001.19.8.2201] [Medline: 11304772]
19. Stiff PJ, Erder H, Bensinger WI, Emmanouilides C, Gentile T, Isitt J, et al. Reliability and validity of a patient self-administered daily questionnaire to assess impact of oral mucositis (OM) on pain and daily functioning in patients undergoing autologous hematopoietic stem cell transplantation (HSCT). Bone Marrow Transplant 2006 Feb;37(4):393-401. [doi: 10.1038/sj.bmt.1705250] [Medline: 16415901]

Abbreviations

HSCT: hematopoietic stem cell transplant
GVHD: graft-vs-host disease
QOL: quality of life

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Protocol

Identifying Subgroups of Patients With Chronic Nonspecific Low Back Pain Based on a Multifactorial Approach: Protocol For a Prospective Study

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Abstract

Background: Low back pain, especially nonspecific chronic low back pain (LBP), the leading cause of disability worldwide, represents both social and economic problems. Different therapeutic management techniques can be used, but their effects vary. Clinicians and researchers attribute the variation in the efficacy of therapeutic and management techniques to the heterogeneity of the nonspecific chronic low back pain population, and they agree that nonspecific chronic LBP must be subgrouped.

Objective: This study aims to identify nonspecific chronic LBP subgroups based on a multifactorial approach, including biomechanical, physical, and psychosocial data.

Methods: A total of 100 nonspecific chronic LBP patients and 30 healthy participants aged between 18 and 60 years will be recruited for this prospective study. A psychosocial profile will be established using questionnaires on anxiety, depression, functional disability, pain, fear of pain, avoidance belief, and physical activity. A physical capacity evaluation will be conducted. It will evaluate flexibility of the hips, lumbar spine, and lateral thoracolumbar segment, as well as trunk (extensor and flexor) muscle endurance. The subjects will perform functional daily life activities, such as walking, object lifting, forward bending, sit-to-stand, stand-to-sit, balance, and usual postures. Full body kinematics, kinetics, and surface electromyography of the trunk and hip muscles will be assessed during these tasks. The clustering classification methods for the statistical analysis will be determined according to the data and will be used to identify the subgroups of nonspecific chronic LBP patients.

Results: Data collection started in September 2017 and will be completed with the inclusion of all the participants (100 nonspecific chronic LBP and 30 control). The study results will be published in peer-reviewed journals and presented at relevant international conferences.

Conclusions: Numerous studies have showed that the therapeutic management of nonspecific chronic LBP is difficult and has inconstant effects caused by the complexity and heterogeneity of nonspecific chronic LBP. Identifying subgroups with a multifactorial approach is more comprehensive and closer to the pathophysiology of nonspecific chronic LBP. It also represents

benefit interests and a challenge both clinically and socially. The perspective of this study is expected to support clinicians for a more adapted therapeutic management for each subgroup.

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KEYWORDS

low back pain; chronic pain; activities of daily living; psychology; electromyography; biomechanical phenomena; classification

Introduction

Background

Low back pain (LBP) has been the leading cause of disability worldwide since 1990 [1] and has a lifetime prevalence of 84% in industrialized countries [2]. LBP is defined as pain and discomfort of varying duration. It is localized below the costal margin and above the inferior gluteal folds, with or without irradiation in the lower limb [3]. LBP is considered chronic when pain duration exceeds 3 months [4,5] and accounts for 10% of the cases and represents 70% to 90% of the total LBP cost [6]. A recent study reported that chronic LBP treatment in the United States costs between US $85 and US $238 billion annually [7]. In Switzerland, chronic LBP costs between 1.6 and 2.3 of the gross domestic product [8]. In France, chronic LBP is one of the costliest diseases with 6-month direct costs of US $ 884,85 per patient [9]. Furthermore, the World Health Organization recently reported that chronic LBP is one of the major causes of professional health-related absences [10]. Therefore, chronic LBP represents a significant worldwide problem with major medical, social, and economic impact.

Knowledge on the LBP pathophysiology is not sufficient. A precise diagnosis can only be obtained in 10%-15% of the cases [11,12]. Therefore, LBP is mostly categorized as nonspecific. Nonspecific LBP is a constellation of symptoms not attributable to a known specific pathology (ie, infection, tumor, osteoporosis, fracture, structural deformity, inflammatory disorder [eg, ankylosing spondylitis], radicular syndrome, and cauda equina syndrome) [2,11,13,14]. In addition, pathologies that are known as possible causes of pain (eg, osteoarthritis, disc disease, or cracked discs) do not explain the onset of symptoms on their own due to a similar prevalence of these pathologies being found in asymptomatic subjects [2,15].

Nonspecific chronic LBP results from a variety of factors which can interact with each other. These include biomechanical, psychosocial, physical, environmental, genetic, and cultural factors [2]. The diversity of these factors and the complexity of their interactions could explain the difficulty in establishing a specific etiology of nonspecific chronic LBP. In the absence of a clear diagnosis, physicians face a therapeutic challenge caused by the large number of available treatments (eg, drugs, physiotherapy, physical exercise), for which the overall effect is small to moderate [16]. The poor efficiency of the available treatments is attributed to the heterogeneity of nonspecific chronic LBP patients [17]. Therefore, identifying nonspecific chronic LBP patient subgroups is essential [18] and will help optimize therapeutic management [19-22]. The need for nonspecific chronic LBP patient subgroups was highlighted by 84% of primary care clinicians on a large-scale survey [18].

Prior Work

Numerous differences between nonspecific chronic LBP patients and healthy subjects were reported using various clinical features. Regarding genetic factors, some studies have reported that genes result in a predisposition to intervertebral disc degeneration [23] or can alter pain perception [24]. Psychological factors, such as pain catastrophyzing, are altered in nonspecific chronic LBP patients and can influence physical performance [25]. In terms of physical capacities, the nonspecific chronic LBP population presented with reduced endurance and higher fatigability of the trunk extensor muscles [26] and lower hip and lumbar flexibility, correlating with nonspecific chronic LBP severity [27]. With regards to biomechanical factors, nonspecific chronic LBP patients exhibited kinematic and muscle activity impairments [28,29]. When compared to healthy subjects, nonspecific chronic LBP patients showed decreased pelvis rotation during gait [29] and an increased stiffness of the spino-pelvic complex [30]. Moreover, nonspecific chronic LBP patients presented with decreased maximum range of motion and velocity between the lumbar spine and the hips during the sit-to-stand (STS) task [31] associated with stiffer spine movements [32]. Meanwhile, during the lifting task, they used different kinematic strategies, especially in lift speed and hip and knee flexion [33] and presented with less variability in kinematic patterns [34]. Alterations were also found in the trunk and hip muscle surface electromyography (sEMG). Nonspecific chronic LBP subjects presented with higher global trunk muscle activity during gait [35] or lifting tasks [36]. Many studies highlighted an exacerbated lumbar erector spinae activity (absence of the flexion-relaxation phenomenon) at full trunk forward flexion [37-39].

Nonspecific chronic LBP patient subgroups have previously been identified based on biomechanical parameters. Slaboda et al [40] identified 2 subgroups based on lift kinematic patterns, whereas Dankearts et al [20] discriminated 2 subgroups based on sitting posture. They also discriminated the subgroups on trunk muscle activity, posture, and movement [20,41], which make the biomechanical analysis of nonspecific chronic LBP patients relevant for a better understanding of this pathology and could help to discriminate different subgroups.

However, identifying subgroups only from a biomechanical analysis is not comprehensive enough due to the emotional and behavioral consequences of pain, which contributes to the persistence of pain and treatment outcomes, and due to the multi-factorial features of nonspecific chronic LBP [42]. Anxiety and depression play a major role in pain chronicity in nonspecific chronic LBP patients [43]. Psychosocial parameters have also been observed to influence kinematic and muscle activities. Indeed, a high level of pain catastrophizing was

associated with a decrease in the activation time of the spinal muscle (multifidus) in LBP patients during forward bending [44] and a lower performance time in the trunk extensor endurance test [25]. Lamoth et al [45] showed that the fear of pain altered muscle activity during gait, with a decrease of the erector spinae sEMG mean amplitude. Thus, the identification of the nonspecific chronic LBP subgroups should be based on the multifactorial parameters (ie, biomechanical, physical, and psychosocial data) linked to nonspecific chronic LBP.

Aim

This study aims to identify the subgroups of nonspecific chronic LBP patients based on a multifactorial approach, including biomechanical, physical, and psychosocial data.

Methods

Study Design

This is a prospective study approved by the Research Ethic Cantonal Commission of the University Hospitals of Geneva (HUG) with reference CER: 14-126. All study data and human material will be handled confidentially and coded with a unique study number. Only the research team will have access to the data.

Participants

The study population consists of 18- to 60-year old adults from the Geneva area and is divided into 2 groups, namely patients suffering from nonspecific chronic LBP (LBP group) and healthy participants (control group). Both groups will be evaluated in the Willy Taillard Laboratory of Kinesiology of the HUG. Patients will be recruited from the Division of Rheumatology and the Division of Orthopaedic and Trauma Surgery of the HUG.

The patient inclusion criteria are as follows; (1) suffering from nonspecific chronic LBP, (2) duration of at least 3 months, (3) pain intensity over 3/10 on a visual analogical scale, (4) aged between 18 and 60 years, (5) no pain on other parts of the body (except irradiation of nonspecific chronic LBP), and (6) no specific pathology such as infection, tumor, osteoporosis, fracture, structural deformity, inflammatory disorder (eg, ankylosing spondylitis), radicular syndrome, and cauda equina syndrome. The healthy participant inclusion criteria are as follows; (1) aged between 18 and 60 years, (2) no back pain for at least 6 months, and (3) no pain in any part of the body.

The subjects who present with a history of back surgery, a body mass index over 30 kg/m^2, inability to understand French, and pregnancy will be excluded from both groups. All participants included in our study will provide written informed consent to participate.

Sample Size

The sample size calculation was computed using GPower software (Heinrich Heine University, Dusseldorf, Germany) [46]. This calculation was based on previous studies which identified 2 nonspecific chronic LBP subgroups from sEMG and posture variables. Dankaerts et al [20] found greater lumbar multifidus activity during slumped sitting among the control group (n=34), pooled nonspecific chronic LBP group (n=33), and within 2 subgroups of nonspecific chronic LBP (n=20 and n=13). Meanwhile, Astfalck et al [47] found a difference between the upper lumbar angle in the sitting posture of the control group (n=28) and the 2 nonspecific chronic LBP subgroups (n=13 and n=15). The number of participants per group should be between 17 to 21 for comparison with healthy participants and between 27 to 32 for each nonspecific chronic LBP subgroup for differentiation between 2 and 3 subgroups with a statistic power up to 80% and a 5% alpha error. Therefore, we will include 100 nonspecific chronic LBP patients and 30 healthy participants.

Data Collection

Task Description

The International Classification of Functioning (ICF) defines the typical spectrum of problems in the functioning of patients with LBP and highlights the main areas and functions of interest in the study of LBP [48]. On the basis of the short version of ICF [49], the physical capacities of the patient will be assessed by assessing the flexibility of the hips in flexion and extension, the lumbar spine in flexion, the thoracolumbar segment in lateral flexion, and the trunk extensor and flexor muscle endurance. Functional abilities will be assessed from daily life activities such as gait, object lifting, forward bending, STS (and the reverse), balance, and usual posture (standing and sitting). Kinematics, kinetics, and sEMG will be assessed during the execution of these functional tasks.

Trunk Muscle Endurance

The Sorensen test, which is considered as the gold standard for this measure [50], will be performed to determine trunk extensor endurance [51,52]. The participants will lie on the examining table in a prone position with the upper edge of their iliac crests' aligned along the edge of the table. The lower body will be fixed to the table by 3 straps located at the level of the pelvis, knees, and ankles. Meanwhile, the Shirado test will be performed to determine trunk flexor endurance [53]. The participants will lie on the examining table in a supine position and will raise their lower extremities until their scapulas' are off the table with a 90° flexion of the hip and knee joints. These tests are considered valid, safe, reliable, and easy to perform in participants with and without nonspecific chronic LBP [54,55]. Participants' arms are folded across the chest for the duration of both trunk muscle endurance tests. Note that the participants will be asked to hold the original positions for as long as possible, but not exceeding a 240 s time limit. A 15 min rest is allowed between the two endurance tests.

Trunk and Hip Flexibility

The hip and trunk muscles flexibility in the nonspecific chronic LBP population will be evaluated using the straight leg raise test, the Thomas test, and the finger-tip-to-thigh test. These are valid, reliable, and largely used tests. The tests will assess hamstring flexibility [17,56-58], hip flexor flexibility (psoas-iliacus and rectus femoris) [59-62], and measure the lateral trunk range of motion [63,64]. All flexibility tests will be performed according to the methods set out by Norkin and White [65].

Balance

Participants' balance in standing and sitting postures will be evaluated. For the sitting condition which limits the influence of the lower limb, the participants will be seated on an adjustable stool with the middle of the thighs on the edge of the stool and with their feet dangling. For the standing posture, the participants will stand with 10 cm between their heels and a self-selected angle between the feet [66]. For both postures, the participants must make sure their trunk is erect, fix their head in a neutral position, look ahead, keep arms along the trunk, and move as little as possible. The participants will stand on a force plate and their balance will be assessed under 4 conditions with 3 repeated trials of 30 s per condition. The conditions under which the balance of the participant will be assessed are eyes closed or opened, with stable or unstable support. To create the unstable support an Airex balance pad (50 cm length × 41 cm width × 6 cm thickness) will be used. The condition with the eyes closed are used to avoid visual compensations [67] and unstable conditions are used to challenge the participants' balance [68].

Usual Postures

The usual sitting and standing postures of each participant will be evaluated. For the sitting posture evaluation, an adjustable stool will be placed on a force plate and the participants will be asked to be seated in a self-selected position with their feet on another force plate. The stool height will be adjusted for each participant to fix the hip and knee flexion at 90°. For the usual standing posture evaluation, the participants will be asked to stand in a self-selected upright position with both feet on the same force plate. For both these usual static postures, the participants will look ahead, and the kinematic will be recorded for 10 s in the posture.

Gait

The participants will be asked to walk barefoot at 3 different speeds (ie, self-selected, fast, and slow) along a 10 m walkway to assess their gait. Data will be collected for at least 10 gait cycles for each participant and the speed will be monitored.

Lifting Task

Two lifting tasks will be performed. For both tasks, the participants will start on a force plate in an upright standing position, bend down to lift a box and return to an upright standing position with 90° flexion of elbows holding the box. They will maintain this posture for 4 s, and then bend down to place the box to the ground before returning to the initial posture. This test will be performed under two conditions. The first condition is a usual lift, where the participants are asked to lift the box with a self-selected strategy, and no more instruction will be given [69]. The second condition is a standardized lift based on deadlift methods [70]. This will be used to compare the muscle strategies for the same movement between the subjects. The usual lift will be performed before the standardized lift to avoid behavioral adaptations.

Three trials will be performed per condition with 2 min rest between each condition. The weight of the box will be adjusted to 10% of the participant's weight for each condition. The participant will be instructed to stay on the force plate for the duration of the test.

Trunk Forward Bending

The participants will start standing in an upright position (standing phase), flex the trunk as far forward as possible with their knees extended (flexion phase), maintain this trunk full-flexion position (full flexion phase), and then return to an upright standing position (extension phase). Each phase will last for 4 s, and an audible metronome will be used to regulate the movement timing. Three trials will be performed, and only the second trial will be used for analysis [71].

Sit-to-Stand

The STS tasks will be performed under the following three conditions: (1) usual STS, (2) standardized STS, and (3) 5 consecutive STSs. In the usual condition, the participants will sit in a self-selected position on a stool placed on a force plate with their feet placed on another force plate. No more instructions on posture will be given for this condition. In the standardized STS, the participants will be barefoot and asked to sit upright on an adjustable stool with their trunk straight and arms crossed on the chest. The stool will be placed on a force plate, the participant's feet will be placed on a second force plate, and the stool height will be adjusted for each participant to fix the hip and knee flexion at 90° in the starting position.

For both the usual STS and standardized STS, the participants will stand up after 4 s of sitting, maintain the upright standing position with knees fully extended for 4 s, return to the initial sitting position, and maintain it for 4 s. Three trials will be performed for both the STS and standardized STS tasks.

The 5 consecutive STS task provides information on the global capacity of the participant to perform the STS task. The participants will have the same start position as the standardized STS task. The participants will then be asked to perform 5 consecutive STS movements as fast as possible. As a precautionary measure, an investigator will stand near the participant to prevent possible falls. To evaluate the total task duration, the start and end points of the task will be defined by the mean value of the anterior-posterior center of the pressure displacement during the usual sitting phase before and after the task was completed [72].

Psychosocial Profile

The psychosocial profile will be explored using patient-reported outcomes to evaluatef anxiety, depression, functional disability, fear of pain, avoidance belief, and physical activity (PA). All the questionnaires will be self-completed before the experiments, except for the PA questionnaire which will be completed by the investigator with the participant during the course of the experiments.

Anxiety and Depression

Anxiety and depression are parameters which play an important role in the sustainability of pain; hence, they are factors of pain chronicity [42]. The Hospital Anxiety and Depression Scale (HADS) [73] is widely used to evaluate mental disorders [74] in the LBP population [75]. This study will use the French version of the HADS introduced by Lépine et al [76], which

has been used in other studies conducted on French-speaking populations [77-79].

Functional Capacity

The functional capacity evaluation is recommended when studying LBP [80]. Functional capacity is indeed an interesting parameter to evaluate the interference of pain on daily life [81]. One of the most used and recognized assessment tools is the Oswestry Disability Questionnaire (ODI) [82], which is specific for LBP [83]. The French validated version of the ODI [84] will be used for this study.

Pain Catastrophizing

A systematic review shows that pain catastrophizing can predict the degree of pain, disability, and mediated treatment efficacy in the nonspecific chronic LBP population [85]. The pain catastrophizing scale (PCS) was introduced by Sullivan et al [86], and his validated French version [87] will be used for this study.

Fear and Belief

Fear avoidance beliefs are reported to be factors for the delayed recovery and chronicity of pain in the nonspecific chronic LBP population [88]. One of the questionnaires used to identify fear avoidance beliefs is the Fear Avoidance Beliefs Questionnaire (FABQ) [89]. This study will use the French version of the FABQ validated by Chaory et al [90].

Physical Activity

PA plays an important role in the prevention of nonspecific chronic LBP. The participant's weekly PA will be assessed using the Global Physical Activity Questionnaire (GPAQ) developed by the World Health Organization [91]. This questionnaire has already been used in studies on the nonspecific chronic LBP population [92].

Pain

Pain is a key symptom in nonspecific chronic LBP, therefore, its evaluation during the course of the study is recommended [49,93]. The intensities of current pain, pain in the last 24 h, pain in the last week, pain in the last month, and pain in the last 3 months will be quantified with a visual analogue scale largely used in the nonspecific chronic LBP population [29,94-96].

Materials and Parameters

Electromyographic Activity

The sEMG will be bilaterally collected from 3 back muscles (ie, lumbar multifidus, iliocostalis lumborum, and lumbar erector spinae), 2 abdominal muscles (ie, transverse fibers of the abdominal external oblique and rectus abdominus), gluteus medius, semitendinosus, and the rectus femoris muscle. Moreover, 16 active surface electrodes (model: Trigno, Delsys Inc, Boston, MA, USA) will be used to collect the sEMG signals at a sampling frequency of 1000 Hz. The skin at the electrode sites will be shaved, abraded, and cleaned with alcohol prior to measurement. The electrodes will then be positioned relative to the muscle fiber direction, following the surface EMG for noninvasive assessment of muscles project recommendations [97].

The sEMG activation pattern, time of cocontraction (TCC), and cocontraction index (CCI) [98] will be calculated for gait, STS, and lift tasks. The TCC is the time for simultaneous activation of a pair of muscle groups over a specified number of data points (activation thresholdbaseline+3 SD; duration activity threshold: 5 ms) [99]. The CCI is defined as the degree of coactivation for a pair of muscle groups over a specified number of data points. The TTC and CCI will characterize muscle coordination. The flexion-relaxation ratio will be calculated and used to detect and quantify exacerbated back muscle activity for trunk forward bending [71]. The muscle fatigability of the back and abdomen muscles will be evaluated using the sEMG median frequency evolution during endurance tasks [100].

Kinematics

The kinematic parameters will be recorded using a 12-camera motion analysis system (Oqus7+, Qualisys, Göteborg, Sweden) set at a sampling frequency of 100 Hz. The participants will have 35 reflective markers (14 mm diameter) placed on the skin at defined anatomical and technical landmarks on the head, trunk, and pelvis and bilaterally on the arms, thighs, shanks, and feet according to the full-body Plug-in-Gait model [101]. Additional markers will be placed on the spinous process of T2, T4, T6, T8, L1, L3, L5, and S1 to assess the sagittal plane curve of the spine [102,103].

The thorax, lumbar, pelvis, hip, knee, and ankle kinematics (maximum angle, range of motion, and speed) will be calculated in 3 planes for all tasks. The lumbar/hip ratio will be calculated for the trunk forward bending, STS, and lift tasks [104,105]. The relative phase between the pelvis and the thorax segment and the spatiotemporal parameters (ie, walking speed, cadence, stance phase, and step length) will be calculated during gait [106]. The thorax movement during the balance tasks will characterize the trunk sway [107].

Kinetics

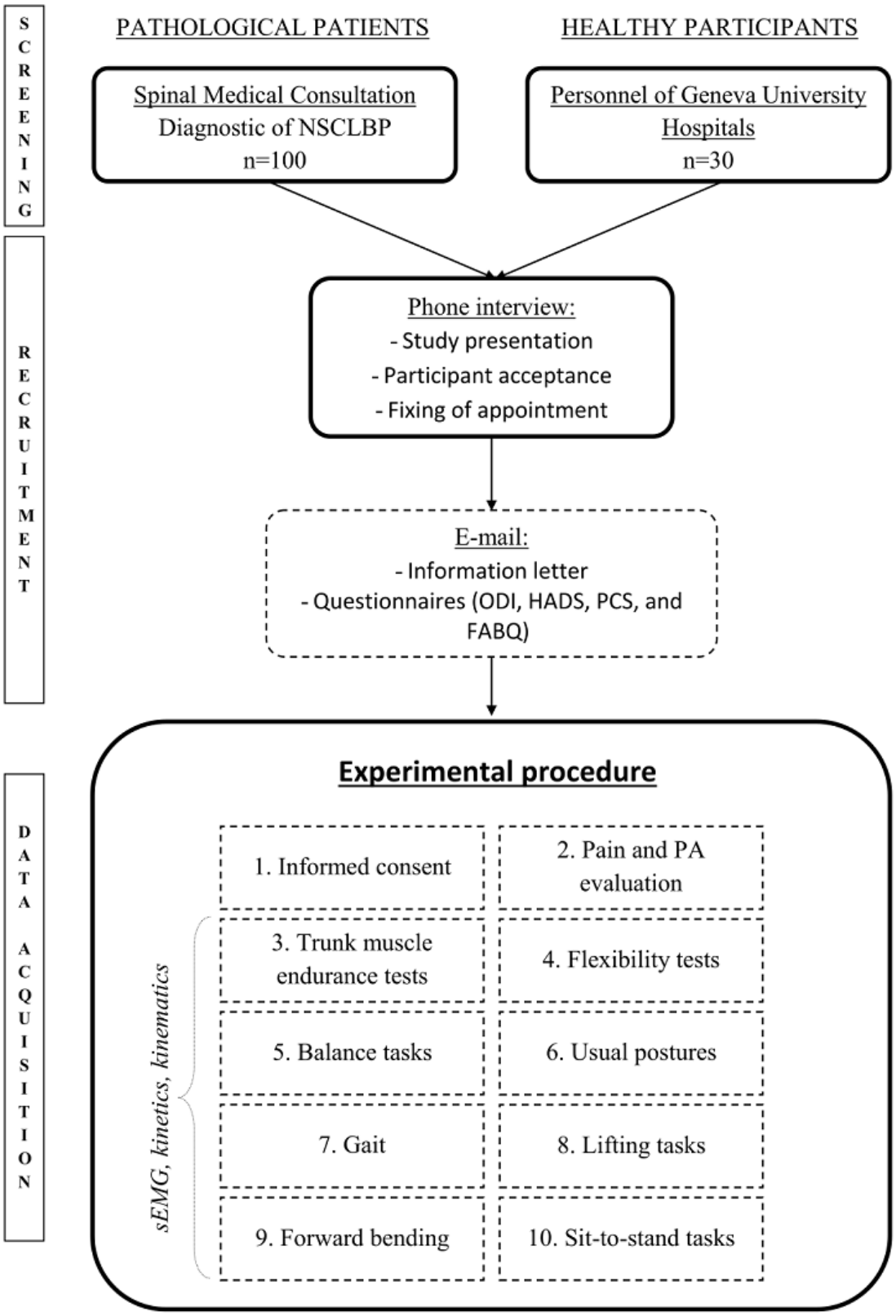
Two force plates (AMTI Accugait, Watertown, NY, USA) at a sampling frequency of 1000 Hz will be used to measure the ground reaction forces. The center of pressure displacement (range and speed) will be calculated for the balance tasks to assess the balance capacity [68,108,109]. All kinetic, kinematic, and sEMG data will be synchronized together.

Experimental Procedure

To introduce the study, a phone interview will be conducted by the investigator after nonspecific chronic LBP is diagnosed by a spinal consultant. An information letter will be sent to the patient (by email or post) once he/she agrees to voluntarily participate in this study. An appointment time will then be scheduled. Upon arrival, the participants will complete the HADS, ODI, and PCS questionnaires. The GPAQ and Pain Evaluation will be completed by the investigator during the interview with the participant. All sEMG sensors will be placed after skin preparation as outlined above. The participants will then perform the flexor endurance, extensor endurance, and flexibility tests. Next, the reflective markers will be placed, and the participants will perform the functional tasks in the order listed above with a minimum rest period of 3 min between each task. A pain assessment will be made after each task to quantify

the pain generated by the task, using current pain as a reference. The total duration of this protocol (Figure 1) will be 120 min per participant.

Figure 1. Flow diagram of the study. FABQ: fear-avoidance belief questionnaire; HADS: Hospital Anxiety and Depression Scale; NSCLBP: nonspecific chronic low back pain; ODI: Oswestry Disability Index; PA: physical activity; PCS: pain catastrophizing scale; sEMG: surface electromyography.



Data Analysis

The joint kinematics and kinetics data will be computed using Visual3D (C-Motion, Inc, Germantown, MD, USA). Data extraction will be performed using MATLAB R2015b (MathWorks, USA) and the open-source Biomechanical ToolKit package for MATLAB [110]. R software v.3.1.3 will be used for all statistical analyses. Data will be reduced with principal component analysis. Meanwhile, *K*-mean or descending hierarchical clustering classification methods will be used to identify the nonspecific chronic LBP subgroups. The clustering classification methods will be determined according to the data. In addition, a statistical inference test (parametric or nonparametric depending on the normality of the data distribution) will be applied to compare the nonspecific chronic LBP patients with healthy participants and to compare the different patient subgroups ($P<.05$).

Results

The data collection started in September 2017 and will be completed with the inclusion of all the participants (100 nonspecific chronic LBP patients and 30 controls). The study results will be published in peer-reviewed journals and presented at relevant international conferences.

Discussion

Principal Consideration

This study presents originality and the opportunity to connect large amounts of data about different features of various conditions with the same population sample. The results should allow for a better understanding of nonspecific LBP. The perspective of this study is expected to support clinicians for more adapted therapeutic management for each subgroup. Furthermore, this study could provide a reference protocol for functional tasks when nonspecific chronic LBP is studied.

Limitations

A limitation of this study could include missing data from the participant and/or to the materials used in the study. For example, a nonspecific chronic LBP patient may not be able to perform all the tasks required because of their functional capacity or pain level. An example of missing data from the study material could include the fact that surface EMG may contain artifacts that alter analysis of the muscle activity. Moreover, patients will be recruited from the Orthopedic and Rheumatology service of Geneva University Hospital, which limits generalization of the results to the global nonspecific chronic LBP population. Finally, because previous studies have found two nonspecific chronic LBP subgroups, three subgroups were used for the sample size calculation to ensure that at least two subgroups could be found, but more groups may be found in the clustering analysis.

Conclusions

Therapeutic management of nonspecific chronic LBP is rather difficult and has inconstant effects because of the complexity of nonspecific chronic LBP and the heterogeneity of nonspecific chronic LBP patients. Identifying subgroups in the nonspecific chronic LBP population represents benefit interests and a challenge both clinically and socially. This study aims to identify subgroups in nonspecific chronic LBP participants which include biomechanical, physical, and psychosocial factors to enhance the targeted therapy.

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Conflicts of Interest

None declared.

References

1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015 Aug 22;386(9995):743-800 [FREE Full text] [doi: 10.1016/S0140-6736(15)60692-4] [Medline: 26063472]
2. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. Lancet 2012 Feb 04;379(9814):482-491. [doi: 10.1016/S0140-6736(11)60610-7] [Medline: 21982256]
3. van Tulder M, Becker A, Bekkering T, Breen A, del Real MT, Hutchinson A, COST B13 Working Group on Guidelines for the Management of Acute Low Back Pain in Primary Care. Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. Eur Spine J 2006 Mar 15;15(Suppl 2):S169-S191 [FREE Full text] [doi: 10.1007/s00586-006-1071-2] [Medline: 16550447]
4. Andersson GB. Epidemiological features of chronic low-back pain. Lancet 1999 Aug 14;354(9178):581-585. [doi: 10.1016/S0140-6736(99)01312-4] [Medline: 10470716]
5. Koes BW, van Tulder M, Lin CC, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. Eur Spine J 2010 Dec;19(12):2075-2094 [FREE Full text] [doi: 10.1007/s00586-010-1502-y] [Medline: 20602122]

6. Waldburger M, Stucki RF, Balagué F, Wittig R. [Early multidisciplinary approach in lumbar pain to prevent development of chronicity]. Rev Med Suisse Romande 2001 Aug;121(8):581-584. [Medline: 11565220]
7. Ma VY, Chan L, Carruthers KJ. Incidence, prevalence, costs, and impact on disability of common conditions requiring rehabilitation in the United States: stroke, spinal cord injury, traumatic brain injury, multiple sclerosis, osteoarthritis, rheumatoid arthritis, limb loss, and back pain. Arch Phys Med Rehabil 2014 May;95(5):986-95.e1 [FREE Full text] [doi: 10.1016/j.apmr.2013.10.032] [Medline: 24462839]
8. Wieser S, Horisberger B, Schmidhauser S, Eisenring C, Brügger U, Ruckstuhl A, et al. Cost of low back pain in Switzerland in 2005. Eur J Health Econ 2011 Oct 12;12(5):455-467 [FREE Full text] [doi: 10.1007/s10198-010-0258-y] [Medline: 20526649]
9. Depont F, Hunsche E, Abouelfath A, Diatta T, Addra I, Grelaud A, et al. Medical and non-medical direct costs of chronic low back pain in patients consulting primary care physicians in France. Fundam Clin Pharmacol 2010 Feb;24(1):101-108. [doi: 10.1111/j.1472-8206.2009.00730.x] [Medline: 19678853]
10. Jäger M, Griefhan B, Luttman A. World Health Organization. 2004. La prévention des troubles musculo-squelettiques sur le lieu de travail URL: http://www.who.int/occupational_health/publications/en/pwh5f.pdf [accessed 2018-03-22] [WebCite Cache ID 6y6hsxmFQ]
11. Deyo RA, Weinstein JN. Low back pain. N Engl J Med 2001 Feb 01;344(5):363-370. [doi: 10.1056/NEJM200102013440508] [Medline: 11172169]
12. Krismer M, van Tuldor M, Low Back Pain Group of the BoneJoint Health Strategies for Europe Project. Strategies for prevention and management of musculoskeletal conditions. Low back pain (non-specific). Best Pract Res Clin Rheumatol 2007 Feb;21(1):77-91. [doi: 10.1016/j.berh.2006.08.004] [Medline: 17350545]
13. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, COST B13 Working Group on Guidelines for Chronic Low Back Pain. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. Eur Spine J 2006 Mar;15 Suppl 2:S192-S300 [FREE Full text] [doi: 10.1007/s00586-006-1072-1] [Medline: 16550448]
14. Chiarotto A, Deyo RA, Terwee CB, Boers M, Buchbinder R, Corbin TP, et al. Core outcome domains for clinical trials in non-specific low back pain. Eur Spine J 2015 Jun;24(6):1127-1142. [doi: 10.1007/s00586-015-3892-3] [Medline: 25841358]
15. Waddell G. The Back Pain Revolution. London: Churchill Livingstone; 2004:1-948.
16. Balagué F, Ochoa Amaya G, Genevay S. [Conservative treatment of chronic low back pain: what is new in 2008?]. Rev Med Suisse 2009 Mar 11;5(194):560-2, 564. [Medline: 19405270]
17. Hayden JA, Cartwright JL, Riley RD, Vantulder MW, Chronic Low Back Pain IPD Meta-Analysis Group. Exercise therapy for chronic low back pain: protocol for an individual participant data meta-analysis. Syst Rev 2012 Dec 21;1:64 [FREE Full text] [doi: 10.1186/2046-4053-1-64] [Medline: 23259855]
18. Kent P, Keating J. Do primary-care clinicians think that nonspecific low back pain is one condition? Spine (Phila Pa 1976) 2004 May 01;29(9):1022-1031. [Medline: 15105677]
19. Leboeuf-Yde C, Lauritsen JM, Lauritzen T. Why has the search for causes of low back pain largely been nonconclusive? Spine (Phila Pa 1976) 1997 Apr 15;22(8):877-881. [Medline: 9127921]
20. Dankaerts W, O'Sullivan P, Burnett A, Straker L. Altered patterns of superficial trunk muscle activation during sitting in nonspecific chronic low back pain patients: importance of subclassification. Spine (Phila Pa 1976) 2006 Aug 01;31(17):2017-2023. [doi: 10.1097/01.brs.0000228728.11076.82] [Medline: 16924221]
21. Kent P, Keating JL, Leboeuf-Yde C. Research methods for subgrouping low back pain. BMC Med Res Methodol 2010 Jul 03;10:62 [FREE Full text] [doi: 10.1186/1471-2288-10-62] [Medline: 20598153]
22. Billis E, McCarthy CJ, Roberts C, Gliatis J, Papandreou M, Gioftsos G, et al. Sub-grouping patients with non-specific low back pain based on cluster analysis of discriminatory clinical items. J Rehabil Med 2013 Feb;45(2):177-185 [FREE Full text] [doi: 10.2340/16501977-1100] [Medline: 23321847]
23. Kalichman L, Hunter DJ. The genetics of intervertebral disc degeneration. Familial predisposition and heritability estimation. Joint Bone Spine 2008 Jul;75(4):383-387. [doi: 10.1016/j.jbspin.2007.11.003] [Medline: 18448379]
24. Reimann F, Cox JJ, Belfer I, Diatchenko L, Zaykin DV, McHale DP, et al. Pain perception is altered by a nucleotide polymorphism in SCN9A. Proc Natl Acad Sci U S A 2010 Mar 16;107(11):5148-5153 [FREE Full text] [doi: 10.1073/pnas.0913181107] [Medline: 20212137]
25. Larivière C, Bilodeau M, Forget R, Vadeboncoeur R, Mecheri H. Poor back muscle endurance is related to pain catastrophizing in patients with chronic low back pain. Spine (Phila Pa 1976) 2010 Oct 15;35(22):E1178-E1186. [doi: 10.1097/BRS.0b013e3181e53334] [Medline: 20881658]
26. Demoulin C, Crielaard JM, Vanderthommen M. Spinal muscle evaluation in healthy individuals and low-back-pain patients: a literature review. Joint Bone Spine 2007 Jan;74(1):9-13. [doi: 10.1016/j.jbspin.2006.02.013] [Medline: 17174584]
27. Radwan A, Bigney KA, Buonomo HN, Jarmak MW, Moats SM, Ross JK, et al. Evaluation of intra-subject difference in hamstring flexibility in patients with low back pain: an exploratory study. J Back Musculoskelet Rehabil 2014 Jun 24. [doi: 10.3233/BMR-140490] [Medline: 24968796]
28. Laird RA, Gilbert J, Kent P, Keating JL. Comparing lumbo-pelvic kinematics in people with and without back pain: a systematic review and meta-analysis. BMC Musculoskelet Disord 2014 Jul 10;15:229 [FREE Full text] [doi: 10.1186/1471-2474-15-229] [Medline: 25012528]

29. Müller R, Ertelt T, Blickhan R. Low back pain affects trunk as well as lower limb movements during walking and running. J Biomech 2015 Apr 13;48(6):1009-1014. [doi: 10.1016/j.jbiomech.2015.01.042] [Medline: 25700607]
30. Lamoth CJ, Meijer OG, Daffertshofer A, Wuisman PI, Beek PJ. Effects of chronic low back pain on trunk coordination and back muscle activity during walking: changes in motor control. Eur Spine J 2006 Jan;15(1):23-40 [FREE Full text] [doi: 10.1007/s00586-004-0825-y] [Medline: 15864670]
31. Shum GL, Crosbie J, Lee RY. Effect of low back pain on the kinematics and joint coordination of the lumbar spine and hip during sit-to-stand and stand-to-sit. Spine (Phila Pa 1976) 2005 Sep 01;30(17):1998-2004. [Medline: 16135992]
32. Christe G, Redhead L, Legrand T, Jolles BM, Favre J. Multi-segment analysis of spinal kinematics during sit-to-stand in patients with chronic low back pain. J Biomech 2016 Dec 05;49(10):2060-2067. [doi: 10.1016/j.jbiomech.2016.05.015] [Medline: 27262182]
33. Rudy TE, Boston RJ, Lieber SJ, Kubinski JA, Stacey BR. Body motion during repetitive isodynamic lifting: a comparative study of normal subjects and low-back pain patients. Pain 2003;105(1):319-326. [doi: 10.1016/S0304-3959(03)00247-1]
34. Seay JF, Sauer SG, Frykman PN, Roy TC. A history of low back pain affects pelvis and trunk mechanics during a sustained lift/lower task. Ergonomics 2013;56(6):944-953. [doi: 10.1080/00140139.2013.781234] [Medline: 23586619]
35. Ghamkhar L, Kahlaee AH. Trunk muscles activation pattern during walking in subjects with and without chronic low back pain: a systematic review. PM R 2015 May;7(5):519-526. [doi: 10.1016/j.pmrj.2015.01.013] [Medline: 25633636]
36. Falla D, Gizzi L, Tschapek M, Erlenwein J, Petzke F. Reduced task-induced variations in the distribution of activity across back muscle regions in individuals with low back pain. Pain 2014 May;155(5):944-953. [doi: 10.1016/j.pain.2014.01.027] [Medline: 24502841]
37. Geisser ME, Ranavaya M, Haig AJ, Roth RS, Zucker R, Ambroz C, et al. A meta-analytic review of surface electromyography among persons with low back pain and normal, healthy controls. J Pain 2005 Nov;6(11):711-726. [doi: 10.1016/j.jpain.2005.06.008] [Medline: 16275595]
38. Kim MH, Yoo WG, Choi BR. Differences between two subgroups of low back pain patients in lumbopelvic rotation and symmetry in the erector spinae and hamstring muscles during trunk flexion when standing. J Electromyogr Kinesiol 2013 Apr;23(2):387-393. [doi: 10.1016/j.jelekin.2012.11.010] [Medline: 23295146]
39. Schinkel-Ivy A, Nairn BC, Drake JD. Quantification of the lumbar flexion-relaxation phenomenon: comparing outcomes of lumbar erector spinae and superficial lumbar multifidus in standing full trunk flexion and slumped sitting postures. J Manipulative Physiol Ther 2014 Sep;37(7):494-501. [doi: 10.1016/j.jmpt.2014.07.003] [Medline: 25109838]
40. Slaboda JC, Boston JR, Rudy TE, Lieber SJ. Classifying subgroups of chronic low back pain patients based on lifting patterns. Arch Phys Med Rehabil 2008 Aug;89(8):1542-1549. [doi: 10.1016/j.apmr.2008.01.016] [Medline: 18674989]
41. Dankaerts W, O'Sullivan P, Burnett A, Straker L, Davey P, Gupta R. Discriminating healthy controls and two clinical subgroups of nonspecific chronic low back pain patients using trunk muscle activation and lumbosacral kinematics of postures and movements: a statistical classification model. Spine (Phila Pa 1976) 2009 Jul 01;34(15):1610-1618. [doi: 10.1097/BRS.0b013e3181aa6175] [Medline: 19564772]
42. Linton SJ, Shaw WS. Impact of psychological factors in the experience of pain. Phys Ther 2011 May;91(5):700-711. [doi: 10.2522/ptj.20100330] [Medline: 21451097]
43. Shaw WS, Hartvigsen J, Woiszwillo MJ, Linton SJ, Reme SE. Psychological distress in acute low back pain: a review of measurement scales and levels of distress reported in the first 2 months after pain onset. Arch Phys Med Rehabil 2016 Dec;97(9):1573-1587. [doi: 10.1016/j.apmr.2016.02.004] [Medline: 26921683]
44. Butler HL, Lariviere C, Hubley-Kozey CL, Sullivan MJ. Directed attention alters the temporal activation patterns of back extensors during trunk flexion-extension in individuals with chronic low back pain. Eur Spine J 2010 Sep;19(9):1508-1516 [FREE Full text] [doi: 10.1007/s00586-010-1403-0] [Medline: 20473625]
45. Lamoth CJ, Daffertshofer A, Meijer OG, Lorimer Moseley MG, Wuisman PI, Beek PJ. Effects of experimentally induced pain and fear of pain on trunk coordination and back muscle activity during walking. Clin Biomech (Bristol, Avon) 2004 Jul;19(6):551-563. [doi: 10.1016/j.clinbiomech.2003.10.006] [Medline: 15234478]
46. Faul F, Erdfelder E, Lang A, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007 May;39(2):175-191. [Medline: 17695343]
47. Astfalck RG, O'Sullivan PB, Straker LM, Smith AJ, Burnett A, Caneiro JP, et al. Sitting postures and trunk muscle activity in adolescents with and without nonspecific chronic low back pain: an analysis based on subclassification. Spine (Phila Pa 1976) 2010 Jun 15;35(14):1387-1395. [doi: 10.1097/BRS.0b013e3181bd3ea6] [Medline: 20195206]
48. World Health Organisation. 2001. International classification of functioning, disability and health internet URL: http://www.who.int/classifications/icf/en/ [accessed 2018-03-22] [WebCite Cache ID 6y6q3oddX]
49. Cieza A, Stucki G, Weigl M, Disler P, Jäckel W, van der Linden S, et al. ICF Core Sets for low back pain. J Rehabil Med 2004 Jul(44 Suppl):69-74 [FREE Full text] [doi: 10.1080/16501960410016037] [Medline: 15370751]
50. Müller R, Strässle K, Wirth B. Isometric back muscle endurance: an EMG study on the criterion validity of the Ito test. J Electromyogr Kinesiol 2010 Oct;20(5):845-850. [doi: 10.1016/j.jelekin.2010.04.004] [Medline: 20471284]
51. Biering-Sørensen F. Physical measurements as risk indicators for low-back trouble over a one-year period. Spine (Phila Pa 1976) 1984 Mar;9(2):106-119. [Medline: 6233709]

52. Demoulin C, Vanderthommen M, Duysens C, Crielaard J. Spinal muscle evaluation using the Sorensen test: a critical appraisal of the literature. Joint Bone Spine 2006 Jan;73(1):43-50. [doi: 10.1016/j.jbspin.2004.08.002] [Medline: 16461206]
53. Ito T, Shirado O, Suzuki H, Takahashi M, Kaneda K, Strax TE. Lumbar trunk muscle endurance testing: an inexpensive alternative to a machine for evaluation. Arch Phys Med Rehabil 1996 Jan;77(1):75-79. [Medline: 8554479]
54. Calmels P, Jacob JF, Fayolle-Minon I, Charles C, Bouchet JP, Rimaud D, et al. [Use of isokinetic techniques vs standard physiotherapy in patients with chronic low back pain. Preliminary results]. Ann Readapt Med Phys 2004 Feb;47(1):20-27. [doi: 10.1016/j.annrmp.2003.07.001] [Medline: 14967569]
55. Evans K, Refshauge KM, Adams R. Trunk muscle endurance tests: reliability, and gender differences in athletes. J Sci Med Sport 2007 Dec;10(6):447-455. [doi: 10.1016/j.jsams.2006.09.003] [Medline: 17141568]
56. Miller ER, Schenk RJ, Karnes JL, Rousselle JG. A comparison of the Mckenzie approach to a specific spine stabilization program for chronic low back pain. J Man Manip Ther 2013 Jul 18;13(2):103-112. [doi: 10.1179/106698105790824996]
57. Shum GL, Crosbie J, Lee RY. Energy transfer across the lumbosacral and lower-extremity joints in patients with low back pain during sit-to-stand. Arch Phys Med Rehabil 2009 Jan;90(1):127-135. [doi: 10.1016/j.apmr.2008.06.028] [Medline: 19154839]
58. Corkery MB, O'Rourke B, Viola S, Yen SC, Rigby J, Singer K, et al. An exploratory examination of the association between altered lumbar motor control, joint mobility and low back pain in athletes. Asian J Sports Med 2014 Nov 01;6(1):e24283. [doi: 10.5812/asjsm.24283] [Medline: 25741418]
59. Winters MV, Blake CG, Trost JS, Marcello-Brinker TB, Lowe LM, Garber MB, et al. Passive versus active stretching of hip flexor muscles in subjects with limited hip extension: a randomized clinical trial. Phys Ther 2004 Sep;84(9):800-807. [Medline: 15330693]
60. Handrakis JP, Friel K, Hoeffner F, Akinkunle O, Genova V, Isakov E, et al. Key characteristics of low back pain and disability in college-aged adults: a pilot study. Arch Phys Med Rehabil 2012 Jul;93(7):1217-1224. [doi: 10.1016/j.apmr.2012.02.013] [Medline: 22516875]
61. Hislop H, Avers D, Brown M. Daniels and Worthingham's Muscle Testing. Techniques of Manual Examination and Performance Testing. Saintt-Louis: Elsevier saunders; 2013.
62. Avrahami D, Potvin JR. The clinical and biomechanical effects of fascial-muscular lengthening therapy on tight hip flexor patients with and without low back pain. J Can Chiropr Assoc 2014 Dec;58(4):444-455 [FREE Full text] [Medline: 25550670]
63. Mellin GP. Accuracy of measuring lateral flexion of the spine with a tape. Clin Biomech (Bristol, Avon) 1986 May;1(2):85-89. [doi: 10.1016/0268-0033(86)90081-1] [Medline: 23906359]
64. Lindell O, Eriksson L, Strender LE. The reliability of a 10-test package for patients with prolonged back and neck pain: could an examiner without formal medical education be used without loss of quality? A methodological study. BMC Musculoskelet Disord 2007 Apr 03;8:31 [FREE Full text] [doi: 10.1186/1471-2474-8-31] [Medline: 17407580]
65. Norkin CC. In: White DJ, editor. Measurement of Joint Motion: A Guide to Goniometry. 4th Revised edition. Philadelphia: F. A. Davis Company; 2009.
66. Brumagne S, Janssens L, Knapen S, Claeys K, Suuden-Johanson E. Persons with recurrent low back pain exhibit a rigid postural control strategy. Eur Spine J 2008 Sep;17(9):1177-1184 [FREE Full text] [doi: 10.1007/s00586-008-0709-7] [Medline: 18594876]
67. Murans G, Gutierrez-Farewik EM, Saraste H. Kinematic and kinetic analysis of static sitting of patients with neuropathic spine deformity. Gait Posture 2011;34(4):533-538. [Medline: 21816615]
68. Schelldorfer S, Ernst MJ, Rast FM, Bauer CM, Meichtry A, Kool J. Low back pain and postural control, effects of task difficulty on centre of pressure and spinal kinematics. Gait Posture 2015;41(1):112-118. [Medline: 25270326]
69. Larivière C, Gagnon D, Loisel P. A biomechanical comparison of lifting techniques between subjects with and without chronic low back pain during freestyle lifting and lowering tasks. Clin Biomech 2002 Feb;17(2):89-98. [doi: 10.1016/S0268-0033(01)00106-1]
70. Legeard E. Force: entraînement & musculation [Strength: Training & Strength Training]. France: Amphora Publishing; 2005.
71. Schinkel-Ivy A, Nairn BC, Drake JD. Evaluation of methods for the quantification of the flexion-relaxation phenomenon in the lumbar erector spinae muscles. J Manipulative Physiol Ther 2013;36(6):349-358. [doi: 10.1016/j.jmpt.2013.05.017] [Medline: 23845199]
72. Pijnenburg M, Brumagne S, Caeyenberghs K, Janssens L, Goossens N, Marinazzo D, et al. Resting-state functional connectivity of the sensorimotor network in individuals with nonspecific low back pain and the association with the sit-to-stand-to-sit task. Brain Connect 2015 Jun;5(5):303-311. [doi: 10.1089/brain.2014.0309] [Medline: 25557846]
73. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67(6):361-370. [Medline: 6880820]
74. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002 Feb;52(2):69-77. [Medline: 11832252]
75. Turk DC, Dworkin RH, Trudeau JJ, Benson C, Biondi DM, Katz NP, et al. Validation of the hospital anxiety and depression scale in patients with acute low back pain. J Pain 2015 Oct;16(10):1012-1021. [doi: 10.1016/j.jpain.2015.07.001] [Medline: 26208762]

76. Lépine JP, Godchau M, Brun P, Lempérière T. [Evaluation of anxiety and depression among patients hospitalized on an internal medicine service]. Ann Med Psychol (Paris) 1985 Feb;143(2):175-189. [Medline: 4037594]
77. Savard J, Laberge B, Gauthier JG, Ivers H, Bergeron MG. Evaluating anxiety and depression in HIV-infected patients. J Pers Assess 1998 Dec;71(3):349-367. [doi: 10.1207/s15327752jpa7103_5] [Medline: 9933941]
78. Friedman S, Samuelian J, Lancrenon S, Even C, Chiarelli P. Three-dimensional structure of the Hospital Anxiety and Depression Scale in a large French primary care population suffering from major depression. Psychiatry Res 2001 Nov 30;104(3):247-257. [Medline: 11728614]
79. Untas A, Aguirrezabal M, Chauveau P, Leguen E, Combe C, Rascle N. [Anxiety and depression in hemodialysis: validation of the Hospital Anxiety and Depression Scale (HADS)]. Nephrol Ther 2009 Jun;5(3):193-200. [doi: 10.1016/j.nephro.2009.01.007] [Medline: 19346177]
80. Ehrlich GE, Khaltev NG, World Health Organization, Chronic Respiratory Diseases and Arthritis Team. In: Ehrlich GE, Khaltev NG, editors. Low back pain initiative. Geneva: World Health Organization; 1999.
81. Bombardier C. Outcome assessments in the evaluation of treatment of spinal disorders: summary and general recommendations. Spine (Phila Pa 1976) 2000 Dec 15;25(24):3100-3103. [Medline: 11124724]
82. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. Physiotherapy 1980 Aug;66(8):271-273. [Medline: 6450426]
83. Calmels P, Béthoux F, Condemine A, Fayolle-Minon I. [Low back pain disability assessment tools]. Ann Readapt Med Phys 2005 Jul;48(6):288-297. [doi: 10.1016/j.annrmp.2005.04.008] [Medline: 15932777]
84. Vogler D, Paillex R, Norberg M, de Goumoëns P, Cabri J. [Cross-cultural validation of the Oswestry disability index in French]. Ann Readapt Med Phys 2008 Jun;51(5):379-385. [doi: 10.1016/j.annrmp.2008.03.006] [Medline: 18501463]
85. Wertli MM, Burgstaller JM, Weiser S, Steurer J, Kofmehl R, Held U. Influence of catastrophizing on treatment outcome in patients with nonspecific low back pain: a systematic review. Spine (Phila Pa 1976) 2014 Feb 01;39(3):263-273. [doi: 10.1097/BRS.0000000000000110] [Medline: 24253796]
86. Sullivan M, Bishop S, Pivik J. APA PsychNET. 1995. The pain catastrophizing scale: development and validation URL: http://psycnet.apa.org/journals/pas/7/4/524/ [accessed 2018-03-22] [WebCite Cache ID 6y6sQHhZH]
87. French DJ, Noël M, Vigneau F, French JA, Cyr CP, Thomas ER. L'Échelle de dramatisation face à la douleur PCS-CF: Adaptation canadienne en langue française de l'échelle «Pain Catastrophizing Scale». Can J Behav Sci 2005 Jul;37(3):181-192. [doi: 10.1037/h0087255]
88. Wertli MM, Rasmussen-Barr E, Weiser S, Bachmann LM, Brunner F. The role of fear avoidance beliefs as a prognostic factor for outcome in patients with nonspecific low back pain: a systematic review. Spine J 2014 May 01;14(5):816-36.e4. [doi: 10.1016/j.spinee.2013.09.036] [Medline: 24412032]
89. Waddell G, Newton M, Henderson I, Somerville D, Main CJ. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. Pain 1993 Feb;52(2):157-168. [Medline: 8455963]
90. Chaory K, Fayad F, Rannou F, Lefèvre-Colau MM, Fermanian J, Revel M, et al. Validation of the French version of the fear avoidance belief questionnaire. Spine (Phila Pa 1976) 2004 Apr 15;29(8):908-913. [Medline: 15082995]
91. Armstrong T, Bull F. Development of the World Health Organization Global Physical Activity Questionnaire (GPAQ). J Public Health 2006 Mar 2;14(2):66-70. [doi: 10.1007/s10389-006-0024-x]
92. Schaller A, Dejonghe L, Haastert B, Froboese I. Physical activity and health-related quality of life in chronic low back pain patients: a cross-sectional study. BMC Musculoskelet Disord 2015 Mar 19;16:62 [FREE Full text] [doi: 10.1186/s12891-015-0527-0] [Medline: 25887138]
93. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005 Jan;113(1-2):9-19. [doi: 10.1016/j.pain.2004.09.012] [Medline: 15621359]
94. Mazaheri M, Heidari E, Mostamand J, Negahban H, van Dieen JH. Competing effects of pain and fear of pain on postural control in low back pain? Spine (Phila Pa 1976) 2014 Dec 01;39(25):E1518-E1523. [doi: 10.1097/BRS.0000000000000605] [Medline: 25271501]
95. Caffaro RR, França FJ, Burke TN, Magalhães MO, Ramos LA, Marques AP. Postural control in individuals with and without non-specific chronic low back pain: a preliminary case-control study. Eur Spine J 2014 Apr;23(4):807-813 [FREE Full text] [doi: 10.1007/s00586-014-3243-9] [Medline: 24570125]
96. Kahraman T, Ozcan Kahraman KB, Salik Sengul Y, Kalemci O. Assessment of sit-to-stand movement in nonspecific low back pain: a comparison study for psychometric properties of field-based and laboratory-based methods. Int J Rehabil Res 2016 Jun;39(2):165-170. [doi: 10.1097/MRR.0000000000000164] [Medline: 27031182]
97. Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G. Development of recommendations for SEMG sensors and sensor placement procedures. J Electromyogr Kinesiol 2000 Oct;10(5):361-374. [Medline: 11018445]
98. Lewek MD, Rudolph KS, Snyder-Mackler L. Control of frontal plane knee laxity during gait in patients with medial compartment knee osteoarthritis. Osteoarthritis Cartilage 2004 Sep;12(9):745-751 [FREE Full text] [doi: 10.1016/j.joca.2004.05.005] [Medline: 15325641]

99. Konrad P. Noraxon. 2006. The ABC of EMG: A Practical Introduction to Kinesiological Electromyography URL: https://www.noraxon.com/wp-content/uploads/2014/12/ABC-EMG-ISBN.pdf [accessed 2018-03-22] [WebCite Cache ID 6y6ssnENy]
100. Mohseni Bandpei MA, Rahmani N, Majdoleslam B, Abdollahi I, Ali SS, Ahmad A. Reliability of surface electromyography in the assessment of paraspinal muscle fatigue: an updated systematic review. J Manipulative Physiol Ther 2014 Sep;37(7):510-521. [doi: 10.1016/j.jmpt.2014.05.006] [Medline: 25204717]
101. Davis RB, Õunpuu S, Tyburski D, Gage JR. A gait analysis data collection and reduction technique. Hum Mov Sci 1991 Oct;10(5):575-587 [FREE Full text] [doi: 10.1016/0167-9457(91)90046-Z]
102. Schmid S, Studer D, Hasler CC, Romkes J, Taylor W, Brunner R, et al. Using skin markers for spinal curvature quantification in main thoracic adolescent idiopathic scoliosis: an explorative radiographic study. PLoS One 2015;10(8):e0135689 [FREE Full text] [doi: 10.1371/journal.pone.0135689] [Medline: 26270557]
103. Mahallati S, Rouhani H, Preuss R, Masani K, Popovic MR. Multisegment kinematics of the spinal column: soft tissue artifacts assessment. J Biomech Eng 2016 Jul 01;138(7). [doi: 10.1115/1.4033545] [Medline: 27151927]
104. Esola MA, McClure PW, Fitzgerald GK, Siegler S. Analysis of lumbar spine and hip motion during forward bending in subjects with and without a history of low back pain. Spine (Phila Pa 1976) 1996 Jan 1;21(1):71-78. [Medline: 9122766]
105. Henchoz Y, Tétreau C, Abboud J, Piché M, Descarreaux M. Effects of noxious stimulation and pain expectations on neuromuscular control of the spine in patients with chronic low back pain. Spine J 2013 Oct;13(10):1263-1272. [doi: 10.1016/j.spinee.2013.07.452] [Medline: 24090825]
106. Lamoth CJ, Daffertshofer A, Meijer OG, Beek PJ. How do persons with chronic low back pain speed up and slow down? Trunk-pelvis coordination and lumbar erector spinae activity during gait. Gait Posture 2006 Feb;23(2):230-239. [doi: 10.1016/j.gaitpost.2005.02.006] [Medline: 16399520]
107. Van Daele U, Hagman F, Truijen S, Vorlat P, Van Gheluwe B, Vaes P. Decrease in postural sway and trunk stiffness during cognitive dual-task in nonspecific chronic low back pain patients, performance compared to healthy control subjects. Spine (Phila Pa 1976) 2010 Mar 01;35(5):583-589. [doi: 10.1097/BRS.0b013e3181b4fe4d] [Medline: 20147880]
108. Ruhe A, Fejer R, Walker B. Center of pressure excursion as a measure of balance performance in patients with non-specific low back pain compared to healthy controls: a systematic review of the literature. Eur Spine J 2011 Mar;20(3):358-368 [FREE Full text] [doi: 10.1007/s00586-010-1543-2] [Medline: 20721676]
109. Ruhe A, Fejer R, Walker B. Is there a relationship between pain intensity and postural sway in patients with non-specific low back pain? BMC Musculoskelet Disord 2011 Jul 15;12:162 [FREE Full text] [doi: 10.1186/1471-2474-12-162] [Medline: 21762484]
110. Barre A, Armand S. Biomechanical ToolKit: open-source framework to visualize and process biomechanical data. Comput Methods Programs Biomed 2014 Apr;114(1):80-87 [FREE Full text] [doi: 10.1016/j.cmpb.2014.01.012] [Medline: 24548899]

Abbreviations

5CSTS: 5 consecutive sit-to-stand
CCI: cocontraction index
FABQ: fear-avoidance belief questionnaire
GPAQ: global physical activity questionnaire
HADS: Hospital Anxiety and Depression Scale
HUG: Geneva University Hospital
ICF: International Classification of Functioning, Disability, and Health
LBP: low back pain
ODI: Oswestry Disability Index
PA: physical activity
PCS: pain catastrophizing scale
STS: sit-to-stand
sEMG: surface electromyography
TCC: time of cocontraction

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Original Paper

Comparison of Online Survey Recruitment Platforms for Hard-to-Reach Pregnant Smoking Populations: Feasibility Study

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Abstract

Background: Recruiting hard-to-reach populations for health research is challenging. Web-based platforms offer one way to recruit specific samples for research purposes, but little is known about the feasibility of online recruitment and the representativeness and comparability of samples recruited through different Web-based platforms.

Objective: The objectives of this study were to determine the feasibility of recruiting a hard-to-reach population (pregnant smokers) using 4 different Web-based platforms and to compare participants recruited through each platform.

Methods: A screener and survey were distributed online through Qualtrics Panel, Soapbox Sample, Reddit, and Amazon Mechanical Turk (mTurk). Descriptive statistics were used to summarize results of each recruitment platform, including eligibility yield, quality yield, income, race, age, and gestational age.

Results: Of the 3847 participants screened for eligibility across all 4 Web-based platforms, 535 were eligible and 308 completed the survey. Amazon mTurk yielded the fewest completed responses (n=9), 100% (9/9) of which passed several quality metrics verifying pregnancy and smoking status. Qualtrics Panel yielded 14 completed responses, 86% (12/14) of which passed the quality screening. Soapbox Sample produced 107 completed surveys, 67% (72/107) of which were found to be quality responses. Advertising through Reddit produced the highest completion rate (n=178), but only 29.2% (52/178) of those surveys passed the quality metrics. We found significant differences in eligibility yield, quality yield, age, number of previous pregnancies, age of smoking initiation, current smokers, race, education, and income (P<.001).

Conclusions: Although each platform successfully recruited pregnant smokers, results varied in quality, cost, and percentage of complete responses. Moving forward, investigators should pay careful attention to the percentage yield and cost of online recruitment platforms to maximize internal and external validity.

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KEYWORDS

socioeconomic status; smoking; nicotine; cognitive bias; Web-based methods; crowdsourcing; delay discounting; vulnerable populations

Introduction

Background

Smoking while pregnant is the leading cause of preventable infant morbidity and mortality, as well as pregnancy complications [1-6]. More than a quarter of women aged from 12 to 44 years in their first month of pregnancy report active cigarette smoking—and this prevalence is no lower than the rate among nonpregnant women aged 12 to 44 who are not pregnant [7]. Effective smoking cessation programs targeted at pregnant women can substantially reduce maternal and infant health outcomes, including infant mortality [8,9]. Although pregnant women who smoke have a higher quit rate during their

pregnancy than any other time in their lives [10,11], only one-third of women are able to remain abstinent [12]. The high burden of disease associated with smoking during pregnancy coupled with the critical window of opportunity for cessation interventions generates substantial interest in research on pregnant smokers [13].

Recruiting a representative sample of pregnant smokers for descriptive or intervention studies is challenging [14]. Pregnant smokers may be reluctant to disclose smoking status due to social stigma (particularly in a clinical setting), making self-reported smoking status an error-prone measure. Furthermore, biologically confirmed smoking status (eg, cotinine testing) is expensive [15,16]. While in-person recruiting in prenatal care settings has been the norm in research to date, new opportunities have emerged to leverage social media and crowdsourcing to more easily recruit pregnant smokers as research subjects. Crowdsourcing platforms are Web-based marketplaces that allow researchers to post research tasks (such as survey completion) that interested subjects can complete for pay. Crowdsourcing offers an easy way to quickly recruit a large sample of study respondents that is more diverse (geographically and sociodemographically) than the typical college student young adult sample or an in-clinic patient sample [17]. Crowdsourcing platforms such as Amazon's Mechanical Turk (mTurk), Soapbox Sample, and Qualtrics Panel Data draw a broad demographic of workers that can meet even very specific and targeted inclusion criteria [18,19]. Compensation for research task completion through crowdsourcing platforms is typically lower than in-person research participation with substantially lower research staffing costs, making crowdsourcing an appealing option for maximizing limited research budgets [14]. To date, Amazon's mTurk has been the largest and best-known crowdsourcing platform due to low costs, flexibility, anonymity of workers, and, for researchers, the demographic diversity of the worker pool [20]. Social media is another online recruitment platform that extends researchers' reach beyond the limitations of in-person recruitment. About 74% of the 2015 US population had Internet access and more than half of that population used at least one form of social media [21,22]. Social media allows for precise targeting of messages (including invitations to participate in research) to specific demographic profiles or interests. For example, the social media platform Reddit comprises many smaller interest groups called "subreddits" where members view other members' posts, news, images, and media links. Advertisers, including researchers, can place ads on specific subreddits, such as a pregnancy or smoking cessation subreddit, to reach the desired target audience.

Objectives

This study compares the characteristics of a sample of pregnant smokers (a small and temporally defined population) recruited through 4 Web-based platforms (3 crowdsourcing platforms and 1 social media site), then describes the feasibility of each platform and the cost per completed survey.

Methods

Study Design

We sought a sample of pregnant smokers aged 18 years and older living in the United States for a cross-sectional survey-based study of decision-making styles and preferences for incentive-based smoking cessation programs during pregnancy. The study was approved by the institutional review board of the University of Pennsylvania. Study respondents were first asked to complete a 6-question screener created on the Qualtrics Web-based survey platform to determine eligibility. Eligible respondents who provided informed consent then completed a 93-question survey about pregnancy history, smoking history, decision-making style, and smoking cessation program preferences (see Multimedia Appendix 1 for a sample of selected questions). Participants who did not consent were not allowed to continue onto the second survey. The recruitment period ran from July 6 to July 27, 2016. In total, 308 eligible respondents completed the survey. We evaluated platforms based off of two yields: eligibility yield, defined as the percentage of participants who met the inclusion criteria out of the number of total number of respondents, and quality yield, defined as the percentage of eligible participants who correctly and appropriately answered attention and quality checks embedded throughout the survey.

Recruitment Platforms

Table 1 describes the recruitment platforms we used and their forms of recruitment flow, general cost, and options for researchers. We chose the platforms Amazon mTurk, Soapbox Sample, Qualtrics Panel, and Reddit due to their ease of use, relatively low cost, and the estimated number of respondents.

Table 1. Recruitment flow, cost for researcher, and options for targeting recruits by recruitment platform used, 2017.

Recruiting channel	Options for targeting recruits	Cost for researcher	Incentives for respondent
Amazon Mechanical Turk	None	Pay per completed task	US $0.01-US $0.02 for screening survey, US $0.10 for completion, up to US $0.70 based on quality
Soapbox Sample	Targeted based on demographics and interests	Pay minimum fee plus per completed survey	2000 points (US $2.00 equivalent)
Qualtrics Panel	Targeted based on demographics and interests	Pay minimum fee plus per completed survey	Paid by Qualtrics Panel
Reddit	Targeted based on interests	Pay when ads clicked or shown	US $10 e-gift card

Amazon Mechanical Turk

We used the third-party service TurkPrime (free to academic researchers) to anonymize respondents and to restrict survey dissemination to eligible and experienced mTurk workers. Participation was limited to those in the United States and those with a 95% approval rating after having completed more than 5000 human intelligence tasks (HITs in mTurk parlance) to maximize data quality. TurkPrime also batch-released the survey to ensure maximum visibility of the HIT. We varied the wording of the HIT titles (more vs less specific about survey content) to maximize participation. The screener survey initially paid US $0.01, but this was increased to US $0.02 to attract more respondents. The main survey paid US $0.10 with a US $0.70 quality bonus.

Soapbox Sample

We contacted Soapbox Sample for a price quote via telephone, and they provided an estimate of US $23 per completed survey for 75 to 100 respondents, with a minimum payment of US $500 after we asked to limit the sample to pregnant smokers in the United States. At no additional cost, Soapbox assigned a project manager who oversaw the number of eligible and completed surveys each day. Soapbox rewarded participants for completing the survey in points that could later be cashed in for gift cards from various retailers. Participants received 2000 points (US $2.00 equivalent) for this survey.

Qualtrics Panel

Qualtrics Panel is a subdivision of Qualtrics, a private research software company specializing in Web-based data collection that partners with over 20 Web-based panel providers to supply diverse, quality respondents. We contacted Qualtrics Panel for a quote via email and they provided an initial estimate price of US $20 per completed survey for 50 eligible respondents (pregnant women in the United States who smoke). However, they could not guarantee that the target sample size of 50 respondents would be met within their existing panels. The Qualtrics project manager noted that pregnancy is a "moving target," in addition to the difficulty of Web assessment and underreporting of smoking status due to social stigma. The manager suggested pushing the survey through all platforms of their crowdsourcing platform, charging US $10 per survey completion with a minimum payment of US $500. This price included a project manager, who added embedded data into the survey for quality assurance and monitored attention checks. Participants were paid directly through Qualtrics.

Reddit

We first identified 4 Reddit subreddits of which pregnant smokers might be members. We initially planned to post a link to our screener survey directly to the most promising subreddits (eg, r/BabyBumps) but were informed by moderators that this type of survey or research promotion did not comply with subreddit guidelines. We quickly discovered that Reddit has an inexpensive and flexible auction-based system for placing advertisements. We ran several advertisements on promising Reddit subreddits pertaining to smoking cessation and pregnancy, including r/BabyBumps, r/TwoXChromosomes, r/stopsmoking, and r/Parenting. We experimented with various formats, text, and images across our different ad campaigns. All advertisements provided a link to the Qualtrics screener survey. We also varied our bid price per 1000 impressions to maximize our advertising budget. Eligible respondents who completed the main survey received a US $10 e-gift cards through GiftBit, a Web-based gift card service.

Attention Checks and Quality Screens

As is typical in Web-based survey research, we employed multiple attention checks and quality screens in our surveys [23]. Attention checks confirmed that Web-based survey respondents were reading questions carefully and thoroughly. Quality screens attempted to confirm self-reported pregnancy and smoking status and confirmed that respondents spent an adequate amount of time completing the survey and were not simply checking response boxes as rapidly as possible (eg, selecting the same column repeatedly in a grid). Qualtrics Panel suggested using one-third of the median time to complete the survey as the cut-off point to determine whether respondents rushed through the survey, so we applied this criterion to every survey platform as a part of the quality screens. By platform, 0% (0/9) of respondents in mTurk, 13% (1/8) of respondents in Qualtrics Panel, 28.9% (31/107) of respondents in Soapbox Sample, and 16.9% (30/178) of respondents in Reddit did not pass the time-quality screens.

To confirm pregnancy status, quality screens checked for consistent self-reported gestational age, last menstrual period, estimated due date, and reports of real vs sham pregnancy symptoms. Quality screens for smoking status included knowing the number of cigarettes in a pack, experience of head rush when smoking (not typical for a regular smoker), and consistent reporting of smoking intensity. Additional quality screens included flagging when a respondent provided the same answers in a matrix of questions (ie, clicked answers in a straight vertical line down the page).

Analysis

Completed eligibility screens and surveys from each recruitment platform were exported from Qualtrics to STATA v 14.2 (StataCorp, College Station, TX) for analysis. Descriptive statistics (mean and 95% CIs or proportions) were calculated for the completed sample by platform for the following measures: age, race, education, income, current smoking status (currently smoking in pregnancy or quit since beginning of this pregnancy), gestational age, and number of previous pregnancies. To analyze the descriptive statistics, we performed chi-square contingency test, analysis of variance, Kruskal-Wallis, and Fisher exact test. Cost data were compiled from invoices and receipts for subject payment and HIT management services (mTurk), gift cards (GiftBit for Reddit respondents), platform payments (Qualtrics Panel Data and Soapbox Sample), and Reddit ad purchases. Cost per completed survey was calculated as total costs per platform divided by number of completed, quality surveys. Eligibility yield was calculated by dividing the number of respondents who met the inclusion criteria by the number of total respondents per platform, whereas quality yield was calculated by dividing the number of quality surveys (number of completed surveys that pass the pregnancy screening, smoking screening, attention

checks, quality checks, and email checks) by the total number of completed surveys per platform.

Results

Recruitment Outcomes

Figure 1 presents recruitment outcomes at each stage of the recruitment process by platform. All platforms could identify pregnant women who smoke and who completed the study with sufficient quality, but the yields of quality surveys from total screen for eligibility varied considerably. We observed significant differences in eligibility yield, quality yield, age, number of previous pregnancies, age of smoking initiation, current smokers, race, education, and income (P<.001).

mTurk collected a total of 30 eligible respondents out of a total 2291 sampled (1.31% eligible). Of those eligible respondents, 17 failed to complete the trial survey (nonscreener portion of the overall survey) and are therefore considered lost to follow-up due to the partitioning of the survey into a screener survey and the trial survey to maximize the quality of the surveys, and 4 produced incomplete surveys, leaving a total of 9 completed surveys. After running the attention and quality screens on the completed mTurk surveys, 0 failed the pregnancy or smoking screener or the attention or quality screens for a quality yield of 100%.

Soapbox produced 20.7% eligible (121/585) respondents out of the total sampled respondents. Of those eligible, 14 produced incomplete surveys, leaving a total of 107 completed surveys. In total, 31 surveys failed the pregnancy check, 2 failed the smoking check, 0 failed the attention checks, and 2 failed quality screens for an overall yield of 60%.

Qualtrics collected a total of 25.9% (178/686) eligible respondents out of the total sampled respondents. Of those eligible, 1 did not provide consent and 163 produced incomplete surveys, leaving a total of 14 completed surveys. One survey failed the pregnancy check, 0 failed the smoking check, 1 failed the attention checks, and 0 failed quality screens for an overall yield of 7%.

Reddit collected a total of 72.3% (206/285) eligible respondents out of the total sampled respondents. Of those eligible, 2 did not provide consent and 26 produced incomplete surveys, leaving a total of 178 completed surveys. In total, 30 surveys failed the pregnancy check, 30 failed the smoking check, 0 failed the attention checks, and 2 failed quality screens for an overall yield of 65%.

Interestingly, the amount of surveys lost between each stage of checks varied across platforms. Although we received 177 eligible respondents in Qualtrics, only 14 (92.1%) completed the survey. mTurk's respondents produced a similar pattern with 4 out of 13 (69%) incomplete surveys. Respondents from Reddit or Soapbox completed the survey more often than respondents from Qualtrics or mTurk, with Reddit's incompletion rates at 12.8% (26 incomplete surveys out of 204 eligible surveys) and Soapbox's at 11.6% (14 incomplete surveys out of 121 eligible surveys). Respondents in mTurk produced higher-quality responses than any other platform, with 0% of respondents failing any of the quality or attention screens. Similar to those recruited through mTurk, respondents from Qualtrics produced high-quality surveys. Out of 14 overall completed surveys, 1 survey failed the pregnancy screening and another survey failed the quality screens. Nearly 29% (one-third) of respondents in Soapbox failed the pregnancy screening, the highest failure rate of the pregnancy screenings across platform. However, aside from this, few others failed any other screenings: 2 failed the smoking screener and 2 failed the quality screens. Reddit had the most number of surveys that failed screeners. In total, 30 surveys failed the pregnancy screening and 30 others failed the smoking screener. Most respondents passed the attention checks and the quality screens. Surprisingly, all respondents passed the attention checks, and only 5 out of 208 total respondents did not pass the quality screen.

During survey collection, we noticed a sudden spike in the number of responses we received via Reddit. The timestamp on many of these responses occurred between midnight and 8 AM. The emails affiliated with them contained domain names from outside the United States—mostly from Eastern Europe—in spite of the fact that the Reddit ads had been geographically specified to target users in the United States. Furthermore, a pattern emerged in the domains of the emails we received from Reddit users, alternating between @me.com, @hotmail.com, and @gmail.com within a relatively short time frame. This series of events led us to believe someone disseminated our survey on the Internet as an easy opportunity to make money. Consequently, we manually combed through the email addresses to check for any repetitious email addresses and suspicious email domains. After closing our survey and ending the Reddit advertisement campaigns, we received a few emails from Reddit users claiming they had completed our survey but had not received payment. Because the 3 users who reached out to our team via Reddit had emails that were similar in structure, we sought to confirm their pregnancy status by asking her due date, last menstrual period, and number of weeks pregnant at the time of survey completion. After we received each response, we compared the information given in the email with the data collected from the survey responses and then sent the payment. Therefore, this decreased Reddit's quality yield from 65% to 29%.

Sample Characteristics

More than 50% of the total sample identified as white. Over half of all respondents have at least some college education. Most of the respondents had an annual family income of US $35,000 to US $74,999. Almost three-fourths of the respondents reported still smoking at the time of survey administration. As seen in Table 2, demographics varied widely across platforms. A substantial variation in the proportion of currently smoking respondents (vs recently quit during this pregnancy) existed: from 8% of Qualtrics respondents to 88% of Reddit respondents.

Figure 1. Recruitment outcomes at each stage of the recruitment process by platform.

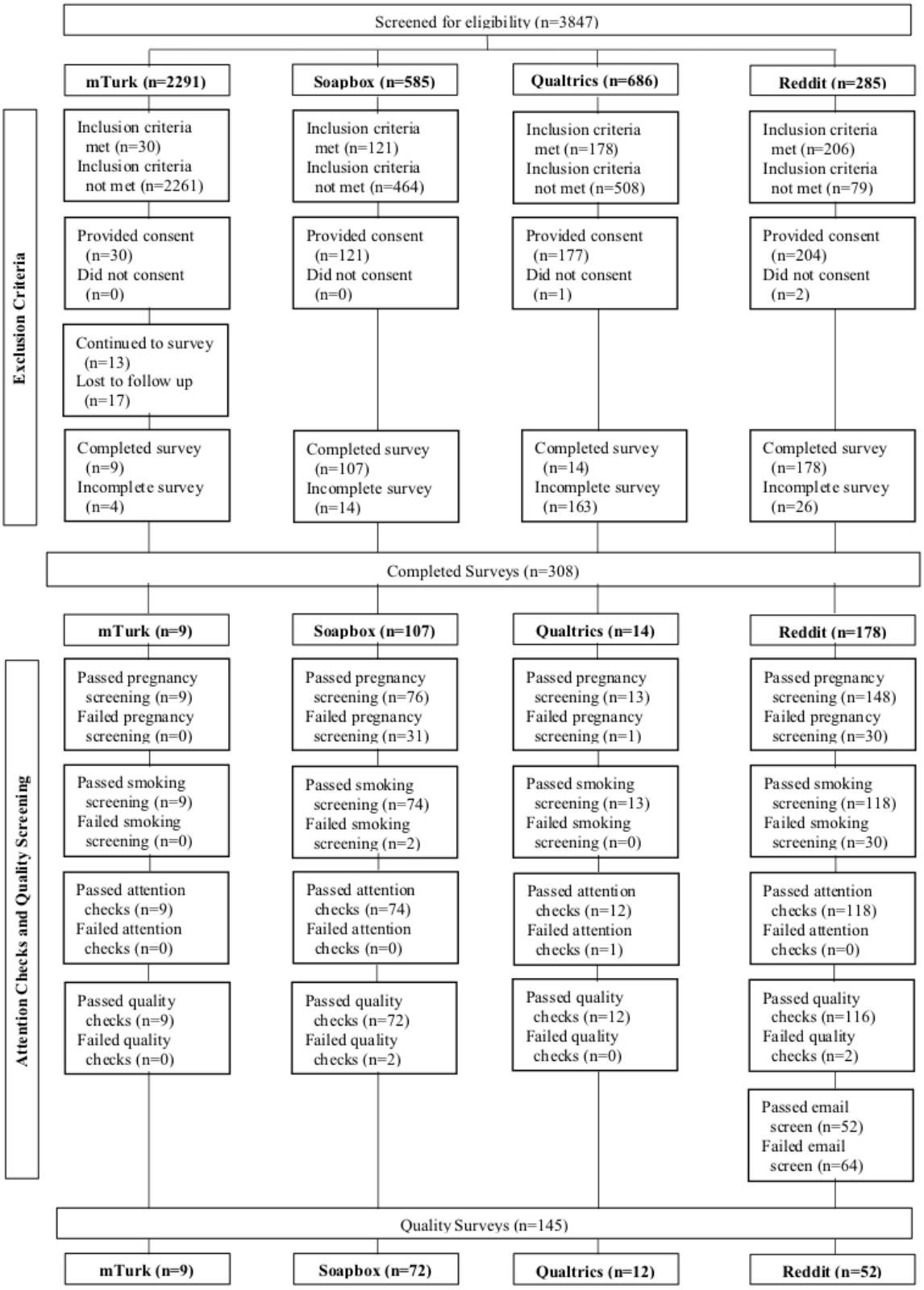


Table 2. Eligibility and quality yield, pregnancy, smoking, and demographic information by total and individual recruitment platforms, 2017.

Platform characteristics	Total (n=3847)	mTurk (n=2291)	Soapbox (n=585)	Qualtrics (n=686)	Reddit (n=285)	*P* value
Proportion eligible[a], n (%)	535 (13.91)	30 (1.31)	121 (20.7)	178 (25.9)	206 (72.3)	<.001
Proportion of eligible deemed quality[a], n (%)	145 (47.1)	9 (100)	72 (67.3)	12 (86)	52 (29.2)	<.001
Age[b] in years, mean (SD)	28 (6.3)	33 (4.4)	30 (6.3)	29 (7.5)	24 (4.1)	<.001
Gestational age[b] in weeks, mean (SD)	20 (12.4)	11 (13.8)	20 (13.0)	22 (9.4)	20 (11.6)	.21
Number of previous pregnancies[b], mean (SD)	1 (1.3)	1 (0.7)	2 (1.6)	1 (1.0)	0.3 (0.7)	<.001
Initial age of smoking[c], median (years)	18 (3.2)	17 (3.5)	17 (3.5)	17 (2.7)	19 (2.5)	.001
Current smokers[a], n (%)	103 (71.0)	6 (67)	50 (69)	1 (8)	46 (89)	<.001
Race[d] , n (%)						
White	82 (56.6)	8 (89)	53 (74)	6 (50)	15 (29)	<.001
Black	28 (19.3)	0 (0)	11 (15)	3 (25)	14 (27)	
Asian	10 (6.9)	0 (0)	4 (6)	1 (8)	5 (10)	
Native American	8 (5.5)	1 (11)	1 (1)	2 (17)	4 (8)	
Native Hawaiian	6 (4.1)	0 (0)	2 (3)	0 (0)	4 (8)	
Prefer not to answer	11 (7.6)	0 (0)	1 (1)	0 (0)	10 (19)	
Hispanic[d] , n (%)						
Non-Hispanic	119 (82.1)	8 (89)	60 (83)	10 (83)	41 (79)	.008
Hispanic	18 (12.4)	1 (11)	12 (17)	1 (17)	3 (6)	
Prefer not to answer	8 (5.5)	0 (0)	0 (0)	0 (0)	8 (15)	
Education[a] , n (%)						
<High school	4 (2.8)	0 (0)	2 (3)	0 (0)	2 (4)	.004
High school/ General Equivalency Diploma	47 (32.4)	0 (0)	16 (22)	5 (42)	26 (50)	
Some college	31 (21.4)	2 (22)	15 (21)	2 (17)	12 (23)	
Associate's	17 (11.7)	1 (11)	11 (15)	0 (0)	5 (10)	
Bachelor's	33 (22.8)	6 (67)	19 (26)	3 (25)	5 (10)	
>16 years	11 (7.6)	0 (0)	9 (13)	2 (17)	0 (0)	
Prefer not to answer	2 (1.4)	0 (0)	0 (0)	0 (0)	2 (4)	
Income[a] (US $), n (%)						
<$10,000	18 (12.4)	0 (0)	7 (10)	1 (8)	10 (19)	.004
$10,000-$14,999	6 (4.1)	1 (11)	3 (4)	0 (0)	2 (4)	
$15,000-$19,999	15 (10.3)	1 (11)	6 (8)	1 (8)	7 (13)	
$20,000-$24,999	21 (14.5)	1 (11)	5 (7)	0 (0)	15 (29)	
$25,000-$34,999	15 (10.3)	0 (0)	5 (7)	4 (33)	6 (12)	
$35,000-$49,999	24 (16.6)	4 (44)	13 (18)	1 (8)	6 (12)	
$50,000-$74,999	21 (14.5)	1 (11)	15 (21)	2 (17)	3 (6)	
≥$75,000	19 (13.1)	1 (11)	14 (19)	3 (25)	1 (2)	
Prefer not to answer	6 (4.1)	0 (0)	4 (6)	0 (0)	2 (4)	

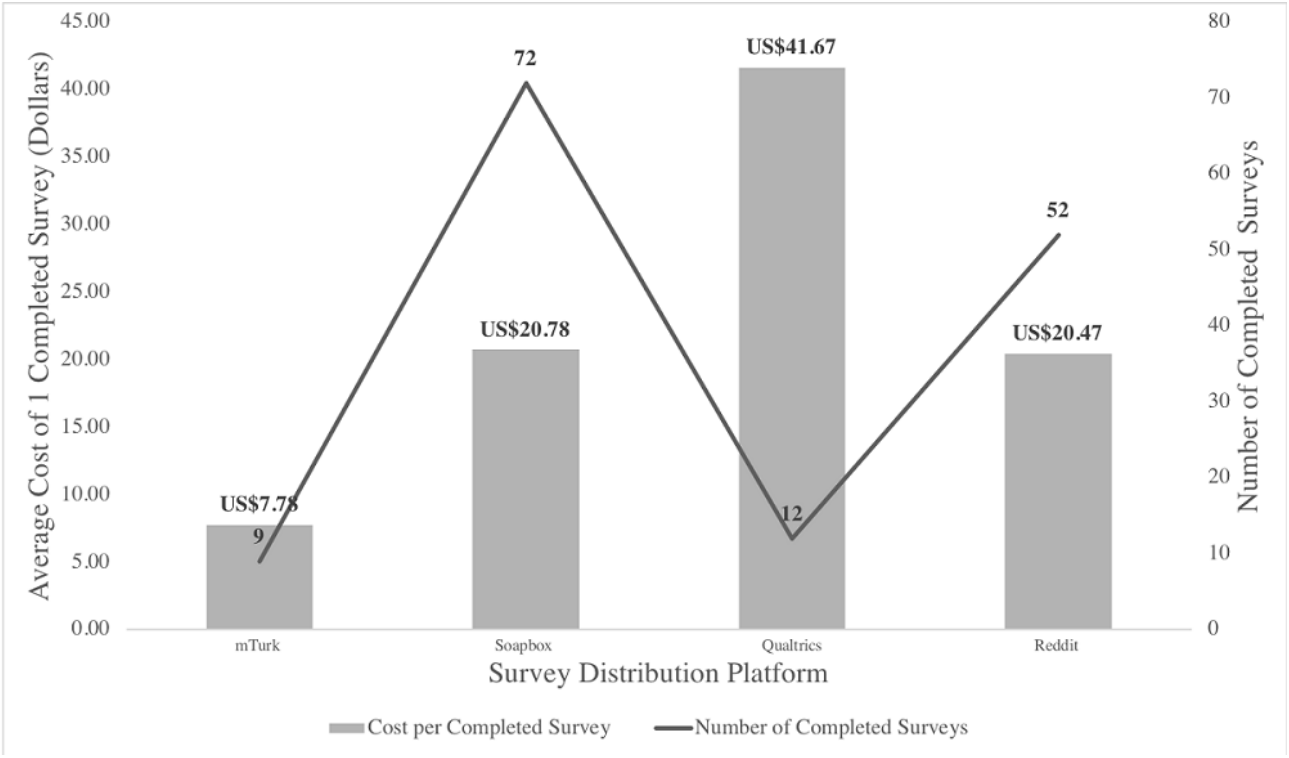
[a]Comparison across platforms by chi-square contingency test.

[b]Comparison across platforms by analysis of variance.

[c]Comparison across platforms by Kruskal-Wallis test.

[d]Comparison across platforms by Fisher exact test.

Figure 2. Cost per completed survey compared with the number of completed quality surveys by platform, 2017.



Cost per Completed Survey

Cost per completed survey and total number of completed surveys are shown in Figure 2. By far the cheapest method for distributing surveys, mTurk had an average cost per completed quality survey of US $7.78 (including the cost of completed screener surveys.) However, there seems to be a trade-off between average cost and survey completion. This platform yielded some of the fewest completed surveys.

Soapbox Sample placed a minimum fee of US $500 and priced each survey at US $24.93; after the amount of surveys we received exceeded US $500, each additional survey cost US $24.93. Because Soapbox produced a relatively high amount of low-quality surveys, the Web-based recruitment company only charged us for 60 high-quality surveys. For a total of US $1495.80 and 72 completed overall surveys, the price per completed survey was US $20.78.

Similar to Soapbox Sample, Qualtrics Panel placed a minimum fee of US $500 until the cost of completed responses exceeded US $500 (at US $10 per completed survey). Qualtrics Panel was unable to guarantee a minimum number of responses given our narrow inclusion criteria. With only 12 completed surveys from Qualtrics Panel, each completed survey cost US $41.67.

For the Reddit platform, we spent US $122.67 on Reddit ads, running a total of 9 ad campaigns on 4 subreddits that received a total of 146,885 impressions and 350 clicks. We received 178 completed responses, 95 of which received a US $10 e-gift card using Giftbit. Of the gift cards sent, 9 respondents accepted the gift but never used their reward. These respondents allowed the gift to expire and 1 respondent even canceled his or her gift. Therefore, we utilized US $850 of the US $950 spent on rewards. The average cost per completed survey was US $20.37.

Discussion

Principal Findings

In this explanatory analysis, we compared the yield from and cost of four Web-based survey respondent platforms for carrying out a cross-sectional study of a hard-to-reach population: pregnant smokers. The quantity, quality, and cost of completed surveys varied widely across platforms. Note that without optimized or standardized recruitment methods, we will have variation in yields by definition.

Soapbox and Qualtrics Panel, two similar services offering existing panels of survey respondents, produced very different yields, with the Soapbox producing more eligible surveys by a factor of 6 (Soapbox, n=72; Qualtrics Panel, n=12). The 2 platforms produced similar quality yields: 67% of Soapbox surveys and 86% of Qualtrics Panel passed the quality screens. Both companies described the challenge of recruiting pregnant smokers to complete our surveys upfront. Although Qualtrics produced a low eligible yield (26%), it produced the second-highest quality percentage of 86%. In contrast, Soapbox recruited a higher number of respondents than Qualtrics Panel could, but only 67% of Soapbox surveys were able to pass the quality screens. Going forward, we would be more likely to use Soapbox than Qualtrics Panel, given the higher yield.

Amazon's mTurk platform, which claims to have over 500,000 workers, produced a very low eligible yield (n=9) but the highest-quality surveys (100%). We attribute the high-quality yield to using only "mTurk Masters" who had a 95% approval rating. However, use of this selective qualification could similarly have limited the number of eligible participants, attributing to our low eligible yields. Loss-to-follow up from our screener to the main survey contributed to the low yield;

going forward, we will likely combine the screener into the main survey, pay a smaller fee for the screener portion, and a quality bonus for eligible completers.

Placing ads on Reddit subreddits initially appeared a promising way to drive eligible respondents to our survey. The ads we placed produced 178 completed surveys with an eligibility yield of 72%. However, its proportion of quality surveys was the lowest, with a quality yield of 29%. We were also subject to an unfortunate "hack" of the survey. This "hack" seriously diminished the credibility of the survey results derived from this platform. Going forward, we would be unlikely to use Reddit to disseminate surveys.

For cross-sectional observational studies such as our survey, the ability to generalize results from the sample to a broader population is crucial [24]. We noted distinct sociodemographic profiles across our 4 platforms, with more variability in Reddit and mTurk samples and less in the Qualtrics and Soapbox samples. This is not surprising given, again, the very narrow inclusion criteria for our sample. Reddit and Soapbox contributed the most demographic variability in terms of gathering responses from people in various races, education levels, and income brackets. This cross-platform variability appears to somewhat alleviate the threats to external validity that come with collecting information solely through one platform. However, the benefits of multiple platform recruiting do come at a significant cost—multiple platform recruiting multiplies the complexity and monetary expenses of running a study.

Limitations

We note 4 important limitations of our explanatory study. We explored only 4 of the various online recruitment platforms that could be leveraged for participant recruitment. At the time when the study was conducted, Reddit identified 12,927,467 active users. Platforms such as Facebook or Twitter may have been able to be used because of their wider user base, with Facebook boasting 1,712,000,000 users and Twitter 313,000,000 users as of the second quarter in 2016. However, Facebook's inability to identify pregnant and smoking women in its advertising options prevented its usage in this study. Although Twitter does allow users to produce ads much like Reddit, Twitter's reach also depends on the sender's popularity. That is, many Twitter users must first "follow" the advertiser in order to see the advertiser's ads. Another limitation of the study is consistency across platforms. For mTurk and Qualtrics, sample size was relatively limited. As with all studies utilizing online recruitment methods, our study relied on self-reported information. This presents the possibility that not all responses are completely accurate. A third limitation is that the method in which we recruited through Reddit may have yielded inaccurate responses. The mentions of "pregnancy" and "smoking" in our ads may have primed potential participants. This also may have been the reason for the "hack" that we experienced toward the end of the advertising campaign. Next, we recognize that we could not verify smoking status via Web. Although we attempted to design our quality screens by asking about the number of cigarettes in a pack and their preferred brand, we realize this is not a proven method of verifying smoking status. This is usually not an issue faced during in-person recruitment. For most in-person studies, smoking verification methods such as urine cotinine tests are more reliable and can be performed in the setting of a clinic. Lastly, it is important to address the intrinsic differences in the platforms that could have led to variation. First, the methods to target pregnant smokers vary by platform such that some, such as Reddit, are based off of subscriptions and readership while others, such as mTurk, are based off of demographic probability. Therefore, platforms that allow for customization and targeting might lead to a higher percentage of eligible participants than platforms that do not allow for customization. Second, given that the method of incentivizing differs across platforms, users of one platform may be more willing to complete the survey than users of another platform. However, to ensure generalizability, we attempted to use each platform as a typical research would and therefore ensured that the incentive participants received in each platform was similar to those of past researchers in the same platform. Finally, although we do not find it to be a limitation, we note that the difference in methods between mTurk and the other platforms may raise concerns. Turk Prime's specific ability to only administer HITs to specific mTurk workers based on their anonymous ID meant that mTurk was the only platform where identifying information would not be collected but researchers could still follow up to respondents. In contrast, the Reddit platform required contact information to use as a screener. Therefore, the addition of the screener for mTurk's platform is more of an asset than a limitation to our study.

More broadly speaking, there are limitations in the use of online recruitment when compared with in-person clinical recruitment. Online recruitment methods are limited by demographic representation, biases, and uncertainties. By nature, samples recruited through Web-based methods are not representative of the broader target population [25]. For example, racial and ethnic disparities exist in the accessibility and frequency of computer use in the United States. However, these are minimized when analyzing Internet access via mobile devices [26]. Similarly, those who participate in studies hosted on mTurk tend to be younger, more liberal, and more familiar with Web-based technology [26-28]. Nevertheless, although mTurk is less representative than Web-based panel services or national probability samples, it may provide a more representative sample of the United States than traditional in-person sampling methods [29]. Online recruitment may also yield lower-quality data as this paper has shown. Accountability and validity are generally more difficult to enforce in online research. Web-based studies tend to rely on self-report, and subjects can more easily provide responses that do not reflect their actual beliefs, values, or behavior. On mTurk, "spammers" and "bots" capitalize on this and find ways to receive rewards offered by a study without successfully completing the intended task [18,30] with obvious adverse consequences for the data validity. Inattention and lack of intrinsic motivation may lead to superficial responses and higher attrition rates, although this can be mitigated somewhat by attention checks—supplementary questions and tasks that determine whether a participant is fully paying attention [18]. While the distance between researcher and subject may reduce social desirability bias, Web-based research is not immune from it [27].

Comparison With Prior Work

Our findings are not consistent with recent studies looking at online recruitment yields, cost, and representativeness. Other studies that have focused on mTurk as a method to recruit participants have concluded that the Web-based service is relatively inexpensive and efficient [31]. Select studies have further suggested that small payment amounts do not appear to significantly detract from quality [20]. Although we have confirmed that mTurk is indeed inexpensive in our study, it may not, however, have been the most cost-effective recruitment method for our purposes. The number of quality responses that we obtained through our mTurk recruitment efforts was smaller than desired. In part, this may have been due to the specificity of our selection criteria. Indeed, research has shown that mTurk samples tend to be more diverse and thus, more representative of the general population than other Web-based and in-person recruitment methods [29]. Consequently, mTurk may be a more attractive method of recruitment for studies that have less stringent selection criteria than ours.

However, our survey confirmed recent literature regarding online recruitment for hard-to-reach populations. In a study conducted by Martinez et al, the researchers acquired tens of thousands of impressions on different Websites such as Facebook and Craigslist and mobile phone apps such as Instagram, Grindr, and Jack'd to recruit HIV-positive gay Latinos [32]. Similarly, our study used various platforms (subreddits) within the large social media Reddit platform to push our survey to populations of interest. After reaching over 100,000 viewers, we received about 200 completed surveys, many of which were of dubious quality or validity. Given that Admon et al used Facebook to recruit a large robust sample of pregnant women through advertisements at very low costs, future research is needed to compare these crowdsourcing platforms and others with more social media sites such as Facebook, Twitter, and Instagram [33]. Furthermore, future studies should use an in-person sample as a baseline to compare the Web-based platforms and determine efficacy.

Conclusions

This explanatory study confirmed significant variability in recruitment success, quality, and cost across multiple Web-based survey research platforms and social media recruitment strategies. With one exception (mTurk), we observed an inverse relationship between cost per completed survey and number of surveys completed; sample characteristics also varied by platform. We procured higher quality samples from portals that prescreened respondents for us (Soapbox and Qualtrics Panel) vs platforms that draw from a larger pool of potential respondents (mTurk and Reddit). The results of these recruitment efforts suggest that it remains challenging to strike an optimal balance between quality and quantity when recruiting hard-to-reach subjects through Web-based platforms.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Sample of questions eligible respondents answered from survey.

[PDF File (Adobe PDF File), 43KB - resprot_v7i4e101_app1.pdf]

References

1. Cliver SP, Goldenberg RL, Cutter GR, Hoffman HJ, Davis RO, Nelson KG. The effect of cigarette smoking on neonatal anthropometric measurements. Obstet Gynecol 1995 Apr;85(4):625-630. [doi: 10.1016/0029-7844(94)00437-I] [Medline: 7898845]
2. DiClemente CC, Dolan-Mullen P, Windsor RA. The process of pregnancy smoking cessation: implications for interventions. Tob Control 2000;9 Suppl 3:III16-III21 [FREE Full text] [Medline: 10982900]
3. DiFranza JR, Lew RA. Effect of maternal cigarette smoking on pregnancy complications and sudden infant death syndrome. J Fam Pract 1995 Apr;40(4):385-394. [Medline: 7699353]
4. Lorencatto F, West R, Michie S. Specifying evidence-based behavior change techniques to aid smoking cessation in pregnancy. Nicotine Tob Res 2012 Sep;14(9):1019-1026. [doi: 10.1093/ntr/ntr324] [Medline: 22318690]
5. Office of the Surgeon General (US), Office on Smoking and Health (US). The Health Consequences of Smoking: A Report of the Surgeon General Internet. Atlanta (GA): Centers for Disease Control and Prevention (US); 2004.
6. Windsor RA, Cutter G, Morris J, Reese Y, Manzella B, Bartlett EE, et al. The effectiveness of smoking cessation methods for smokers in public health maternity clinics: a randomized trial. Am J Public Health 1985 Dec;75(12):1389-1392. [Medline: 4061709]
7. Alshaarawy O, Anthony JC. Month-wise estimates of tobacco smoking during pregnancy for the United States, 2002-2009. Matern Child Health J 2015 May;19(5):1010-1015 [FREE Full text] [doi: 10.1007/s10995-014-1599-4] [Medline: 25112459]

8. Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev 2009 Jul 08(3):CD001055 [FREE Full text] [doi: 10.1002/14651858.CD001055.pub3] [Medline: 19588322]
9. Higgins ST, Washio Y, Heil SH, Solomon LJ, Gaalema DE, Higgins TM, et al. Financial incentives for smoking cessation among pregnant and newly postpartum women. Prev Med 2012 Nov;55 Suppl:S33-S40 [FREE Full text] [doi: 10.1016/j.ypmed.2011.12.016] [Medline: 22227223]
10. McBride CM, Emmons KM, Lipkus IM. Understanding the potential of teachable moments: the case of smoking cessation. Health Educ Res 2003 Apr;18(2):156-170 [FREE Full text] [Medline: 12729175]
11. Ershoff DH, Quinn VP, Boyd NR, Stern J, Gregory M, Wirtschafter D. The Kaiser Permanente prenatal smoking-cessation trial: when more isn't better, what is enough? Am J Prev Med 1999 Oct;17(3):161-168. [Medline: 10987630]
12. Centers for Disease Control and Prevention. 2002 Aug 30. Women and smoking: a report of the Surgeon General. Executive summary URL: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5112a4.htm [accessed 2018-04-05] [WebCite Cache ID 6yRdVvDYK]
13. Vardavas CI, Chatzi L, Patelarou E, Plana E, Sarri K, Kafatos A, et al. Smoking and smoking cessation during early pregnancy and its effect on adverse pregnancy outcomes and fetal growth. Eur J Pediatr 2010 Jun;169(6):741-748. [doi: 10.1007/s00431-009-1107-9] [Medline: 19953266]
14. Greenlaw C, Brown-Welty S. A comparison of web-based and paper-based survey methods: testing assumptions of survey mode and response cost. Eval Rev 2009 Oct;33(5):464-480. [doi: 10.1177/0193841X09340214] [Medline: 19605623]
15. Chapple A, Ziebland S, McPherson A. Stigma, shame, and blame experienced by patients with lung cancer: qualitative study. BMJ 2004 Jun 19;328(7454):1470 [FREE Full text] [doi: 10.1136/bmj.38111.639734.7C] [Medline: 15194599]
16. Carter-Harris L, Bartlett ER, Warrick A, Rawl S. Beyond traditional newspaper advertisement: leveraging Facebook-targeted advertisement to recruit long-term smokers for research. J Med Internet Res 2016;18(6):e117 [FREE Full text] [doi: 10.2196/jmir.5502] [Medline: 27306780]
17. Kristan J, Suffoletto B. Using online crowdsourcing to understand young adult attitudes toward expert-authored messages aimed at reducing hazardous alcohol consumption and to collect peer-authored messages. Transl Behav Med 2015 Mar;5(1):45-52 [FREE Full text] [doi: 10.1007/s13142-014-0298-4] [Medline: 25729452]
18. Mason W, Suri S. Conducting behavioral research on Amazon's Mechanical Turk. Behav Res Methods 2012 Mar;44(1):1-23. [doi: 10.3758/s13428-011-0124-6] [Medline: 21717266]
19. Briones EM, Benham G. An examination of the equivalency of self-report measures obtained from crowdsourced versus undergraduate student samples. Behav Res Methods 2017 Feb;49(1):320-334. [doi: 10.3758/s13428-016-0710-8] [Medline: 26907746]
20. Buhrmester M, Kwang T, Gosling SD. Amazon's Mechanical Turk: a new source of inexpensive, yet high-quality, data? Perspect Psychol Sci 2011 Jan;6(1):3-5. [doi: 10.1177/1745691610393980] [Medline: 26162106]
21. Amante DJ, Hogan TP, Pagoto SL, English TM, Lapane KL. Access to care and use of the Internet to search for health information: results from the US National Health Interview Survey. J Med Internet Res 2015;17(4):e106 [FREE Full text] [doi: 10.2196/jmir.4126] [Medline: 25925943]
22. Chang T, Chopra V, Zhang C, Woolford SJ. The role of social media in online weight management: systematic review. J Med Internet Res 2013;15(11):e262 [FREE Full text] [doi: 10.2196/jmir.2852] [Medline: 24287455]
23. Goodman JK, Cryder CE, Cheema A. Data collection in a flat world: the strengths and weaknesses of Mechanical Turk samples. J Behav Decis Mak 2012 Apr 02;26(3):213-224. [doi: 10.1002/bdm.1753]
24. Lane TS, Armin J, Gordon JS. Online recruitment methods for Web-based and mobile health studies: a review of the literature. J Med Internet Res 2015;17(7):e183 [FREE Full text] [doi: 10.2196/jmir.4359] [Medline: 26202991]
25. Leach LS, Butterworth P, Poyser C, Batterham PJ, Farrer LM. Online recruitment: feasibility, cost, and representativeness in a study of postpartum women. J Med Internet Res 2017 Mar 08;19(3):e61 [FREE Full text] [doi: 10.2196/jmir.5745] [Medline: 28274906]
26. Gee GC, Ford CL. Structural racism and health inequities: old issues, new directions. Du Bois Rev 2011 Apr;8(1):115-132 [FREE Full text] [doi: 10.1017/S1742058X11000130] [Medline: 25632292]
27. Chandler J, Mueller P, Paolacci G. Nonnaïveté among Amazon Mechanical Turk workers: consequences and solutions for behavioral researchers. Behav Res Methods 2014 Mar;46(1):112-130. [doi: 10.3758/s13428-013-0365-7] [Medline: 23835650]
28. Christenson DP, Glick DM. Crowdsourcing panel studies and real-time experiments in MTurk. Polit Methodol 2013;20(2):27-32 [FREE Full text]
29. Berinsky AJ, Huber GA, Lenz GS. Evaluating online labor markets for experimental research: Amazon.com's Mechanical Turk. Political Anal 2012;20(3):351-368 [FREE Full text] [doi: 10.1093/pan/mpr057]
30. Chan C, Holosko MJ. An overview of the use of Mechanical Turk in behavioral sciences: implications for social work. Res Soc Work Pract 2015 Jul 06;26(4):441-448. [doi: 10.1177/1049731515594024]
31. Brandon DM, Long JH, Loraas TM, Mueller-Phillips J, Vansant B. Online instrument delivery and participant recruitment services: emerging opportunities for behavioral accounting research. Behav Res Account 2014 Apr;26(1):1-23. [doi: 10.2308/bria-50651]

32. Martinez O, Wu E, Shultz AZ, Capote J, López RJ, Sandfort T, et al. Still a hard-to-reach population? Using social media to recruit Latino gay couples for an HIV intervention adaptation study. J Med Internet Res 2014 Apr 24;16(4):e113 [FREE Full text] [doi: 10.2196/jmir.3311] [Medline: 24763130]
33. Admon L, Haefner JK, Kolenic GE, Chang T, Davis MM, Moniz MH. Recruiting pregnant patients for survey research: a head to head comparison of social media-based versus clinic-based approaches. J Med Internet Res 2016 Dec 21;18(12):e326 [FREE Full text] [doi: 10.2196/jmir.6593] [Medline: 28003174]

Abbreviations

HIT: human intelligence task
mTurk: Amazon Mechanical Turk

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Original Paper

Capturing Ultraviolet Radiation Exposure and Physical Activity: Feasibility Study and Comparison Between Self-Reports, Mobile Apps, Dosimeters, and Accelerometers

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Abstract

Background: Skin cancer is the most prevalent cancer in Australia. Skin cancer prevention programs aim to reduce sun exposure and increase sun protection behaviors. Effectiveness is usually assessed through self-report.

Objective: It was the aim of this study to test the acceptance and validity of a newly developed ultraviolet radiation (UVR) exposure app, designed to reduce the data collection burden to research participants. Physical activity data was collected because a strong focus on sun avoidance may result in unhealthy reductions in physical activity. This paper provides lessons learned from collecting data from participants using paper diaries, a mobile app, dosimeters, and accelerometers for measuring end-points of UVR exposure and physical activity.

Methods: Two participant groups were recruited through social and traditional media campaigns 1) Group A—UVR Diaries and 2) Group B—Physical Activity. In Group A, nineteen participants wore an UVR dosimeter wristwatch (University of Canterbury, New Zealand) when outside for 7 days. They also recorded their sun exposure and physical activity levels using both 1) the UVR diary app and 2) a paper UVR diary. In Group B, 55 participants wore an accelerometer (Actigraph, Pensacola, FL, USA) for 14 days and completed the UVR diary app. Data from the UVR diary app were compared with UVR dosimeter wristwatch, accelerometer, and paper UVR diary data. Cohen kappa coefficient score was used to determine if there was agreement between categorical variables for different UVR data collection methods and Spearman rank correlation coefficient was used to determine agreement between continuous accelerometer data and app-collected self-report physical activity.

Results: The mean age of participants in Groups A (n=19) and B (n=55) was 29.3 and 25.4 years, and 63% (12/19) and 75% (41/55) were females, respectively. Self-reported sun exposure data in the UVR app correlated highly with UVR dosimetry (κ=0.83, 95% CI 0.64-1.00, P<.001). Correlation between self-reported UVR app and accelerometer-collected moderate to vigorous physical activity data was low (ρ=0.23, P=.10), while agreement for low-intensity physical activity was significantly different (ρ=-0.49, P<.001). Seventy-nine percent of participants preferred the app over the paper diary for daily self-report of UVR exposure and physical activity.

Conclusions: This feasibility study highlights self-report using an UVR app can reliably collect personal UVR exposure, but further improvements are required before the app can also be used to collect physical activity data.

(JMIR Res Protoc 2018;7(4):e102) doi:10.2196/resprot.9695

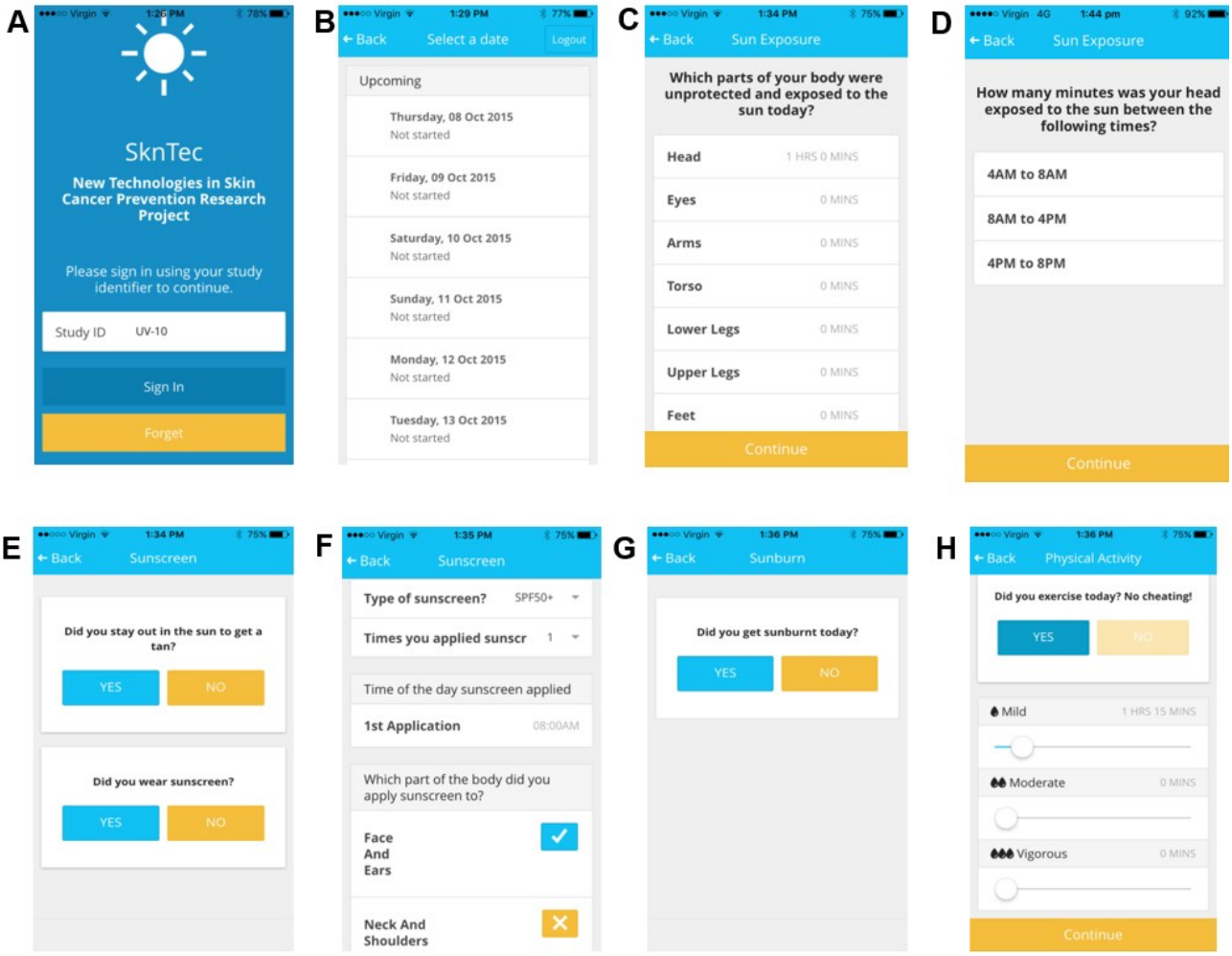
KEYWORDS

sun-protection; sunburn; health behaviour; health promotion; formative research

Introduction

In the United States, the number of new cases of melanoma is predicted to rise from 70,000 in 2007-2011 to 116,000 in 2026-2031 [1], and similar increases are expected in other countries around the world. Ultraviolet radiation (UVR) is the main environmental risk factor for melanoma. Accurate measurement of UVR exposure is important for skin cancer prevention studies, which aim to reduce peoples' sun exposure. Monitoring physical activity levels is also important in skin cancer prevention studies as three large-scale cross-sectional studies have shown increased levels of physical activity among adults were associated with higher levels of sunburn [2-5].

Figure 1. Ultralight radiation diary app. A) Log-in screen for participants to enter their unique study identifier. B) Home screen. In the home screen, participants select the date to enter their sun exposure and sun protection used for that day. The app will not let participants enter their data for the days ahead. They can only enter data for the current day or previous days. C) The participant enters which parts of the body were unprotected and exposed to the sun. In this image, the participant has specified that the head was exposed for 1 hour. D) Once a body site is selected, the next screen asks participants how many minutes they were exposed to the sun for each timeblock: 4am- 8am, 8am-4pm, and 4pm-8pm. E) The participant selects "yes" or "no", depending on whether they stayed in the sun to get a tan and whether they wore sunscreen for the day. If a participant selects "yes" to the sunscreen question, the panel F screen appears, which details the sunscreen sun protection factor (SPF), number of times applied, time of day applied, and area of application to the body, for each application. F) This screen illustrates a participant that applied SPF 50+ sunscreen once at 8am to their face and ears. Users can scroll down to select different parts of the body where sunscreen was applied. G) The participant selects "yes" or "no", depending on whether they were sunburnt that day. H) The participant selects "yes" or "no", depending on whether they excercised that day, recording the duration and level of activity as mild, moderate, or vigorous.



UVR exposure data can be collected via direct observation, UVR dosimeters, or self-report, particularly for current or recent exposures. Objective measures of chronic/cumulative UVR exposure are silicone casts of the dorsum of the hand [6], DNA mutation loads of eye lids [7], and measurements of eye conjunctival ultraviolet autofluorescence [8]. The selection of the measurement tool depends on the research question, feasibility, costs, and burden to study participants [9]. Self-reported paper UVR diaries are a common form of data collection [10]. However, there are limitations to paper diaries. For example, they can be burdensome to complete, participants may miss questions, and they do not allow for real-time monitoring of compliance. Electronic data collection could overcome some of these barriers, streaming data directly into an electronic database, thus permitting real-time monitoring of participants' entries and generating automated reminders to input data regularly, thereby reducing missing data.

UVR dosimeter technology varies greatly ranging from low-tech solutions such as polysulphone film dosimeters [11] to electronic time-stamped dosimeters [12]. Their use is not always feasible in large-scale population studies due to cost and logistics [13]. The limitations of UVR dosimeters include the device's requirement to be worn with a clear orientation to the sun for accurate measurements and its inability to record other context-relevant information, such as use of sunscreen or protective clothing by participants. Previous studies have shown acceptable correlation between UVR dosimeter dose and paper questionnaire–reported time outdoors [10].

Similar measurement issues apply to physical activity, which can be collected using self-reported questionnaires or via objective assessment, with the use of accelerometers as the most popular choice. It is accepted that self-report and objective measures capture distinct and complementary aspects of physical activity [14,15]. There are no clear trends in the over- or under-reporting of physical activity when comparing self-report and objective methods [16]. A systematic review of 148 studies found low correlation between self-reported and objective measurements of physical activity [17].

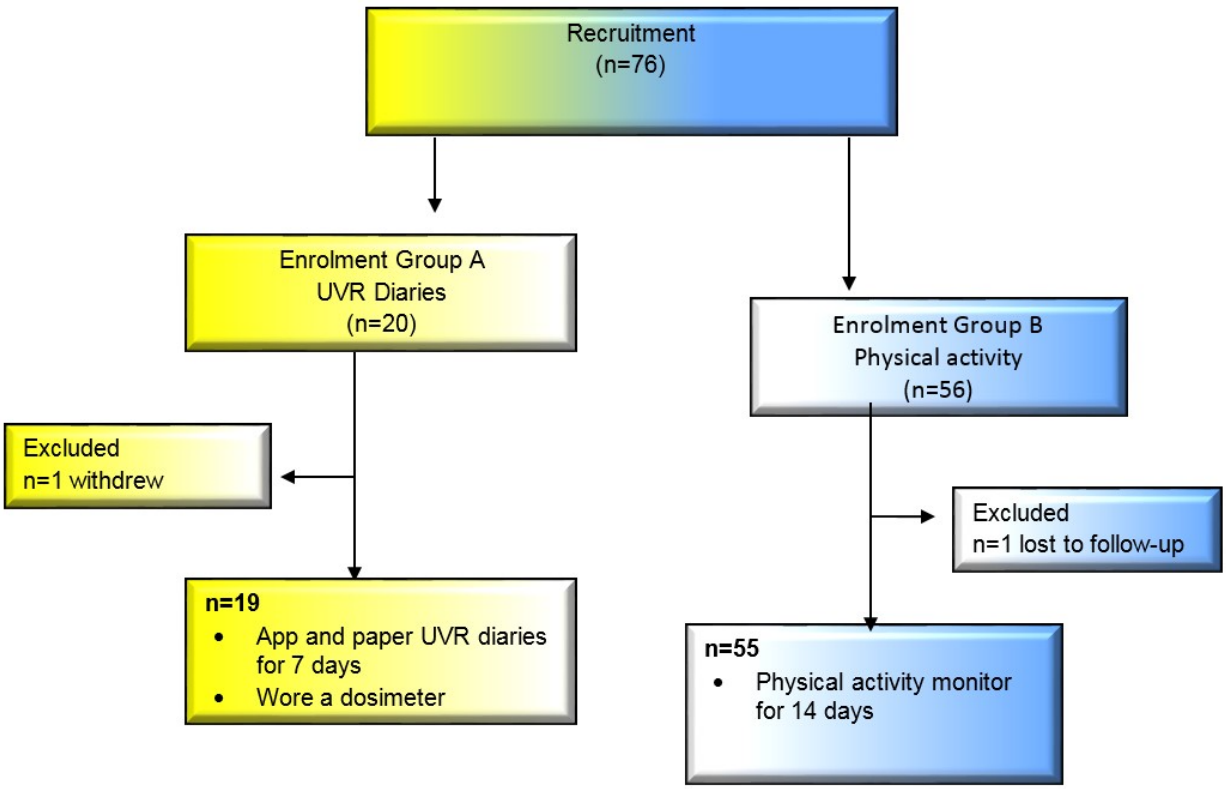
It was the primary aim of this study to compare UVR exposure data collected using paper diaries to those collected via a mobile app (Figure 1; Multimedia Appendix 1: UVR diary app), and compare both to objectively collected data from UVR dosimeters. A secondary aim was to compare physical activity collected via the app to data from accelerometers.

Methods

Recruitment

Participants were recruited in Brisbane, Australia (September 2015-February 2016, during spring and summer in Australia). The Queensland University of Technology's Human Ethics Committee approved the study and all participants gave written informed consent in line with the Declaration of Helsinki (Approval-1400000302). A convenience sample of participants were recruited using television, media, university email, social media, and flyers distributed at local sporting centers or clubs. Eligibility criteria included males and females, 18 to 35 years, who have never been diagnosed with a melanoma and own a smartphone. Participants completed an online demographic questionnaire and were recruited consecutively into 2 participant groups 1) Group A—UVR Diaries; and 2) Group B—Physical Activity (Figure 2).

Figure 2. Flow chart of study participants.



Ultraviolet Radiation Exposure Behavior

In Group A, participants recorded their sun exposure, sunburn, and physical activity levels using both the UVR app and a paper UVR diary for 7 consecutive days. During these 7 days, participants were also asked to wear an UVR dosimeter wristwatch (University of Canterbury, New Zealand) when outside. At the end of the 7-day assessment period, participants completed an audio-recorded telephone or in-person interview. This was conducted to assess in-depth the usability and convenience of the app and paper diaries. Example interview questions include: "What barriers did you experience using each of the diaries?" and "How helpful were each of the diaries to track your sun behavior?" In the interview, participants were also asked to select whether they preferred to complete a UVR diary method either 1) on paper or 2) via an app.

Devices Used to Capture UVR Exposure

Ultraviolet Radiation Dosimeter

The features of the dosimeter were previously described in detail [12]. Each UVR dosimeter device was calibrated to the UVR levels in Queensland using the Australian Radiation Protection and Nuclear Safety Agency weather station data. Briefly, each device captured data for 3 hours between 11am to 2pm on a cloud-free day in an open field 100 metres from the weather station. Any device that recorded data greater than 5% outside the weather station output was adjusted and retested following the above protocol. Three dosimeters malfunctioned (3/19) during the study with data unusable when downloaded from the device by the research team. Participants were not reissued another dosimeter to replace the nonfunctioning one as the data collection period had ended.

Paper Ultraviolet Radiation Diaries

The paper diary (Multimedia Appendix 2) was adapted from previous studies [9,18].

Ultraviolet Radiation App

The app questions were modified from the paper diaries for the smaller mobile screen. Figure 1 displays each question the user is asked to complete in the app. An advantage of the app was data fields need to be completed before the user can continue to the next section.

Physical Activity

In Group B, participants used the same UVR app as Group A and wore an Actigraph wGT3X-BT accelerometer (Actigraph, Pensacola, FL, USA) on the hip for 14 consecutive days.

Accelerometer

Data were processed and scored using ActiLife software (version 6.11.9) [19]. Raw data were converted into 1 minute epochs. Sufficient wear time was defined as ≥10 hours/day. Days with insufficient wear time were excluded.

Statistical Analysis

SPSS software (version 23.0) was used to calculate Cohen kappa coefficient score to determine if there was agreement between categorical variables for different UVR data collection methods. Spearman rank correlation coefficient was used to determine correlation between accelerometer data and app-collected self-report physical activity. Values of >0.4 to 0.6 were considered moderate, >0.6 to 0.8 substantial, and >0.8 to 1.0 almost perfect agreement [20]. The qualitative data was coded into 3 themes: enablers, barriers to use, and behavior change.

Personal UVR exposure variables were dichotomised to categorical data: UVR diary app data was coded "yes" if the participant responded affirmative when asked "Did the participant report sun exposure between 8am to 4pm?" UVR dosimeter data was coded "yes" if the dose of UVR detected between 8am to 4pm was above 0.05 standard erythemal dose (SED), and the UVR dosimeter data was coded "no" if the dose of UVR detected between 8am to 4pm was below 0.01 SED. Paper diary data was coded "yes" if the participants reported any sun exposure between 8am to 4pm.

Personal physical activity variables were coded into intensity levels: UVR diary app data was coded "yes" if the participant responded affirmative when asked "Did you exercise today?" and was further coded into intensity levels based on the selection of "mild", "moderate", or "vigorous." The length of time that exercise was conducted was also collected; accelerometer data between 100 to 2019 counts per minute were scored as low intensity and ≥2020 counts per minute were scored as moderate to vigorous intensity. This was done using ActiLife software (version 6.11.9) [19].

Results

Participant Characteristics

The mean age of participants in Groups A and B was 29.3 and 25.4 years, respectively. In Group A and B, most participants were female (12/19, 63% and 41/55, 75% respectively) and the majority had fair skin (10/19, 53% and 33/55, 60% respectively). Participant characteristics are reported in Table 1. Complete data is available for 19 participants in Group A and 55 participants in Group B. One participant in Group A (1/20, 5%) withdrew due to time constraints and 1 participant in Group B (1/56, 2%) was lost to follow-up as contact could not be re-established. All 19 participants in Group A completed 7 days of app and paper diaries, and a total of 112 days with dosimeter data were available from 16 of these participants. Forty-two per cent of participants (8/19) had 1 or more answer fields missing in the paper diary. There was no missing data in the UVR app diary. In Group B, 53 participants had sufficient accelerometer wear time and corresponding app data for at least 1 day, with on average, 7 days of objective and self-reported physical activity data available per participant (SD 3.5; total days=372).

Table 1. Participant characteristics. UVR: ultraviolet radiation.

Characteristics	Group A UVR diaries (n=19), n (%)	Group B physical activity (n=55), n (%)
Age mean (range 18-35)	29.3	25.4
Gender		
Female	12 (63)	41 (75)
Male	7 (37)	14 (25)
Highest completed education		
Completed high school	3 (16)	10 (18)
Trade or technical certification or diploma	2 (10)	6 (11)
University or college degree	14 (74)	39 (71)
Current work situation		
Employed full-time	9 (48)	12 (22)
Employed part-time or casual	5 (26)	12 (22)
Student	5 (26)	31 (56)
Is your main job now		
Mainly indoors	16 (84)	49 (89)
Mainly outdoors	0 (0)	0 (0)
About equal amounts indoors and outdoors	3 (16)	6 (11)
Eye color		
Blue or gray	8 (42)	15 (27)
Green	3 (16)	6 (11)
Brown	8 (42)	27 (49)
Other	0 (0)	7 (13)
Skin color		
Fair	10 (53)	33 (60)
Medium	8 (42)	15 (27)
Olive/Dark	1 (5)	6 (11)
Black	0 (0)	1 (2)
Would your skin burn in strong summer sun for 30 minutes without protection?		
My skin would not burn at all	3 (16)	7 (13)
My skin would burn lightly	3 (16)	17 (31)
My skin would burn moderately	10 (52)	18 (33)
My skin would burn severely	3 (16)	13 (23)
Would your skin tan if you spend several weeks at the beach and you are often in the strong sun without any protection?		
My skin would not tan	1 (5)	6 (11)
My skin would tan lightly	5 (26)	10 (18)
My skin would tan moderately	9 (48)	24 (44)
My skin would tan deeply	4 (21)	15 (27)

Table 2. Overall agreement between measurements. UVR: ultraviolet radiation.

Measurement	Sun exposure, n		Cohen kappa coefficient score (95% CI)
	Yes	No	
Did the participant report sun exposure between 8am to 4pm (yes/no, n=16)			0.83 (0.64-1.00)
UVR diary app	98	14	
UVR dosimeter[a,b]	95	15	
Did the participant report sun exposure between 8am to 4pm (yes/no, n=19)			0.64 (0.44-0.84)
UVR diary app	114	19	
Paper sun diary	117	16	
Did the participant report sunscreen use (yes/no, n=19)			0.97 (0.93-1.00)
UVR diary app	55	78	
Paper sun diary	57	76	

[a]"Yes" defined by a dose of UVR detected above 0.05 standard erythemal dose, between 8am to 4pm.

[b]Missing data due to dosimeter not being worn (n=2 days; 2 participants forgot to wear their dosimeter on 1 day of their intervention).

Ultraviolet Radiation Exposure Behavior

Self-reported unprotected UVR exposure had high agreement with dosimeter data (κ=0.83, 95% CI, 0.64-1.00, *P*<.001, Table 2). There was moderate agreement between UVR exposure reported using the paper diary and the app (κ=0.64, 95% CI 0.44-0.84, *P*<.001). There was almost perfect agreement for sunscreen use between the app and paper formats, (κ=0.97, 95% CI, 0.93-1.00, *P*<.001).

Physical Activity

The Spearman rank coefficient for low-intensity physical activity collected via self-report and accelerometer was ρ=–0.488, *P*<.001, which represents low agreement. It was ρ=0.230, *P*=.10 for moderate-to-vigorous–intensity physical activity, which represents low agreement. The mean difference in estimated minutes per day between measures was –201 minutes/day for low-intensity and –18 minutes/day for moderate-to-vigorous–intensity physical activity.

Interviews with Participants

In the interviews, participants reported that the UVR app was easier (16/19, 84%) and quicker (on average, 6 minutes for paper and 4 minutes for app) to use. Most people preferred the app over the paper diary (15/19, 79%), and all would prefer to use the app for monitoring periods of more than 7 days. Eight out of nineteen participants (42%) experienced barriers using the app including: insufficient phone battery (1/19, 5%); app crashing (2/19, 11%); lack of internet access (1/19, 5%); or smartphone update required (1/19, 5%). Eight out of nineteen participants (42%) reported barriers for the paper diary, including no pen (4/19, 21%); no surface to write on (1/19, 5%); flipping pages to view clothing coding (4/19, 21%); and inconvenience for travel (3/19, 16%). No participants reported losing their paper diary or mobile phone. Fifty-three per cent of participants (10/19) reported that recording their UVR exposure on a daily basis made them aware and encouraged them to use more sun protection.

Discussion

Principal Findings

Objectively measured UVR exposure via a dosimeter and self-reported UVR exposure via an app demonstrated substantial agreement. This finding adds to the evidence base that self-report using an app can be a valid form of UVR exposure data collection. Our study results were similar to previous studies which also supported the validity of self-reported diary-collected UVR exposure compared to dosimeters [10,21-23]. An Australian study (n=47) of older adults compared agreement between a self-reported UVR diary and dosimeters over 7 days, similar to our study (Spearman rank correlations r_s=0.41; 95% CI 0.10, 0.64; *P*=.01) [10]. The reliability and validity of sun exposure questions were compared to polysulphone dosimeter badges in 125 school children aged 14-15 years. Data were collected over 4 consecutive weekend days and the strongest Pearson correlation coefficient was between the questions "time in the sun"/"time spent outdoors" and dosimeters with r=0.52, *P*<.001 [21]. Glanz et al [22] also found correlations between a self-reported UVR diary and 2 days of dosimeter measurements were fair to good in a US sample of lifeguards, parents, and children (n=515). In a US sample of radiologic technologists (n=124) the Pearson correlation coefficient between UVR diaries and dosimeters was high for northern (r=0.69, *P*<.001) and southern (r=0.57, *P*<.001) regions [23].

Our qualitative data showed paper-based diaries can be inconvenient and cumbersome to access and may not be completed in a timely manner (such as when backfilling diaries). Reported barriers for the paper diary in our study included requiring a pen, a surface to write on, flipping pages to view clothing coding, and inconvenience for travel. Overall, participants preferred the app over the paper diaries for recording UVR exposure for more than 1 week. However apps are not without problems of their own, with 42% (8/19) of participants in our study experiencing technical barriers when accessing the UVR app. Technical software support should be available for

participants during the intervention period. Most of the barriers encountered were easily fixed by the participant (ie, insufficient phone battery; smartphone update required). There were advantages of the app for the research team. The data collected from participants in the UVR app was exported into the analysis software and reduced the staff workload required for data entry. There were 13 variables to input into the analysis software from the paper diary, which also required a 10% double data entry check quality control measure.

Our qualitative data showed recording personal UVR exposure on a daily basis made participants more sun aware and encouraged them to use more sun protection. Previous work by Koster et al [24] reported similar results, which showed using a UVR dosimeter or keeping a diary increased attention towards the behavior examined and therefore may influence this behavior. Consideration when designing studies with a measurement-only control arm should be taken in light of these findings. Interventions that use smartphones are increasingly used to improve adherence to preventive behavior [25,26], and the app diary could be embedded into these already electronic interventions.

We found participants under-reported the actual amount of low-intensity, but not moderate-to-vigorous–intensity physical activity compared to accelerometer data. This may be because accelerometers detect both incidental (ie, unstructured) and purposeful (ie, structured) physical activity. In contrast, participants may have only recalled their purposeful activity [27]. The low agreement observed was in line with studies published in the literature on physical activity, with a review of 148 studies reporting an average agreement of 0.37 (SD 0.25) [17]. The duration and intensity level of physical activity was captured in the online app. However, whether this activity was conducted “indoors” or “outdoors” should be included in future versions. This would allow for the tracking of time spent in sun-exposed, outdoor physical activity in future studies. Further extending the app to include a question on sunbed use would also be relevant to international settings.

Limitiations

While this small study provided feasibility data, larger studies are required to further validate the app. Three dosimeters in the study malfunctioned due to technical error. Further limitations of this study were the self-reported outcome measures, which can be subject to recall and social desirability biases. The study used convenience sampling in a university setting recruiting a young age group, hampering generalization of the findings to the broader population. However, reducing excessive UVR exposure in young people is important for skin cancer prevention, as previous studies have shown that young people are at higher risk of sunburns, with adults aged 18 to 24 years 7 times more likely to report sunburn than those over 65 years. This group was therefore an appropriate initial target group for the use of the UVR app [28].

Conclusion

Technology advances have the potential to increase the reach and impact of prevention programs. Our study demonstrates self-report using an app can result in reliable and convenient personal UVR exposure data collection. There are several advantages to recording UVR exposure in an app notably: 1) functions to alert and remind users to input data, thereby reducing missing data, 2) direct data entry by participants to eliminate data entry errors when paper diaries are transferred to an electronic database, which have been previously reported [29], 3) the ability to monitor daily data entry compliance, 4) minimizing the risk of participants losing the paper diary, and 5) streamlining the analysis process.

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Conflicts of Interest

None declared.

Authors' Contributions

EH coordinated and designed the study. EH and CH managed the data collection process. EH, CH and AN conducted and interpreted the analysis. EH, CH and MJ led the writing of the manuscript. All authors were involved in interpretation of findings and the critical review of the final manuscript.

Multimedia Appendix 1

Ultraviolet Radiation (UVR) app.

[MP4 File (MP4 Video), 67MB - resprot_v7i4e102_app1.mp4]

Multimedia Appendix 2

Example of Paper Sun Diary adapted from previous studies [9,18]. A) Sun diary clothing and physical activity guide. B) Daily sun diary entry sheet.

[PDF File (Adobe PDF File), 321KB - resprot_v7i4e102_app2.pdf]

References

1. Whiteman DC, Green AC, Olsen CM. The Growing Burden of Invasive Melanoma: Projections of Incidence Rates and Numbers of New Cases in Six Susceptible Populations through 2031. J Invest Dermatol 2016 Jun;136(6):1161-1171 [FREE Full text] [doi: 10.1016/j.jid.2016.01.035] [Medline: 26902923]
2. Holman DM, Berkowitz Z, Guy GP, Hartman AM, Perna FM. The association between demographic and behavioral characteristics and sunburn among U.S. adults - National Health Interview Survey, 2010. Prev Med 2014 Jun;63:6-12 [FREE Full text] [doi: 10.1016/j.ypmed.2014.02.018] [Medline: 24589442]
3. Hall HI, Saraiya M, Thompson T, Hartman A, Glanz K, Rimer B. Correlates of sunburn experiences among U.S. adults: results of the 2000 National Health Interview Survey. Public Health Rep 2003;118(6):540-549 [FREE Full text] [doi: 10.1093/phr/118.6.540] [Medline: 14563911]
4. Coups EJ, Manne SL, Heckman CJ. Multiple skin cancer risk behaviors in the U.S. population. Am J Prev Med 2008 Feb;34(2):87-93. [doi: 10.1016/j.amepre.2007.09.032] [Medline: 18201637]
5. Lawler S, Sugiyama T, Owen N. Sun exposure concern, sun protection behaviors and physical activity among Australian adults. Cancer Causes Control 2007 Nov;18(9):1009-1014. [doi: 10.1007/s10552-007-9041-5] [Medline: 17641981]
6. Lucas RM, Ponsonby A, Dear K, Taylor BV, Dwyer T, McMichael AJ, et al. Associations between silicone skin cast score, cumulative sun exposure, and other factors in the ausimmune study: a multicenter Australian study. Cancer Epidemiol Biomarkers Prev 2009 Nov;18(11):2887-2894 [FREE Full text] [doi: 10.1158/1055-9965.EPI-09-0191] [Medline: 19843682]
7. Martincorena I, Roshan A, Gerstung M, Ellis P, Van LP, McLaren S, et al. Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. Science 2015 May 22;348(6237):880-886 [FREE Full text] [doi: 10.1126/science.aaa6806] [Medline: 25999502]
8. Kearney S, O'Donoghue L, Pourshahidi LK, Richardson PM, Saunders KJ. The use of conjunctival ultraviolet autofluorescence (CUVAF) as a biomarker of time spent outdoors. Ophthalmic Physiol Opt 2016 Dec;36(4):359-369. [doi: 10.1111/opo.12309] [Medline: 27350182]
9. King L, Xiang F, Swaminathan A, Lucas RM. Measuring sun exposure in epidemiological studies: Matching the method to the research question. J Photochem Photobiol B 2015 Dec;153:373-379. [doi: 10.1016/j.jphotobiol.2015.10.024] [Medline: 26555640]
10. Cargill J, Lucas RM, Gies P, King K, Swaminathan A, Allen MW, et al. Validation of brief questionnaire measures of sun exposure and skin pigmentation against detailed and objective measures including vitamin D status. Photochem Photobiol 2013;89(1):219-226. [doi: 10.1111/j.1751-1097.2012.01221.x] [Medline: 22891914]
11. Parisi AV, Kimlin MG. Personal solar UV exposure measurements employing modified polysulphone with an extended dynamic range. Photochem Photobiol 2004 May;79(5):411-415. [Medline: 15191049]
12. Blesić SM, Stratimirović DI, Ajtić JV, Wright CY, Allen MW. Novel approach to analysing large data sets of personal sun exposure measurements. J Expo Sci Environ Epidemiol 2016 Nov;26(6):613-620. [doi: 10.1038/jes.2016.43] [Medline: 27553989]
13. Sun J, Lucas RM, Harrison S, van DMI, Armstrong BK, Nowak M, et al. The relationship between ambient ultraviolet radiation (UVR) and objectively measured personal UVR exposure dose is modified by season and latitude. Photochem Photobiol Sci 2014 Dec;13(12):1711-1718. [doi: 10.1039/c4pp00322e] [Medline: 25311529]
14. Atienza AA, Moser RP, Perna F, Dodd K, Ballard-Barbash R, Troiano RP, et al. Self-reported and objectively measured activity related to biomarkers using NHANES. Med Sci Sports Exerc 2011 May;43(5):815-821. [doi: 10.1249/MSS.0b013e3181fdfc32] [Medline: 20962693]
15. Kelly P, Fitzsimons C, Baker G. Should we reframe how we think about physical activity and sedentary behaviour measurement? Validity and reliability reconsidered. Int J Behav Nutr Phys Act 2016 Mar 01;13:32 [FREE Full text] [doi: 10.1186/s12966-016-0351-4] [Medline: 26931142]
16. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor GS, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act 2008;5:56 [FREE Full text] [doi: 10.1186/1479-5868-5-56] [Medline: 18990237]
17. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor GS, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act 2008 Nov 06;5:56 [FREE Full text] [doi: 10.1186/1479-5868-5-56] [Medline: 18990237]
18. Thieden E, Philipsen PA, Wulf HC. Compliance and data reliability in sun exposure studies with diaries and personal, electronic UV dosimeters. Photodermatol Photoimmunol Photomed 2006 Apr;22(2):93-99. [doi: 10.1111/j.1600-0781.2006.00207.x] [Medline: 16606414]

19. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008 Jan;40(1):181-188. [doi: 10.1249/mss.0b013e31815a51b3] [Medline: 18091006]
20. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977 Mar;33(1):159-174. [Medline: 843571]
21. Dwyer T, Blizzard L, Gies PH, Ashbolt R, Roy C. Assessment of habitual sun exposure in adolescents via questionnaire--a comparison with objective measurement using polysulphone badges. Melanoma Res 1996 Jun;6(3):231-239. [Medline: 8819126]
22. Glanz K, Gies P, O'Riordan DL, Elliott T, Nehl E, McCarty F, et al. Validity of self-reported solar UVR exposure compared with objectively measured UVR exposure. Cancer Epidemiol Biomarkers Prev 2010 Dec;19(12):3005-3012 [FREE Full text] [doi: 10.1158/1055-9965.EPI-10-0709] [Medline: 20940277]
23. Chodick G, Kleinerman RA, Linet MS, Fears T, Kwok RK, Kimlin MG, et al. Agreement between diary records of time spent outdoors and personal ultraviolet radiation dose measurements. Photochem Photobiol 2008;84(3):713-718 [FREE Full text] [doi: 10.1111/j.1751-1097.2007.00236.x] [Medline: 18435619]
24. Køster B, Søndergaard J, Nielsen JB, Allen M, Bjerregaard M, Olsen A, et al. Effects of smartphone diaries and personal dosimeters on behavior in a randomized study of methods to document sunlight exposure. Prev Med Rep 2016 Jun;3:367-372 [FREE Full text] [doi: 10.1016/j.pmedr.2016.04.002] [Medline: 27419038]
25. Finch L, Janda M, Loescher LJ, Hacker E. Can skin cancer prevention be improved through mobile technology interventions? A systematic review. Prev Med 2016 Sep;90:121-132. [doi: 10.1016/j.ypmed.2016.06.037] [Medline: 27374946]
26. Badawy SM, Kuhns LM. Texting and Mobile Phone App Interventions for Improving Adherence to Preventive Behavior in Adolescents: A Systematic Review. JMIR Mhealth Uhealth 2017 Apr 19;5(4):e50 [FREE Full text] [doi: 10.2196/mhealth.6837] [Medline: 28428157]
27. Milton K, Clemes S, Bull F. Can a single question provide an accurate measure of physical activity? Br J Sports Med 2013 Jan;47(1):44-48. [doi: 10.1136/bjsports-2011-090899] [Medline: 22522584]
28. Green AC, Marquart L, Clemens SL, Harper CM, O'Rourke PK. Frequency of sunburn in Queensland adults: still a burning issue. Med J Aust 2013 May 06;198(8):431-434. [Medline: 23641994]
29. Thieden E, Philipsen PA, Wulf HC. Compliance and data reliability in sun exposure studies with diaries and personal, electronic UV dosimeters. Photodermatol Photoimmunol Photomed 2006 Apr;22(2):93-99. [doi: 10.1111/j.1600-0781.2006.00207.x] [Medline: 16606414]

Abbreviations

SPF: sun protection factor
UVR: ultraviolet radiation

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Protocol

Addressing Participant Validity in a Small Internet Health Survey (The Restore Study): Protocol and Recommendations for Survey Response Validation

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Abstract

Background: While deduplication and cross-validation protocols have been recommended for large Web-based studies, protocols for survey response validation of smaller studies have not been published.

Objective: This paper reports the challenges of survey validation inherent in a small Web-based health survey research.

Methods: The subject population was North American, gay and bisexual, prostate cancer survivors, who represent an under-researched, hidden, difficult-to-recruit, minority-within-a-minority population. In 2015-2016, advertising on a large Web-based cancer survivor support network, using email and social media, yielded 478 completed surveys.

Results: Our manual deduplication and cross-validation protocol identified 289 survey submissions (289/478, 60.4%) as likely spam, most stemming from advertising on social media. The basic components of this deduplication and validation protocol are detailed. An unexpected challenge encountered was invalid survey responses *evolving* across the study period. This necessitated the static detection protocol be augmented with a dynamic one.

Conclusions: Five recommendations for validation of Web-based samples, especially with smaller difficult-to-recruit populations, are detailed.

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KEYWORDS

fraudulent data; data accuracy; research and design; research activities; data analysis

Introduction

Misrepresentation in Web-Based Studies as a Challenge to Scientific Validity

Internet-based research is growing in popularity and usability among social science, behavioral science, and health researchers, in part because of the ease and efficiency in recruiting large samples [1,2]. It is also advantageous-to-essential in recruiting niche, hidden, and hard-to-reach populations [3]. A Web-based survey design software has become so user friendly that virtually anyone can design and implement surveys. Web 2.0 survey software such as Survey Monkey, Google Forms, Survey Gizmo, Qualtrics, and others work on a range of electronic devices, are compliant with health regulation for clinical data management, participant privacy and security (eg, Health Insurance Portability and Accountability Act, HIPPA), and offer in-app data analysis and user metrics.

A unique characteristic in Web-based health research is that the researcher(s) typically never meet the participants. This creates a unique challenge to participant validity. As new software technologies have eased implementation from the researchers' end, a whole new scope of technologies has also developed to complete surveys, fraudulently. In Web 1.0, early research focused on survey item validity to demonstrate that asking health information online could yield truthful responses. In this study, 2 key findings emerged. First, misrepresentation online was not uniform but varied across health foci [4], and for socially sensitive items, computerized surveys yielded higher (interpreted as more truthful) response rates [5]. The first case studies of multiple participation by a single person were reported [6], followed by studies reporting participation by ineligible individuals posing as eligible subjects [7]. The evolution of user-friendly software created not only Web 2.0 but also the capability for spamming technologies and approaches that create new risks to Web-based research validity.

Wikipedia defines spam as *unsolicited or undesired electronic messages*. Applied to social science and health research, "spam" is used as a catch-all term referring to sets of invalid or fraudulent data responses. Web-based survey spam has been categorized with the assumption that the source of spam comes from an individual person or group of people who, for a variety of reasons (eg, to earn compensation, to politically influence survey findings, or out of interest), would complete a Web-based survey multiple times [8]. In response, protocols to verify the validity and uniqueness of each survey are considered essential in distance studies [7]. Deduplication is the process used to confirm that each survey is from a unique person, whereas cross-validation comprises internal validity checks to ensure the data are consistent and interpretable across the study. The major challenge in both deduplication and cross-validation is detection: how to ensure such protocols can distinguish valid from invalid data [7]. As spamming has evolved to become a greater threat to Web-based research integrity, deduplication and cross-validation protocols need to be more sophisticated.

Data Validation Protocols

Most data validation protocols rely on a 2-part algorithm consisting of partially automated validation checks and manual validation checks [7]. Manual, automated, or hybrid manual-automated protocols use combinations of data to verify the survey responses (internal validity) while ensuring non-duplication. Typical analytic data used include tracking all attempts made on study entry (including documenting repeated attempts at study entry by changing answers to screening information), internet protocol (IP) address, a timestamp of the survey start and end date, duration of the survey, and completion status. Examples of issues that have emerged in regard to using survey metadata to determine eligibility are IP masking and data-generating software. Tran et al [9] describe the functioning of the software, explaining that users can generate a complete dataset, each assigned with a unique ID and easily downloadable in a comma-separated value file. Spammers can easily obtain this kind of software as well. One of the first results in a cursory Google search for "software to auto fill an online survey" pulls up "Coby 2.0," a Bot program that advertises undetectable, human-like data, with unique virtual private network (VPN), live panel statistics, an automated info generator, and fake email generator (registers the emails with a host site to pass verification), and Captcha verification software, with instructions on how to run this software on a Web-based survey. The implication for social science behavior and health researchers is that spam itself is evolving, shifting from being manually created by individuals to automated by software. This development introduces new threats to Web-based research validity and challenges to the survey validation process.

In internet-based social science, behavioral science, and health research, there is little published information in the area of data validation and fraud. All the case studies we could find refer to protocols designed to handle large survey populations. Take, for example, research on HIV prevention on gay, bisexual, and other men who have sex with men (GBM), an area of research where Web-based recruitment and distance surveys have become popular. At least 3 Web-based studies have published data deduplication and cross-validation protocols: the *Wyoming Rural AIDS Prevention Project* (*WRAPP*) [10], total attempts N=1900; the *American Men's Internet Survey* (*AMIS*) [11], total attempts N=14,899; and the *Sexually Explicit Media* or *SEM study* [7], total attempts N=1254 surveys. All 3 studies published data validation protocols using some mix of automated detection to flag "suspicious" surveys, followed by manual confirmation to confirm duplicate and/or invalid surveys.

Recruiting smaller "niche" populations in Web-based research introduces special challenges to validity. When the population is small, it may not be cost-effective to computerize validation checks. Smaller samples are typical when a behavior or health concern is rare or novel, 2 situations where typically less is known about the phenomenon. This makes it difficult to detect and verify atypical cases. In such a situation, researchers may need to institute a manual data validation protocol with multiple external validation checks to ensure high-quality data. Using the *Restore* study as a case study, and comparing it with the current standards in the field, this paper addresses the issue of detecting Web-based survey spam, detailing an appropriate

protocol necessary to identify suspect surveys in this small-sample study. This paper has 3 aims: (1) to outline the basic components of a data validation protocol for smaller samples, (2) to identify challenges encountered and solutions tried to address these challenges, and (3) to make recommendations for future research.

Restore: Study Description

The *Restore* study was a Web-based study of GBM treated for prostate cancer completed in 2015-2016. The study focus was the effects of treatment to inform development of a Web-based rehabilitation curriculum tailored to the population. Only the second prostate cancer in GBM study to be funded by the National Institutes of Health, *Restore* had the challenge to recruit for a rare event (as prostate cancer is a disease of older men) within a sexual minority. The challenge in recruiting a "minority within a minority" is illustrated by the sample sizes in the extant literature. At the start of the study, only 4 quantitative studies of GBM prostate cancer survivors had been published and a fifth doctoral thesis abstracted, with GBM sample sizes of 12 [12], 15 [13], 92 [14,15], 96 [16,17], and 111 [18], respectively. Given GBM represents a geographically diverse population, internet recruitment and Web-based surveys have become the standard methods in GBM health research. Sexual minorities were early adopters of new technology [19] and remain disproportionately likely to be online. GBM comprise a vibrant virtual community whose uses of the internet and apps include dating and sex-seeking online, community building, sharing information, and accessing goods and services [20].

Studies of GBM prostate cancer survivors are rare, in part because of challenges in recruiting this demographic. Prostate cancer registries typically do not collect data on sexual orientation, leaving this population invisible to clinical research. Except for a few cities with large geographic concentrations of GBM, most cities lack sufficient numbers of GBM seeking prostate cancer treatment at any one time to make in-person support groups, viable. Sexual minority status [21], prostate cancer [22], and the sexual and urinary effects of treatment [23] are all potentially stigmatizing, creating further psychological barriers to participation. Unlike HIV, some survivors of prostate cancer may no longer identify as such after successful treatment. Thus, for multiple reasons, GBM prostate cancer survivors represent a hidden, difficult-to-reach population who may only be accessible in significant numbers through the internet [24,25]. Given the social isolation and dual stigma—GBM with prostate cancer experience—Web-based support groups have become an important, vital place for these men to have access to counseling, support, and care.

Generating a sample from a virtual community has specific challenges. Without a precise enumeration of the population, it is difficult-to-impossible to establish the sampling frame from which to sample. Web-based surveys face additional recruitment challenges as it is often more difficult to restrict access to a Web-based survey and to guarantee the validity of the population and consequent quality of the data. This was true in the case of the *Restore* study when, not long after advertising the Web-based survey on social media, it became subject to a spam attack.

Another significant challenge in the case of the *Restore* study was the need to balance survey protection with accessibility. Prostate cancer largely impacts an older demographic (mean age of this sample was 63.42 years, standard deviation, SD, 8.19). So, the survey needed to be designed for participants who were less technology-savvy. Some of the survey design solutions that were considered and could be useful in other circumstances presented potential obstacles to recruiting the study's population. For example, requiring participants to first contact the study to obtain a unique ID, password, or individualized link to the study could both protect a Web-based survey while externally validating the population. This option can and should be considered when a researcher or organization sponsoring the research has an existing relationship with the target group. In case of the *Restore* study, such a relationship was more tenuous, with most of the prostate cancer survivors having no explicit relationship with the university-based researchers conducting the study. In addition, although these men were active online, it was unclear what level of internet familiarity they possessed, and so, it was important to make the process of recruitment and enrollment as welcoming, easy, and streamlined as possible.

Methods

Study Design

In many ways, the *Restore* study reflects a typical formative research study in the social sciences, behavioral, and/or health fields. The study design involved a formative qualitative research phase (listening to GBM's experience of prostate cancer in individual interviews) and a measurement development phase (to measure treatment outcomes specific to the target population). The third aim, to conduct a cross-sectional, Web-based, quantitative survey assessing GBM prostate cancer survivor's sexual functioning and rehabilitation needs following treatment, is the focus of this report. The core components of the Web-based survey included the following domains: eligibility screener, consent process, demographic questionnaire, sexual identification, prostate cancer treatment history, measures of sexual functioning, an HIV/ sexually transmitted infection status and risk inventory, a section on primary relationships, measures of physical and mental health, alcohol and tobacco use, and a tailored needs assessment of what GBM with prostate cancer want in rehabilitation [26].

Recruitment/Enrollment

The study was launched on October 21, 2015, and ended on January 1, 2016 (72 days). Given the difficulties identifying and recruiting GBM with prostate cancer into studies, a methods goal was to establish the utility of using Web-based methods to recruit this population. The primary focus of recruitment was through a community partner's email listserv. *Malecare* is a nonprofit organization providing support and advocacy for survivors of cancer who agreed to send an email invitation to their members. Email invitations were sent seeking to recruit men treated for prostate cancer, residing in the United States and Canada, aged 18 years or older, and who identified as GBM (by self-report). (Given prostate cancer is a disease of older adults, the age criterion was a technicality, reflecting the minimum legal age to consent to research, and was not

anticipated to restrict the study). After much discussion, a link to the survey, noting a US $50 gift card as compensation, was advertised on the social media site, Facebook. This allowed the advertisement to be "shared" by other public pages of prostate cancer community organizations.

To complete the survey, participants first completed a screening tool verifying eligibility and then a Web-based questionnaire, which took about 45 to 60 min to complete. For an additional US $10 incentive, participants could refer their partners, friends, and family to take a companion survey on caregiving and social support. Consent for this low-risk study warned participants that some questions were sexually explicit and potentially embarrassing. All research was undertaken under the oversight of the University's human subjects' protection program.

Data Validation

Initial validation was confirmed at study entry by completion of the screener. This required all enrollees to click through (from the email sent out by *Malecare*), confirm each eligibility criterion by checking 4 boxes (≥18 years, residing in the United States or Canada, and identifying as a GBM who has completed treatment for prostate cancer), and provide consent (by clicking on multiple screens that they had understood key aspects of the survey and wished to participate). A summary page required them to verify again that they met all the eligibility criteria, and to confirm they had not completed the survey previously.

Initial survey protection features included "Prevent Ballot Box Stuffing," a feature of Qualtrics that stores a cookie on the user's browser, and "Prevent Indexing," a feature that prevents the survey from being indexed by search engines.

Our manual protocol for data validation was adapted from our prior large studies on GBM (using automated and hybrid protocols), utilizing the standards summarized by Baker and Downes-LeGuin [8] who identify 8 indicators of suspect survey entries (see Textbox 1). Similar to Baker and Downes-LeGuin's "3 strikes and you're out" rule, no 1 indicator was deemed sufficient to call a survey invalid. Rather, indicators were used to "flag" survey entries as suspicious to study staff.

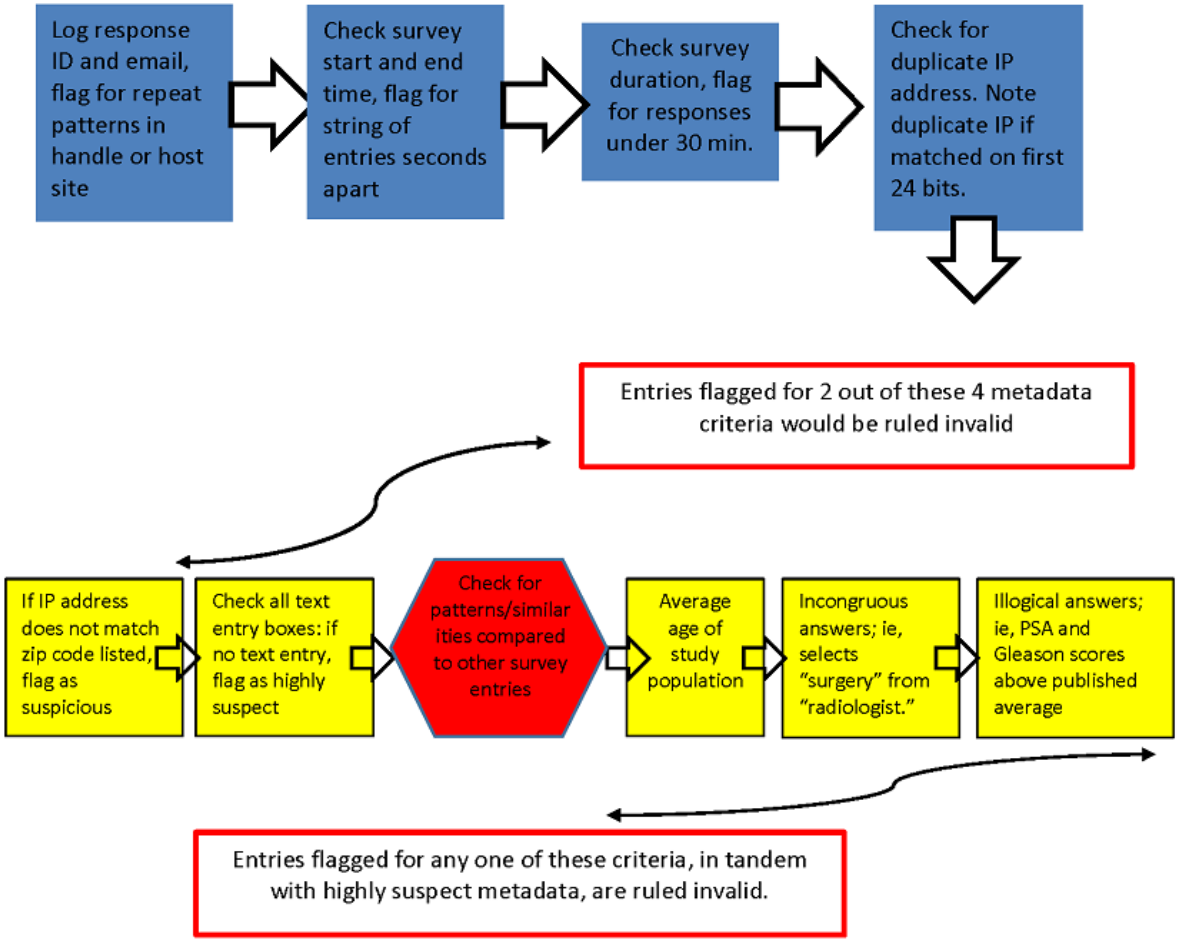
In addition, internal checks of survey metadata were conducted against the participant log and survey responses (see Figure 1). Submissions were flagged automatically for incongruity between these items and then checked manually by study staff and independently by the principal investigator. In the case when suspicious responses to medical questions arose, responses were flagged and sent to the team's prostate cancer medical expert to confirm if the response pattern was clinically impossible and/or statistically highly improbable.

For all analyses, duplicate and/or invalid submissions were treated as 1 invalid group. A priori, only complete survey submissions were to be included in data analysis. Thus, any incomplete survey submissions were to be assigned as invalid.

Textbox 1. Baker and Downes-Le Guin's 8 characteristics of suspicious surveys.

Unusually short completion times compared with the median interview length
Selection of all items in a multiple response or other obvious cheating behavior in qualifying questions
Selection of bogus or low probability answers
Internal inconsistencies
Low differentiation or "straight lining" in grids
High levels of item nonresponse
Failure of verification items in grids
Gibberish or duplicated responses in text entry boxes

Figure 1. Restore study data validation protocol. ID: identification; IP: Internet Protocol; PSA: Prostate-Specific Antigen Test.



Results

Participants

Participants' characteristics are summarized in Multimedia Appendix 1. To summarize, the typical participant in this study is a white, non-Hispanic, well-educated male, in his 60s, living in the United States, and self-identified as gay. Geographically, the sample appears diverse living across North America as validated by a residence zip code (see Figure 2), and cross-validated by where they sought treatment. Medically, 69.4% (134/193) reported their cancer as having been successfully treated, the remainder reporting either still undergoing treatment or reporting their cancer has progressed. Against the stereotype that older participants are not online, most participants reported being online 20 or more hours per week and most reported using multiple platforms to access the internet.

Evidence of a Spam Attack

A spam attack on the survey began in the second recruitment blast (Wave 2), 2 days after US $50 online gift certificate compensation was advertised on Facebook (see Figure 3). Study staff noticed a sudden increase in survey attempts, many of which at first seemed potentially valid. Ultimately, staff rejected each survey as suspect for multiple reasons, based on survey metadata and survey responses. A total of 289 survey submissions, representing 60.4% (289/478) of submitted surveys, were ultimately rejected as likely spam.

Metadata issues that suggested a common source were flagged as suspicious and ultimately rejected as spam. Criteria included short response time (under 30 min), IP addresses that did not match the zip code provided by respondent, duplicate IP address, an email address that followed an unusually predictable convention in the handle, and all were from the same host site (eg, abc123@.me.com). Initially, survey entries that were flagged followed a consistent pattern. First, these surveys provided a highly improbable age (18-35 years) at which to receive a diagnosis of prostate cancer. (Less than 1 in 10,000 men under age of 40 years is diagnosed with prostate cancer). The data on prostate cancer specific items were either "forgotten" or also statistically less likely (>20 for prostate-specific antigen or PSA tests and >6 for Gleason). The information on treatment combined statistically improbable-to-impossible treatment regimens (eg, radical prostatectomy, then watchful surveillance then radiation treatment, then diet). In addition, there were mismatches of treatments experienced with the providers seen (eg, radiation from an urologist or surgery from an oncologist). On the discrimination experiences scale, reports of serious discrimination experienced in hospital were common but based

on unusual attributes (eg, weight, height, and appearance discrimination but not race or sexual orientation). In terms of rehabilitation, the surveys reported rare treatments that would be highly unlikely if the patient had not disclosed their sexual orientation and behavior to their provider (eg, recommended use of dilators and dildos, and butt plugs to a man who had not disclosed his sexual orientation, or to a man who stated he exclusively engaged in insertive sex). Consistent with Baker and Downes-LeGuin (2007), suspicious surveys consistently left text entry boxes for qualitative responses blank. None of these items by itself would rule out a survey as invalid, rather each participant's answers was read as a case study to see if the overall profile was credible. This meant the consistent combination of multiple statistically or medically unlikely response items would flag them as suspect, and ultimately, the combination of multiple items or profile as suspect would result in them being rejected as invalid.

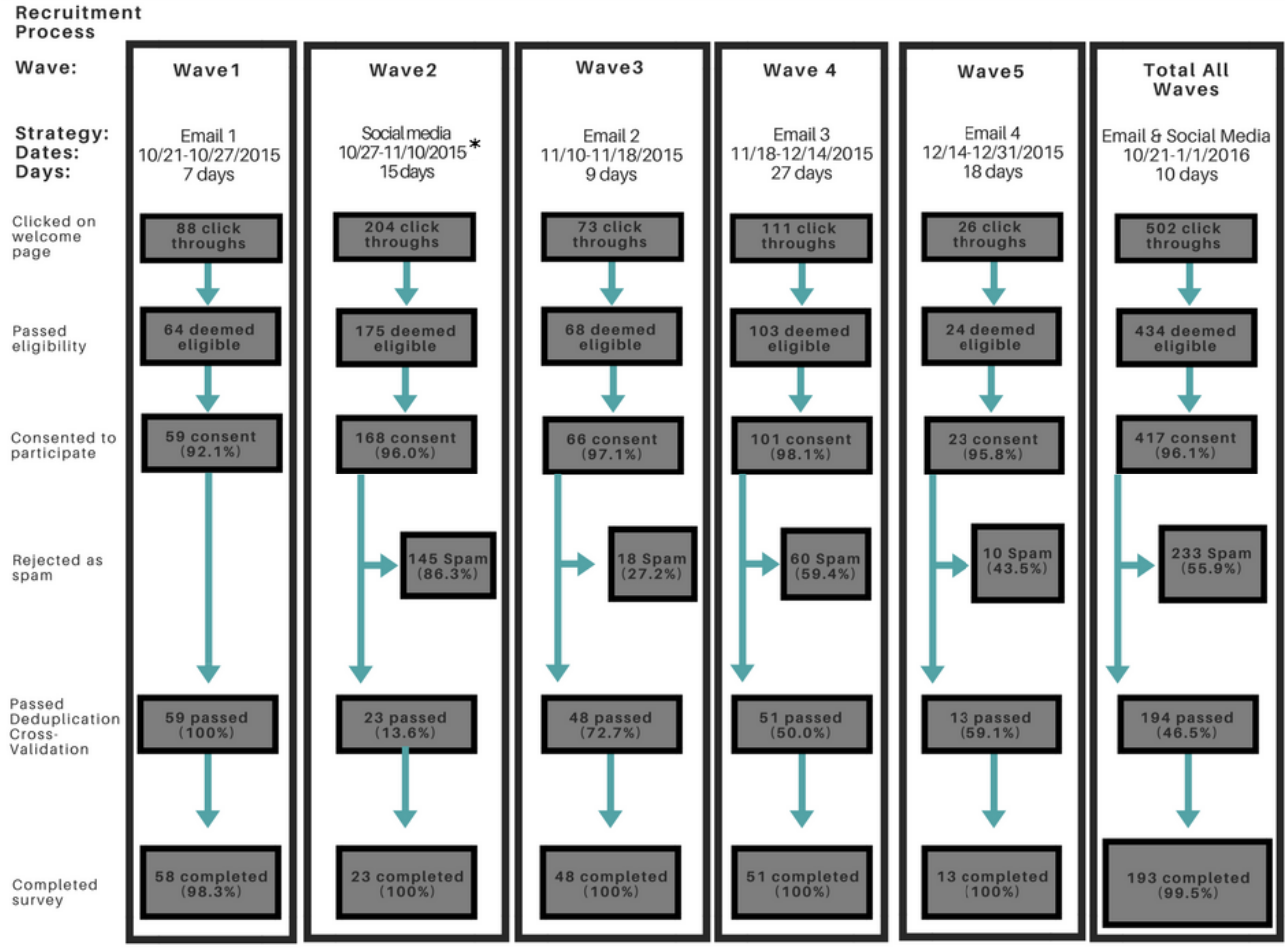
Over time, the answer patterns began to shift making detection of spam more difficult. Although completing time remained suspicious, some survey demographics were within a probable range, whereas other data stayed improbable. For example, age at diagnosis and PSA and Gleason scores all were within the plausible range of responses. This shift in how invalid responding was coming in was significant enough to require adaptations to the study's data validation and deduplication protocol. First, the invalid entries were able to "pass" through some aspects of the protocol (eg, entries had non-duplicate IP and valid zip code, respondent passed reCAPTCHA verification). Next, the invalid entries to some of the medical and behavioral questions shifted toward becoming more plausible. Fortunately, other responses in the suspicious surveys still followed a convention in the metadata that identified them as suspicious. Key suspicious data entries included repetitious email address at the same host site, entries that began seconds after a previous submission had ended, and IP addresses that did not match the zip codes listed in the demographic questionnaire. Across 1 set of spam, a consistent mistake was observed on 1 datum involving a misinterpretation of how to state a date of birth. Across others, suspicious surveys tended to be completed in the early hours of the morning. These were only identifiable by checking the process analytics, manually reading each whole survey interpreting all data in relationship to each other, and reviewing each survey's demographics (eg, start and end completion times, style of email address provided) in relationship to other surveys.

After 21 days of reviewing the spam entries on the survey, the flow of spam was diverted. We kept the old link open while launching a copy of the survey with a stricter recruitment protocol (restricted to email invitations and no social media, with more validation steps between the screener, consent, and survey). This new link was only advertised through the community partner's email listserv and was never spammed. Within a very short period (2-3 days), the original link only received spam, whereas the restricted new link only received valid surveys.

No compensation was paid to surveys that were identified as spam. When requests for payment were received from respondents whose surveys were identified as invalid/spam, they were informed there was a question about some of their data and asked to call on the 1-800 study line to leave a call back number to verify their answers. This was sent to all the spam surveys, but no one followed through with this request.

Figure 2. Geographic distribution of the sample (N=193 gay, bisexual, and other men who have sex with men [GBM] prostate cancer survivors).

Figure 3. Recruitment process and participation rates in the Restore study. All advertising on social media removed on 11/5, but survey link left open to keep spammers on the site while members sent to new link.



Discussion

Detecting Fraudulent Surveys

Ensuring the quality of data in Web-based surveys is essential to maintain the credibility of Web-based research. In situations where external validation is not possible or appropriate, a rigorous deduplication and cross-validation protocol can provide researchers with confidence in their data. We highlight that the majority of surveys received in *Restore* were rejected as spam. Clearly, even in small-sample studies, fraudulent participation is a serious threat.

Detecting fraudulent responses in Web-based surveys is a rapidly evolving challenge. To ensure the highest data quality from Web-based surveys, researchers need to adapt existing data validation protocols and publish their experience in detecting spam. In this case study, although some of the spam attack may have been completed in-person by a human being, it is also possible the invalid entries on the survey were automatically generated by software. Both explanations would account for how the spamming evolved across the study.

There are 4 main lessons learned from this case study. First, the identification and rejection of 289 (60.4%) surveys as spam reinforces the need for similar Web-based studies to monitor the threat of spam. Studies without such protocols should be viewed as methodologically weak, potentially not meeting minimum standards for publishable research. Best practices to monitor and reduce the danger of spam include keeping the recruitment period short and, given the experience of the *Restore* study, avoidance of advertising on publically accessible social media sites (wherever possible). Second, the standard to develop a written deduplication and cross-validation protocol for the duration of a study, which was previously identified as a "best practice," now needs to be updated. Given how the spam responses evolved across this study, instead of a static protocol, written before the start of recruitment and implemented consistently across a study, researchers need dynamic protocols that can evolve in response to evolving spam attacks. To ensure consistency over the study period, "evolving protocols" may need to vary rules as the study proceeds and necessitate a retrospective analysis phase that applies uniform standards after the recruitment period has ended. Moreover, this reinforces the essential element of having manual checks by multiple staff to detect subtle shifts in responding patterns. Third, although a common practice in validation is to assign human-like attributes to the spammer (ie, giving a name, character, or identity to the spammer), the risk of spam from automatically software-generated programs is an emerging threat. To the extent that assigning human-like attributes reinforces perceiving the attack as human, consistent, and static, it should be avoided. Instead, to remove spam, even in small-sample size studies, a mix of manual inspection and automated review to flag suspicious entries is needed. Fourth, when spam attacks occur,

researchers should consider a novel solution piloted in the *Restore* study. Maintaining an old link to collect spam, while opening an alternative more restricted link for members, enabled the *Restore* study to quickly recover from the spam attack and complete the study.

Considerations in Designing Web-Based Survey Validation Protocols

In this case study, we encountered several design considerations with implications from validating survey samples. First, like many recruitment studies using email invitations, the *Restore* study sent out invitations to a large listserve, resulting in rapid initial recruitment. Given the volume of response, it was initially challenging to carefully process each survey. An alternative approach would be to have a gradual recruitment roll out. This would have allowed staff more time to gain experience in detecting suspicious surveys. But it is a trade-off, as it also allows more time and opportunity for spammers to gain experience in spamming the study. Second, detailed record keeping of all incomplete entries throughout every stage of the survey, especially those who did not complete the screener and consent, could have helped early identification of spam patterns.

Third, all the published protocols in the field to date, to the best of our review, report using a static standard or rigorous protocol to categorize an entry as "valid" or "invalid." Although this is consistent with rigorous best practices, in the case of the *Restore* study, it proved insufficient. Dynamic protocols designed to adapt or evolve will be more responsive, but inherently vulnerable to behavioral drift. Fourth, with permission from the institutional review board (IRB), including some form of retrospective external validation (such as a phone call, Skype contact, or other personal validation) proved useful both to confirm the survey as suspicious and to provide a process where, in the case of a survey incorrectly rejected, a participant could confirm its validity. Although for large studies this may introduce feasibility concerns, for smaller studies, building retrospective external validation into the protocol may minimize fraudulent attacks.

Finally, if most spamming was motivated to earn compensation, does removing compensation solve the threat of spamming? We think not. Although compensation may increase the threat of spam, in a recent study, spamming by those not seeking compensation was actually higher than by those seeking compensation [7]. Discussions with colleagues who have conducted Web-based health surveys without compensation have revealed similar concerns about spamming (undertaken for political gain). Ethically, the US $50 compensation in this study reflects the US research practice to compensate for time, effort, and other costs. It was chosen to be sufficient to compensate for time, computer use, and effort, but not be so great as to incentivize or induce respondents to participate.

Comparisons With Prior Literature

There are 2 examples of best practices in the field of social and behavioral research: the American Men's Internet Survey and the Wyoming Rural AIDS Prevention Project. The main similarities here are the study population and time frame—*Restore*, AMIS, and WRAPP all used Web-based research methods to study GBM in the past decade. All 3 studies have published data validation protocols and cross-validation strategies based off of automated validation checks. Distinctively, AMIS conducted one of the largest studies of online GBM to date, with minimal occurrence of invalid entries. The goal of this study was to collect 10,000 surveys annually to monitor behavior patterns among GBM internet users. Of 14,899 total "eligible" (ie, adult GBM) participants screened, only 709 (4.76%) surveys were determined to be from duplicate participants. In the case of the WRAPP study, a Web-based HIV intervention evaluation project targeting rural GBM, a similar spam pattern to that of *Restore* occurred. Of 1900 submissions, 627 (33%) were considered to be invalid.

Strength of the AMIS protocol includes its use of both metadata and survey response flagging to determine eligibility, noting automated and manual data of the respondent (IP address, completion rate, demographic characteristics, GBM status, etc). The AMIS protocol does not attempt to categorize or source ineligible participants with any particular quality, but simply refers to valid/complete/nonduplicate entries as "successful" and all others as "unsuccessful." A limitation of the AMIS protocol would be framing the overall method as "deduplication," and when based on more current findings, it can be deduced that some spam can now look unique/nonduplicate but still be invalid.

The WRAPP protocol's strength is also in its 2-part approach, using both survey responses and internal metadata (such as IP address, Web browser information, user-determined variables such as username, password, and email, as well as optional user-provided variables such as phone number). Furthermore, they report invalid data broken down into 4 categories: "Infrequent, Persistent, Very persistent, and Hacker" [10]. Future research in this area should focus on how to present invalid data and possibly even comparison of invalid data within categories.

Both studies represent state-of-practice data validation researcher. The *Restore* study builds on these in 2 significant ways: first, by tailoring such research to small sample studies, and second, by testing a dynamic protocol.

Recommendations for Future Research in Small Web-Based Studies

We recommend researchers consider 6 recommendations when designing small Web-based samples.

Use a Formal, Written Deduplication and Cross-Validation Protocol

Given the number of studies reporting suspicious surveys, and the percent of surveys identified as spam, validation of each survey as a unique contribution from an eligible participants is essential for all Web-based survey research. We encourage investigators, reviewers, IRBs, and everyone involved in Web-based research to promote survey validation as a minimum standard of rigor. Studies where external validation of participants is not possible or appropriate, there is a need for some kind of survey deduplication and cross-validation process. Else, they should be rejected as below minimal scientific standards. To aid the field, researchers should make their protocols available, either by publishing them as a case study

as done here or as Web-based appendices to the main paper reporting the results. Because each study is unique, existing protocols will need to be tailored to the target population and adapted to best fit the needs of the study.

Adopt a Rigorous Authentication Protocol While Carefully Considering Who May Be Excluded

Designing a deduplication and cross-validation protocol involves complex tradeoffs, balancing authentication against both subject burden and potential exclusion. Overly simplistic protocols—for example, checking name or IP address duplicates—are weak and too easily circumvented. Rigor may also exclude some valid participants. For example, in our study, some male couples might live together, share the same IP address, and both be diagnosed with prostate cancer. In another study, skip patterns might lead to short completion times. When rejecting a survey, we recommend encouraging anyone who thinks they have been "excluded in error" to contact the study directly.

Decide Upon an Automated, Manual, or Automanual Hybrid Validation Approach

When establishing a survey deduplication and cross-validation protocol, consider the cost versus the benefit of automated and manual validation checks. Although a combination is likely optimal, for small-sample Web-based studies, automated validation may not be cost-effective or possible. For manual checks, especially in the first weeks of a study, multiple people independently assessing validity is preferred. Multiple people have at least 2 advantages. First, different staff might likely develop different strategies to detect fraudulent patterns, whereas some may not pick up on some patterns at all. By using a team approach, staff can act as reliability checks on each other, ultimately helping to ensure that a rigorous validation is achieved. Second, in the situation where spam evolves, multiple staff monitoring validity is more likely to recognize subtle changes than 1 person working alone.

Consider External Validation Checks Either Prospectively or Retrospectively

Any study, regardless of sample size, should consider adding an external validation process in Web-based surveys. Similar to in-person study protocols where researchers confirm a person's identity, Web-based studies should consider whether a prospective external validation check (eg, a phone or video call to the study) is needed. In studies on sensitive topics, with stigmatized populations, or with hard-to-reach populations (all of which we experienced in the *Restore* study), researchers need to recognize a trade-off. Although external validation may be optimal, it also can introduce a sizable (possibly even insurmountable) barrier to participation. Before requiring external validation checks, acceptability studies and consultation with the community (eg, through community advisory boards) would appear prudent to avoid overly restrictive and intrusive validation procedures with potential to defeat the aims of the study. An alternative approach, which we piloted in this trial, is to state as part of the consent process, that the researchers may require a phone call to the study before the payment if researchers have questions about the survey responses. This is especially useful for research restricted to a geographical area (eg, *Restore* was restricted to North America), as it creates an additional deterrent to fraudulent participation from outside that geographic region.

Rapid Recruitment May Be Preferable to Rolling Recruitment

A key observation from the *Restore* study was that invalid entries evolved over time approximating valid responses. Although we cannot know whether this was human learning or automated shaped responses, a rapid recruitment protocol prevents spammers and programs from becoming savvy to the subject area and limits the time frame for evolution of responses to occur.

For Small Datasets, a Written Protocol Can Only Go So Far

Although data-validation protocols are the gold standard, for novel areas of research and areas where little is known about the population, valid responses can be hard to predict. For highly innovative research, protocols need to be flexible enough to allow for adaptability. In such cases, starting with an initial "base" protocol and then evolving the protocol with close monitoring (as was done here) may be necessary. Then, reading each survey as a whole to understand how the story fits (or fails to fit) together is crucial to assessing its internal validity.

Conclusions

In summary, spam on internet-based health surveys appears common, pernicious, and detrimental to Web-based research in the social sciences, behavior, and health disciplines. The threat of spam requires complex and comprehensive solutions to confirm and validate survey responses. Spam appears to be changing in significant ways, including from individual spammers generating multiple, falsified survey responses to spammers using software to autogenerate smarter fraudulent data. Updated protocols that address these advances in technology, and are tailored to the size and nature of the population, are necessary to address these threats.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Demographic, sexual, and medical characteristics of study participants (N=193 gay, bisexual, and other men who have sex with men treated for prostate cancer).

[PDF File (Adobe PDF File), 44KB - resprot_v7i4e96_app1.pdf]

References

1. Pew Research Center. 2016. Internet use over time URL: http://www.pewinternet.org/fact-sheet/internet-broadband/ [accessed 2018-03-20] [WebCite Cache ID 6y4DkW8y6]
2. Rea L, Parker R. Designing and Conducting Survey Research: A Comprehensive Guide. Fourth Edition. San Francisco, CA: Jossey-Bass; 2014.
3. Fielding NG, Lee RM, Blank G. The SAGE Handbook of Online Research Methods. Thousand Oaks, CA: Sage Publications Inc; 2008.
4. Ross MW, Rosser BR, Coleman E, Mazin R. Misrepresentation on the Internet and in real life about sex and HIV: a study of Latino men who have sex with men. Cult Health Sex 2006 Mar;8(2):133-144. [doi: 10.1080/13691050500485604] [Medline: 16641062]
5. Turner CF, Ku L, Rogers SM, Lindberg LD, Pleck JH, Sonenstein FL. Adolescent sexual behavior, drug use, and violence: increased reporting with computer survey technology. Science 1998 May 08;280(5365):867-873 [FREE Full text] [Medline: 9572724]
6. Konstan JA, Rosser BR, Ross MW, Stanton J, Edwards WM. The story of Subject Naught: a cautionary but optimistic tale of Internet survey research. J Comput Mediat Commun 2005;10(2):00 [FREE Full text] [doi: 10.1111/j.1083-6101.2005.tb00248.x]
7. Grey JA, Konstan J, Iantaffi A, Wilkerson JM, Galos D, Rosser BR. An updated protocol to detect invalid entries in an online survey of men who have sex with men (MSM): how do valid and invalid submissions compare? AIDS Behav 2015 Oct;19(10):1928-1937 [FREE Full text] [doi: 10.1007/s10461-015-1033-y] [Medline: 25805443]
8. Baker RP, Downes-LeGuin T. Separating the wheat from the chaff-ensuring data quality in internet samples. In: Trotman M, Burrell T, Gerrard L, Anderton K, editors. The Challenges of a Changing World Proceedings of the Fifth ASC International Conference. Berkeley, UK: Association for Survey Computing; 2007:157-166.
9. Tran KN, Vatsalan D, Christen P. GeCo: an online personal data generator and corruptor. : ACM; 2013 Nov 01 Presented at: Proceedings of the 22nd ACM international conference on Information & Knowledge Management; San Francisco, CA p. 2473-2476. [doi: 10.1145/2505515.2508207]
10. Bowen AM, Daniel CM, Williams ML, Baird GL. Identifying multiple submissions in Internet research: preserving data integrity. AIDS Behav 2008 Nov;12(6):964-973 [FREE Full text] [doi: 10.1007/s10461-007-9352-2] [Medline: 18240015]
11. Sanchez TH, Sineath RC, Kahle EM, Tregear SJ, Sullivan PS. The annual American men's internet survey of behaviors of men who have sex with men in the United States: protocol and key indicators report 2013. JMIR Public Health Surveill 2015;1(1):e3 [FREE Full text] [doi: 10.2196/publichealth.4314] [Medline: 27227126]
12. Motofei IG, Rowland DL, Popa F, Kreienkamp D, Paunica S. Preliminary study with bicalutamide in heterosexual and homosexual patients with prostate cancer: a possible implication of androgens in male homosexual arousal. BJU Int 2011 Jul;108(1):110-115 [FREE Full text] [doi: 10.1111/j.1464-410X.2010.09764.x] [Medline: 20955264]
13. Lee TK, Breau RH, Eapen L. Pilot study on quality of life and sexual function in men-who-have-sex-with-men treated for prostate cancer. J Sex Med 2013 Aug;10(8):2094-2100. [doi: 10.1111/jsm.12208] [Medline: 23742184]
14. Hart S, Coon D, Kowalkowski M, Latini D. 163 Gay men with prostate cancer report significantly worse HRQOL than heterosexual men. J Urol 2011;185(4S):e68-e69. [doi: 10.1016/j.juro.2011.02.231]
15. Hart TL, Coon DW, Kowalkowski MA, Zhang K, Hersom JI, Goltz HH, et al. Changes in sexual roles and quality of life for gay men after prostate cancer: challenges for sexual health providers. J Sex Med 2014 Sep;11(9):2308-2317 [FREE Full text] [doi: 10.1111/jsm.12598] [Medline: 24888965]
16. Dowsett GW, Lyons A, Duncan D, Wassersug RJ. Flexibility in men's sexual practices in response to iatrogenic erectile dysfunction after prostate cancer treatment. Sex Med 2014 Aug;2(3):115-120 [FREE Full text] [doi: 10.1002/sm2.32] [Medline: 25356308]
17. Wassersug RJ, Lyons A, Duncan D, Dowsett GW, Pitts M. Diagnostic and outcome differences between heterosexual and nonheterosexual men treated for prostate cancer. Urology 2013 Sep;82(3):565-571. [doi: 10.1016/j.urology.2013.04.022] [Medline: 23768520]
18. Allensworth-Davies D. Open.bu.edu. Boston University: School of Public Health, Boston University School of Public Health; 2012. Assessing localized prostate cancer post-treatment quality of life outcomes among gay men URL: https://open.bu.edu/handle/2144/12263 [accessed 2018-03-14] [WebCite Cache ID 6xusjDWml]
19. Rosser BR, Wilkerson JM, Smolenski DJ, Oakes JM, Konstan J, Horvath KJ, et al. The future of Internet-based HIV prevention: a report on key findings from the Men's INTernet (MINTS-I, II) Sex Studies. AIDS Behav 2011 Apr;15 Suppl 1:S91-100 [FREE Full text] [doi: 10.1007/s10461-011-9910-5] [Medline: 21360127]
20. Pequegnat W, Rosser BR, Bowen AM, Bull SS, DiClemente RJ, Bockting WO, et al. Conducting Internet-based HIV/STD prevention survey research: considerations in design and evaluation. AIDS Behav 2007 Jul;11(4):505-521. [doi: 10.1007/s10461-006-9172-9] [Medline: 17053853]
21. Mohr JJ, Daly CA. Sexual minority stress and changes in relationship quality in same-sex couples. Journal of Social and Personal Relationships 2008 Dec;25(6):989-1007. [doi: 10.1177/0265407508100311]

22. Else-Quest NM, LoConte NK, Schiller JH, Hyde JS. Perceived stigma, self-blame, and adjustment among lung, breast and prostate cancer patients. Psychol Health 2009 Oct;24(8):949-964. [doi: 10.1080/08870440802074664] [Medline: 20205038]
23. Fergus KD, Gray RE, Fitch MI. Sexual dysfunction and the preservation of manhood: experiences of men with prostate cancer. J Health Psychol 2016 Jul;7(3):303-316. [doi: 10.1177/1359105302007003223] [Medline: 22114252]
24. Prescott TL, Phillips Ii G, DuBois LZ, Bull SS, Mustanski B, Ybarra ML. Reaching adolescent gay, bisexual, and queer men online: development and refinement of a national recruitment strategy. J Med Internet Res 2016 Aug 04;18(8):e200 [FREE Full text] [doi: 10.2196/jmir.5602] [Medline: 27492781]
25. Wright KB. Researching Internet-based populations: advantages and disadvantages of online survey research, online questionnaire authoring software packages, and web survey services. J Comput Mediat Commun 2005 Apr;10(3):00-00 [FREE Full text] [doi: 10.1111/j.1083-6101.2005.tb00259.x]
26. Rosser B, Kohli N, Lesher L. The sexual functioning of gay and bisexual men following prostate cancer treatment: results from the Restore study. In review 2018 (forthcoming). [doi: 10.1016/j.urpr.2017.05.001]

Abbreviations

AMIS: American Men's Internet Survey
GBM: gay, bisexual, and other men who have sex with men
IP: Internet protocol
IRB: institutional review board
PSA: prostate-specific antigen
WRAPP: Wyoming Rural AIDS Prevention Project

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Corrigenda and Addenda

Metadata Correction: Immune-Enhancing Formulas for Patients With Cancer Undergoing Esophagectomy: Systematic Review Protocol

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Related Article:

Correction of: http://www.researchprotocols.org/2017/11/e214/

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In the paper by Astrid Naranjo et al, "Immune-Enhancing Formulas for Patients With Cancer Undergoing Esophagectomy: Systematic Review Protocol" (JMIR Res Protoc 2017;6(11):e214), mistakes were made when listing the authors' degrees. Laisa Teleni's highest qualification was incorrectly listed as PhD. The correct degrees for Laisa Teleni are "BBiomedSci (Hon), MND". Elisabeth Isenring's degrees were incorrectly listed as "BHSc (Nut & Diet, Hons 1, GradCertHighEd)". The correct degrees for Elisabeth Isenring are "BHSc (Nut & Diet, Hons 1), PhD". The affiliations of the authors have not been changed.

The corrected article will appear in the online version of the paper on the JMIR website on April 27, 2018, together with the publication of this correction notice. Because this was made after submission to PubMed, Pubmed Central, and other full-text repositories, the corrected article also has been re-submitted to those repositories.

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Viewpoint

The Unanticipated Challenges Associated With Implementing an Observational Study Protocol in a Large-Scale Physical Activity and Global Positioning System Data Collection

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Abstract

Background: Large-scale primary data collections are complex, costly, and time-consuming. Study protocols for trial-based research are now commonplace, with a growing number of similar pieces of work being published on observational research. However, useful additions to the literature base are publications that describe the issues and challenges faced while conducting observational studies. These can provide researchers with insightful knowledge that can inform funding proposals or project development work.

Objectives: In this study, we identify and reflectively discuss the unforeseen or often unpublished issues associated with organizing and implementing a large-scale objectively measured physical activity and global positioning system (GPS) data collection.

Methods: The SPACES (Studying Physical Activity in Children's Environments across Scotland) study was designed to collect objectively measured physical activity and GPS data from 10- to 11-year-old children across Scotland, using a postal delivery method. The 3 main phases of the project (recruitment, delivery of project materials, and data collection and processing) are described within a 2-stage framework: (1) intended design and (2) implementation of the intended design.

Results: Unanticipated challenges arose, which influenced the data collection process; these encompass four main impact categories: (1) cost, budget, and funding; (2) project timeline; (3) participation and engagement; and (4) data challenges. The main unforeseen issues that impacted our timeline included the informed consent process for children under the age of 18 years; the use of, and coordination with, the postal service to deliver study information and equipment; and the variability associated with when participants began data collection and the time taken to send devices and consent forms back (1-12 months). Unanticipated budgetary issues included the identification of some study materials (AC power adapter) not fitting through letterboxes, as well as the employment of fieldworkers to increase recruitment and the return of consent forms. Finally, we encountered data issues when processing physical activity and GPS data that had been initiated across daylight saving time.

Conclusions: We present learning points and recommendations that may benefit future studies of similar methodology in their early stages of development.

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KEYWORDS

physical activity; children; data collection; postal survey

Introduction

Although there has been a strong movement to publish study protocols within the sociobehavioral sciences before or during data collection [1,2], particularly for trials [3] and more recently larger scale observational work [4], there is very little published material that attempts to describe how the specific protocol was implemented, the hitherto unidentified challenges encountered, and lessons learned. This reflective process is commonplace in the stages of trial/intervention work where a high degree of testing is usually built in during the design, using the lessons learned to refine the intervention [5]. It is also required when conducting rigorous evaluation of a new treatment or public health intervention, including the assessment of outcomes and processes (eg, implementation, mechanisms, and context) [6,7]. It is important for those who are involved in observational research, particularly large-scale national survey work, to build more of these reflective processes into their design. With more of such work being published, researchers can gain insightful knowledge that can be translated to other contexts, which in turn may prevent similar mistakes from being made, thereby minimizing time-consuming unexpected work.

The main aim of this study is to share the experiences gained when conducting a large scale, nationally representative study collecting physical activity and global positioning system (GPS) data from 10- to 11-year-old children across a whole country (Scotland). To do so, this study describes the original methods and processes of the project with particular reference to the recruitment, delivery of project materials, and data collection phases. We then present the issues and challenges experienced when trying to implement our intended design and conclude with recommendations for future research.

Methods

Intended Study Design

The study we describe here, Studying Physical Activity in Children's Environments across Scotland (SPACES), aimed to investigate the ways in which the built environment influences children's physical activity. The project employed an observational, cross-sectional design that sampled from the Growing Up in Scotland study (GUS; [8]). SPACES data was collected between May 2015 and May 2016 by the Medical Research Council (MRC) and Chief Scientist Office (CSO) funded Social and Public Health Sciences Unit (SPHSU), University of Glasgow. Ethical approval was gained from the College of Social Sciences, University of Glasgow (CSS:400140067).

Participant Selection—SPACES (Studying Physical Activity in Children's Environments Across Scotland) Sample

GUS is a nationally representative ongoing longitudinal cohort study that began in 2005 with the aim of tracking the lives of Scottish children. The Birth Cohort 1 (BC1; n=5217) was the first of 2 GUS birth cohorts to have been followed up from age 10 months (sweep 1) until 10 years old (sweep 8 was conducted throughout 2014 and finished in February 2015). The BC1 cohort is split across 2 academic years. The SPACES project included children who started Primary 6 (age approximately 10 years old) in August 2014 (approximately three-fourths of the full GUS BC1, n=2402). As part of the GUS age 10 and 11 interview sweep, parent or carers (n=2402) were provided with brief information about SPACES and asked if their contact details could be passed on to SPACES staff.

Recruitment

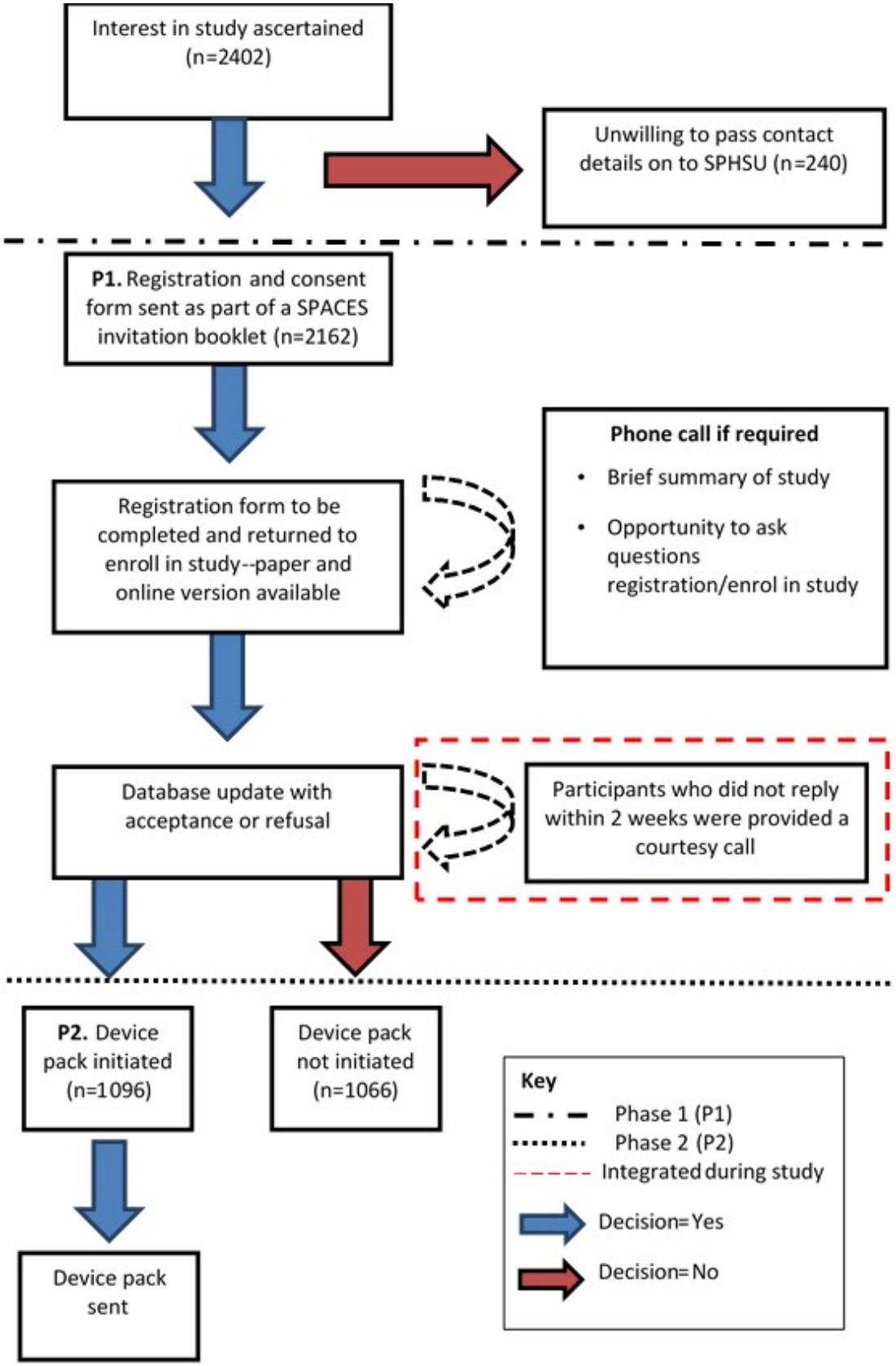
Due to the considerable budgetary and logistical constraints associated with a country-wide study, the primary method of communication was by post. Although we did use other forms of communication (eg, email, text messages [short message service, SMS], and phone) throughout the study, we wanted to maintain a consistent method that minimized burden on the participant (ie, having to use personal printers to print consent forms). Initial recruitment was based primarily on those members (parents and children) of the GUS cohort who consented to being contacted by SPHSU. The details of the GUS participants willing to be contacted by SPACES were sent by ScotCen Social Research—the GUS study management body—to a dedicated member of the project team at SPHSU (database manager). These details included the following: parent and child's full names, postal address, and telephone number.

For those willing to be contacted, we sent invitation packs, by post (P1 in Figure 1), in waves (approximately 200-300 per wave) starting in May 2015 and finishing in November 2015 (excluding the months of July and August for school holidays), containing a letter for the parent and one for the child participant; an information booklet (Multimedia Appendix 1) including a consent form; and a registration document (Multimedia Appendix 2). The registration document was provided in paper format, but the participants were given an option, stated within the information booklet, to complete this via an SPHSU maintained secure webpage on the Internet. The form provided space to request a phone call for further information, or if this was not required, space was given to register for the next stage of the process (P2 Device pack). As part of this document we also asked for an approximate measurement of the participant's waist size (for the elasticated belt that would hold study devices), and whether a mobile contact number could be requested for SMS reminders. Finally, we asked the parents/participants to propose a start date for the measurement period. To progress to the P2 phase, parents/participants were required to complete and return the registration document.

Delivery of Project Materials—Device Pack Contents

As part of this phase of the project (P2, Figure 1), we sent participants all the necessary equipment and survey materials to complete the study protocol. The following sections provide brief information on the content of these packs.

Figure 1. Flow diagram of participant recruitment and registration. SPACES: Studying Physical Activity in Children's Environments across Scotland; SPHSU: Social and Public Health Sciences Unit.



Objectively Measured Physical Activity—The ActiGraph GT3X+

The ActiGraph GT3X+ (ActiGraph, Pensacola, FL, USA) is a validated activity monitor [9,10] that measures acceleration in three orthogonal planes. The device is small (4.6×3.3×1.5 cm), lightweight (19 g), and unobtrusive; it is one of the most widely used monitors in the physical activity field and has been calibrated to accurately capture physical activity of varying intensity (eg, light and moderate) and also sedentary time [11]. Participants were asked to wear the ActiGraph on an elasticated waist belt, during waking hours, for 8 consecutive days. Devices were set to sample acceleration data 100 times per second (100 Hz). This device and the belt were included in the device pack.

Spatial Measurement—The Qstarz BT-Q1000XT Travel Recorder

The Qstarz BT-Q1000XT travel recorder is a validated GPS device [12], measuring 7.2×4.6×2.0 cm, that records the location of physical activity. Recognized for its acceptable static and dynamic accuracy [12], the device has sufficient battery life, which suited the requirements of our study. The participants were asked to wear the device concurrently with the ActiGraph monitor (held in a "pouch" attached to the same belt), during waking hours, for 8 consecutive days. The devices were set to record location (x/y coordinates) and supporting information (eg, number of visible satellites, elevation) at 10-second intervals. The GPS devices were required to be charged overnight throughout the study period and were set to stop recording when storage capacity had been reached (as opposed to rewriting over that which had already been stored). To assist, each device pack contained a charging cable (universal serial bus, USB) and UK AC adapter (with USB connection). Participants received the devices switched off and were instructed to turn them on when starting the measurement period.

Self-Reported Physical Activity—Physical Activity Questionnaire-Children (PAQ-C)

Participants were asked to complete the Physical Activity Questionnaire for Children (PAQ-C) following their activity monitoring period (Multimedia Appendix 3). The PAQ-C is a 7-day recall questionnaire that measures habitual levels of physical activity. Validated in children of similar ages [13], the questionnaire was chosen to reflect the cognitive abilities of the age group. It takes approximately 20 min to complete and was available to complete online, or by paper and pen.

Wear Time Log and Travel Diary

Participants were also provided a log booklet and asked to fill in the times where the accelerometer and GPS were not worn. This allowed us to identify periods in the accelerometer data files where the software would otherwise assume that the participant had been sedentary. The participants were also asked to complete the travel diary by recording the journey mode and associated time when traveling to and from school (Multimedia Appendix 4).

Instruction Guide

Each participant was sent a short instruction guide for wearing both activity monitor and GPS device (Multimedia Appendix 5). The activity monitor was instructed to be worn with the monitor placed above the right hip and the GPS device above the left hip. The guide included answers to frequently asked questions and specific instructions to charge the GPS device overnight. Our pilot indicated that the GPS devices would have enough storage capacity to record for the 8-day duration of the study and as such participants were initially asked to switch devices on before their first day of data collection and leave them in this position for the remainder of the study. The guide documented the process required to switch the GPS devices to record.

Data Collection and Processing

A dedicated room with secure access was employed throughout the project, equipped with necessary equipment, including desktop computers. Each computer was installed with the necessary software (ActiLife v.6.11.9 and QTravel V1.48) to initialize and download data from the devices. Fieldworkers were involved in the project at specific times to assist with particular tasks, for example, the period where participants were required to be contacted by telephone at the invite stage of the process.

Our data collection timeline was initially based on a 4-week issue/return cycle. This was put in place to allow us to plan the time required to collect the data for a full participating cohort, based on a working stock number of 400 devices (ie, 400 accelerometers and 400 GPS devices) and contingency of 25 devices for any technical issues/device losses that may have arisen and necessitated replacement during data collection. Devices plus accompanying instructions, time log sheet, and prepaid return envelope were sent out by Royal Mail 1st class post. Participants set their own preferred start date as part of the completed registration document, and our processes were matched to meet these dates. To act as a reminder to wear the devices and increase compliance with the protocol, SMSes were sent midway through the projected device wear period (based on confirmed start date by participant) to parents who provided their details during registration.

Results

Issues and Challenges Experienced—Ethics and Informed Consent

In light of the United Nations Convention on the Rights of the Child [14], the research team wanted to ensure that the children of the study (all younger than 16 years) were actively involved in the full consent process: both participants and parents were required to read study documentation, initial consent substatements (eg, consent to share data, or access previously collected data from GUS), and sign consent forms. Three main issues arose regarding ethical approval and are summarized below.

Gaining Ethical Approval for Nonclinical Research

It was unclear which committee the SPACES project should be submitted to: the College of Social Science university ethics committee, as sponsors of the SPACES study, or the National Health Service (NHS) Research Ethics Committee (REC), as sponsors of the GUS longitudinal study. This lack of clarity led

to the creation of applications to both committees and a lengthy period of correspondence between ScotCen, the University, and REC ethics advisors.

Informed Consent Procedures Were Markedly Different Depending on Committee

The two committees had different policies regarding Patient Information Sheets and Informed Consent Forms (ICF). This reflects the uncertainty and ambiguity that exists between taking part in medical research or traditional clinical trials and taking part in research more generally. Clinical Trial Regulations exist for the former, yet no real definitive process exists for the latter. The University of Glasgow committee required parental consent for all participating children younger than 18 years, in the view of the age of childhood according to common law as practiced in England, Wales, and Northern Ireland, whereas the NHS committee, operating within Scottish law, requested signed consent from children deemed competent to understand the process and from parents when deemed less competent. In England, no legal precedence or statute exists under common law for those younger than 16 years to give consent for medical treatment or research, although some treatment examples exist within case law (eg, Gillick case with respect to treatment, [15]). Scottish statute states that young people under the age of 16 years can give legally binding consent to participate in *medical* research as long as they are believed by the medical practitioner to be competent. The Guidance by the Medical Research Council [16], the funders of our study, states: "…It is not entirely clear whether this Scottish statute covers consent to participate in research…but in the absence of law dealing specifically with research, the principles of Scottish law relating to consent to procedures and treatment might be reasonably applied."

Registration Packs Were Sent by Post to Participants and Included a Consent Form

The completion and return of this registration document (returning a paper copy by post, completion online, or completion in a phone call with study staff) allowed research equipment to be *sent* to participants. In most cases, a consent form was returned by post alongside the registration document—but not in all cases. To prevent doubling of resources and time, permission was granted by the ethics committee to send research equipment upon affirmation that the participant was *willing* to take part. However, research data could only be *included* in any analyses, where participants and parents both "opted in" to the study by returning a signed consent from. These were returned in a prepaid envelope.

Retrieval of missing consent forms was much more challenging than first anticipated. Our main concern was the increased likelihood of receiving valid data from participants without an accompanying consent form, thereby rendering the data unusable. Participants were given prepaid envelopes to return all study equipment, and in a number of cases (n=182), participants had forgotten to send a consent within this envelope. As such, the following process was created and implemented to retrieve those missing consent forms (see Figure 2). The costs associated with introducing a multistage process such as that in Figure 2 includes additional research assistant time costs to manage the preparation and sending of letters; the cost of the letters, postage, and packaging; and the field worker costs if physical collection is required. This final stage may not be possible in extremely large data collections that span across spatially diverse countries. For ethical reasons, the retrieval of consent forms is vitally important, and our study suggests that approximately 16.60% (182/1096) of participants were actively (by phone call or house visit) followed up.

Recruitment

Participants had the choice to register for the study by returning the registration document by post, completing the registration online, or by making contact via a free phone number. Table 1 presents the recruitment sample by registration type. Approximately 20% (19.70%, 426/2162) registered by post, 4% (3.75%, 81/2162) online, and less than 1% (0.83%, 18/2162) actively called the study team to register.

As a result of poor return within the first wave of invitation letters, the study team made a decision within the first month of P1 that a further stage should be integrated, namely, a follow-up phone call if no registration document had been completed and returned within 2 weeks (see Figure 1). Approximately 2000 phone calls were attempted, with this stage resulting in the recruitment of a further 571 participants. Although a valuable opportunity to explain more about the study, this additional stage required extra resources, including field workers working out-of-office hours to contact the parents of participants.

Study Equipment

During our pilot work, it became evident that the pouches containing the GPS devices were of variable size, meaning that some GPS devices were not being securely held. Feedback from participants suggested that devices were falling out when the children ran or jumped. To resolve this issue, we fashioned an elasticated strap with Velcro attachments that ran across the opening of the pouch (Figure 3). This small modification prevented any further GPS devices from falling out of the pouch.

Delivery of Study Materials

Reliance on a postal delivery method meant that we had to consciously consider the size of the items being delivered to ensure they would fit through a standard UK letterbox. During our pilot, we encountered an issue where the purchased GPS charging adapters were in fact too large (alongside the other pack contents) to fit through our pilot letterboxes, rendering these unusable for our project. No commercial plug by any major UK suppliers could be found to meet the project budget; however, we were able to source affordable smaller plugs from an Internet source in China. Upon a subsequent pilot phase—where study packs were sent to members of the study team to assess the postal delivery time and to ascertain whether they were successfully posted through the letterbox—the modified device packs were deemed suitable for the project.

Figure 2. Staged process of retrieving missing consent forms.

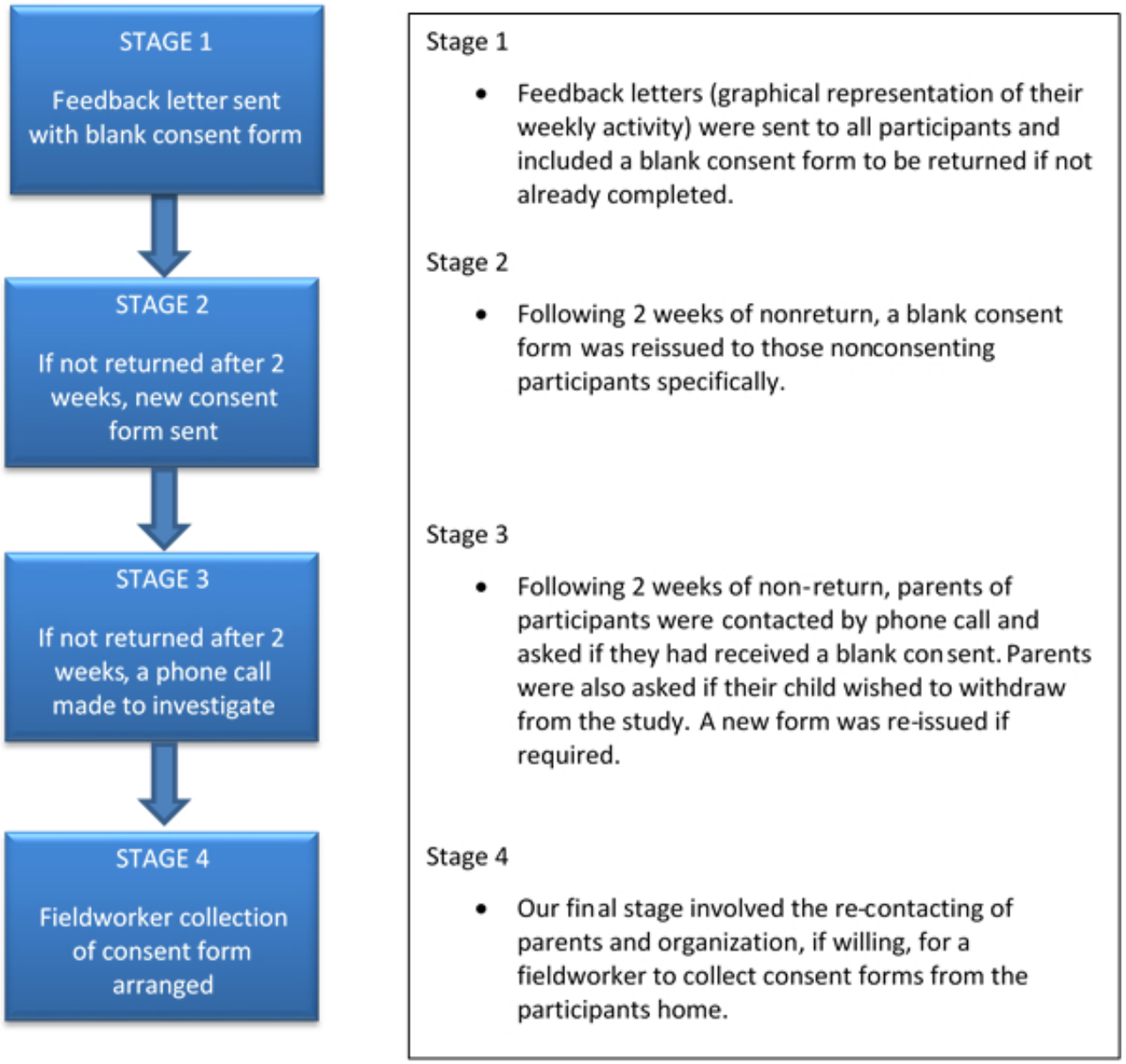
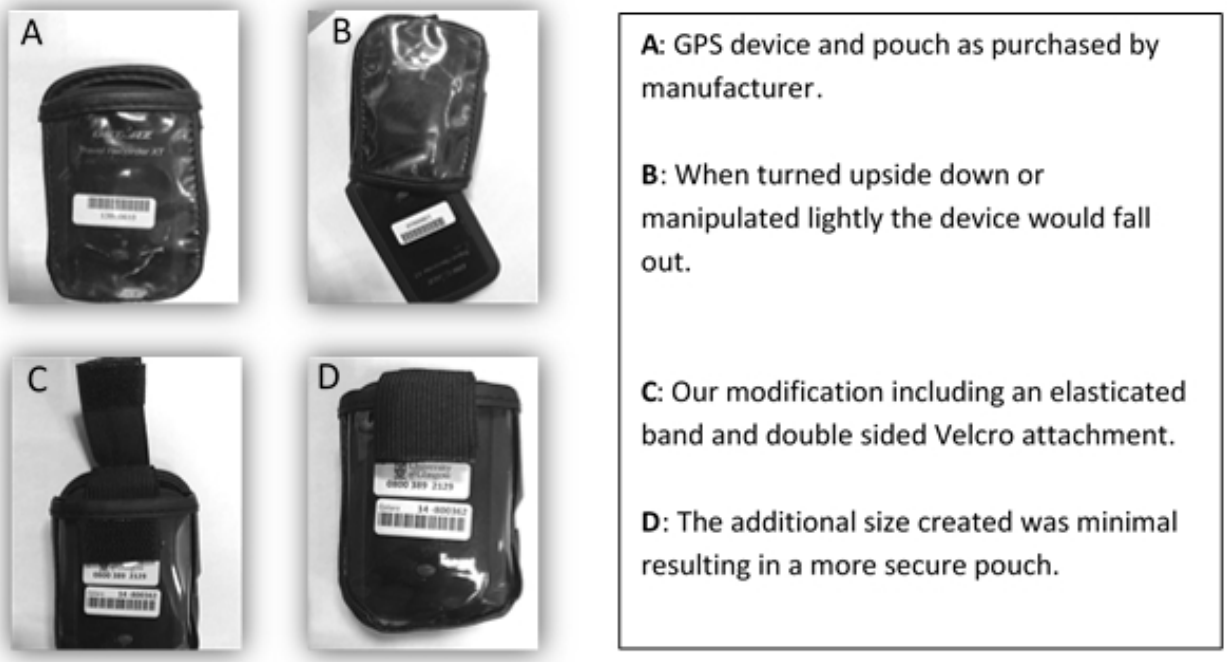


Table 1. Response to take part in SPACES (Studying Physical Activity in Children's Environments across Scotland) study.

Type of response	n (%), N=2162
Returned registration form in post	426 (19.70)
Online completion	81 (3.75)
Phone call from parent	18 (0.83)
Registered on phone	571 (26.41)
Withdrawal/refusal	337 (15.59)
Unable to contact	729 (33.72)

Figure 3. Demonstration of unsecure global positioning system (GPS) devices and our textile modifications to secure devices within their pouches. A: GPS device and pouch as purchased by manufacturer; B: When turned upside down or manipulated lightly the device would fall out; C: Our modification including an elasticated band and double sided Velcro attachment; and D: The additional size created was minimal resulting in a more secure pouch.



The delivery of devices was subject to two postal systems: the university internal system and the national Royal Mail system. SPHSU is an off-campus unit and is located at a distance of around 2 miles from the main university campus. As such, this had important practical and logistical considerations when sending out device packages to match participants' preferred start dates: staff members from the main campus visited the off-site unit once each day to take all post back to be processed and sent. Subsequently, additional time (usually 1 day) had to be integrated into the physical process of delivering study materials as a result. As the project involved two postal systems, we increased the number of potential weak points in the chain, and this was particularly evident in relation to device loss. We seldom encountered issues when sending our device packages to participants, however, a number of participants were adamant that they had sent devices back to the unit, but these devices never arrived. From the 1096 device packages sent, we had 51 confirmed lost as missing 51 (4.65%), and a further 25 (total=76, 6.93%) presumed lost because of the inability to contact the participants in question or in cases where we were told the devices had been sent back but not arrived. This issue is not unique to the United Kingdom, and most research studies will consider using different methods of delivery for their study. An interesting comparison by Heath and Stewart [17], in a study of Australian football club members, found that an email approach was less expensive than a postal method (Aus $ 1.16 vs Aus $4.84 per useable response) and resulted in a faster response speed to the study (3.9 days vs 10.8 days). However, total response level for the postal method (46%) was more than double than that of the online method (21%) and was similar to that found in this study. Each research context will be different, and future work should consider all possible options and choose based on what most adequately suits their needs.

Data Collection Phase

Our SMS message system seemed to work successfully, and feedback from a sample of parents was positive. The system was initially created to act as a reminder to wear the devices at the midpoint of the data collection; however, in a small number of cases the SMS acted as a prompt to the parent to inform us that the participant had yet to start the study period or had started a few days later than originally intended. Our system was built around the preferred start date of the participant, meaning that our SMS messages were either ineffective or had to be recalculated and resent. To enhance the effectiveness of this system, it may be beneficial to integrate a simple secondary process whereby parents can alert the research team when the data collection period has begun. This of course adds another stage of compliance and consideration should be given to the costs and benefits of doing so. Although we had strong compliance from the participants, future work may want to consider the benefits of increasing the SMS component to a daily reminder. This may be dependent on the population group or age, for instance if implementing a similar design with working adults or older populations. Doing so would involve a relatively small cost, so this should be considered and factored into a grant or funding proposal.

Our initial pilot work and subsequent protocol had organized for the GPS devices to record continuously at 10-second intervals for the 8 days of the study period (initially switched on by the participant). The default setting meant that the devices should have been able to record approximately 200,000 data points, however, with all of the aforementioned additional options selected (eg, visible satellites, elevation), we realized from the data recorded by the first few returned devices that the recordings were being stopped at day 7. In response, we sent

updated instructions to all active participants to turn their devices off before going to bed and turn them back on upon waking. This enabled a full 8 days recording (memory capacity) but could have influenced the number of data points returned, as some participants may have forgotten to activate their devices on certain days.

Data Processing Issues

We also encountered several software issues throughout the period of data collection and included a number of firmware updates (ActiGraph). Several updates created problems for the study. One particular update prevented access to the data stored on the device and was only solved by obtaining a customized piece of software from the manufacturer. This resulted in a delay of several weeks and hindered more collections and rewears during that period. A further firmware update resulted in reduced battery life for Bluetooth versions of the activity monitor. Fortunately, this issue was quickly spotted and it resulted in the loss of all ActiGraph data for only 5 participants.

A final unforeseen issue encountered in both activity monitors and GPS devices, arose as a result of UK daylight saving time (DST), where depending on time of the year, clocks either gain (October) or lose (March) an hour. Depending on when the devices were initiated and worn, the timestamps (ie, the date and hour/minute/second) of the downloaded data were incorrect by 1 hour. Where the GPS device software (QTravel) has an option to correct for DST when downloading and exporting the data, this option can be missed and is not necessarily well signposted. Even if this is selected, all timestamps are adjusted by 1 hour rather than only those recorded during DST. In addition, there appears to be a software bug in the correction across midnight that transitions back and forth across different times. This is an issue that will impact any research taking place in a geographical region that experiences DST. As such, this should be thought about in advance. Care should be taken when using this option and a few test cases should be pilot-tested in advance. A helpful paper by Hurvitz [18] is recommended reading for anyone using this type of data. A further issue discussed by Hurvitz relates to the issues that arise with the activity monitors during this period. The activity monitors are initiated by the software using the internal computer clock. As such, if these devices are initiated before the clocks changing, and the participants wear the device across the clock change, the file must be corrected to reflect this change. For the SPACES project, the activity monitor manufacturers were contacted, and they produced a piece of software that corrected all device files that were affected.

Discussion

Recommendations

Our experiences should be useful to any researcher who is planning to embark on a data collection study but may prove even more beneficial to those who implement similar designs. In general, the unanticipated challenges experienced as part of the implementation of the SPACES study resulted in substantial impact across four main categories: project timeline challenges; cost, budget and funding; participant engagement; and data challenges. Table 2 presents a summary of these issues in addition to suggested recommendations for researchers who may be planning similar projects. A major timeline issue that we experienced related to ethical approval. Our learning suggests that, within the UK context at least, only one ethics committee needs to review and approve an application. Provided they are a formally constituted body (whether through a Higher Education or a recognized Health Institute) then this will generally be sufficient for a research project. An important caveat is the distinction between clinical and nonclinical research projects involving the NHS. From a UK perspective, a nonclinical research project will usually be submitted to an ethics committee of the associated Higher Education institute. If the research is clinical in nature and is linked to the NHS (eg, potential participants are patients or users of the NHS, or the research would be require access to, or the use of, NHS premise), then formal applications should be submitted under the Department of Health/NHS framework.

Consent of underage children in all research is one that continues to be debated. With reference to this study, the issue was resolved by satisfying the College of Social Sciences ethics committee at the University of Glasgow, by having both parent and child complete and sign the ICFs. Ultimately, the process for our study ethics was ambiguous and complicated and very little legislation exists that deals specifically with children consenting to nonclinical trial-related research. If working with children younger than 18 years, and in partnership with an ongoing external study, it will be important to have this issue resolved at an early stage of the design development.

The cost implications for these types of studies require significant preplanning and forecasting, and all projects will have costed for the items such as personnel, instruments, and services. Our unit has a dedicated research support team with years of expertise in project management, budgeting, forecasting, and delivery, and this was a significant resource that made our data collection successful. We estimate that a project of this size and similarity would cost approximately £500k to conduct. Some considerations for future studies include the costs associated with database management of participants and study materials if necessary (ie, managing activity monitors and GPS devices); study documentation costs; data entry costs; and field work costs (eg, phone calls to participants). For those who use technology such as activity monitors or GPS devices, it is imperative that staff time is costed for device management (eg, charging, initializing, packaging, and downloading). Each device takes approximately 20 min to initialize and download. If you had 1000 participants in a study, this would “cost” approximately 330 hours. Future studies could use this information to cost their projects more realistically. One particular unanticipated example of a “cost” and “participant engagement” issue was that of project materials (GPS AC adapters) not passing through letterboxes. With this type of project design, we had to maximize the likelihood of participation, and this may have been reduced through the inconvenience of the respondents having to collect the package from a post office or collection office, especially for participants living in rural areas where this could be many miles away (in our study it might have meant a 40-mile round trip for some respondents).

Table 2. Issues experienced during study implementation, and suggested learning for future studies.

Project stage	Detail	Main implication	Suggested learning
Recruitment (P1)			
Ethical approval	Advised to submit to more than one ethics committee	Timeline	It is not necessary to submit to more than one committee as long as the approving body is formally constituted. Consideration should still be given to which committee is chosen.
Informed consent of minors	Informed consent process with children under 16/18 years of age is ambiguous and unclear	Timeline	Early discussion with an ethics committee is paramount. Guidance exists within the United Kingdom to assist with the decision-making process [16].
Informed consent process	The postal delivery method created a logistical issue with gaining participant consent	Timeline	In discussion with an ethics committee, researchers may want to raise the option of two distinct consent processes: consent to take part, and consent for data to be used. This may allow the study to proceed while waiting for final signed consent. Consideration should also be given to developing a phone-based consent procedure (ie, recorded consent) if accepted by ethics committee.
Participant recruitment	Success rates of registering varied by post, online, and by phone	Timeline; Budget	Active recruitment, where study staff can discuss, converse, and answer questions from participants, will result in greater numbers involved. Where possible, build the resources for this type of recruitment.
Device pack (P2)			
Postal delivery method	Using the UK Royal Mail system and the University's internal postal service extended the time needed to deliver and retrieve devices	Timeline	Researchers should consider how they will deliver the study materials to participants. If by post, multiple nodes and points of weakness may exist. These should be factored into the design.
Study material delivery	If using a postal delivery method, study materials should be of size to fit through letterboxes	Participant engagement; Budget	Careful planning and pilot-testing of study materials should be conducted to ensure participants receive study equipment.
Device loss	Physical equipment used in studies will be lost, broken, or go missing.	Budget, participant engagement	Minimize loss by ensuring all devices stay secure when being carried. Researchers should build in an anticipated loss of approximately 7% of devices if conducting a similar method.
Technical issues			
Storage capacity	Study equipment (eg, global positioning system, GPS) should meet the storage requirements of the study period	Data; participant engagement	If using GPS devices, rigorous piloting that mimics full study conditions should be conducted to ensure all data can be recorded across study period.
Software problems	Software glitches rendered some study devices inoperable	Data; Timeline	Consumer focused manufacturers should assist with faulty devices/software. It is also advisable to have access to software support within the study team.
Daylight saving time (DST)	Devices that require an internal clock to regulate accurate recording will be impacted by DST	Data	Software/programming support will be beneficial to alter affected data. Alternatively, consideration should be given to stopping data collection around the changes in DST.

In addition, since we had purchased AC adapters in large quantities we added an unnecessary cost to the project by having to purchase more. Although specific to this study, we can extend our learning to any study that proposes to use a postal method to deliver study instruments or materials. We recommend that future studies—that plan on using similar delivery methods—consider and test whether their materials will be successfully delivered by fully pilot-testing these processes in the formative stages.

A final, "data" issue recommendation relates to the technical specifications of any device used in a study. Our decision was to collect location (GPS) data at a higher resolution, and as such we chose to keep the 10-second interval but to ask participants to turn their devices off during the night. Subsequently, we introduced a further step for the children involved in the study which could have impacted both participation in the study, as well as the quality of the data recorded. An alternative approach could have been to increase this to 15-second intervals, thus

increasing storage capacity, or we could have decided against collecting so many of the additional options. Work by Schipperijn et al [12], for instance, has indicated that some of these additional variables may not be necessary to improve accuracy or assist with data cleaning and need not be recorded. However, we also suggest it is worthwhile to run analyses as part of the piloting process to inform the utility of these variables in specific study contexts.

Conclusions

The purpose of this study was to describe the methods and unforeseen challenges experienced by the SPACES study, a nationally representative accelerometry and GPS data collection study in Scottish 10- to 11–year-olds children. The particular strength of this study is the description of our experiences with previously unidentified issues that can arise in studies of this design. Few reflective pieces exist within the literature, yet in preparing this study, we hope that this type of information will prove beneficial to those developing large-scale primary data collections, particularly those involving postal methods, as well as those using wearable technologies. We see a particular benefit during the funding proposal stage where information from this study can be used to build a more realistic picture of cost, particularly with regard to time and unforeseen staff costs. In conclusion, we hope that this study highlights some of the potential complications that can arise during studies of this nature with the desire of making other researchers aware, in advance, thereby allowing plans to be put in place to mitigate these issues.

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Authors' Contributions

AE was the principal investigator on the project, and PM led the data collection. PM and AE proposed the idea for the study, and PM led on drafting. DW was the research assistant on the project and assisted with the writing of the technical method/design processes.

Conflicts of Interest

None declared.

Multimedia Appendix 1

SPACES information booklet and consent form given to participants.

[PDF File (Adobe PDF File), 1MB - resprot_v7i4e110_app1.pdf]

Multimedia Appendix 2

SPACES registration document to take part in the study.

[PDF File (Adobe PDF File), 159KB - resprot_v7i4e110_app2.pdf]

Multimedia Appendix 3

SPACES self-reported physical activity questionnaire (PAQ-C).

[PDF File (Adobe PDF File), 681KB - resprot_v7i4e110_app3.pdf]

Multimedia Appendix 4

SPACES travel diary and device log book.

[PDF File (Adobe PDF File), 384KB - resprot_v7i4e110_app4.pdf]

Multimedia Appendix 5

SPACES guidebook to manage the accelerometer and GPS device.

[PDF File (Adobe PDF File), 1MB - resprot_v7i4e110_app5.pdf]

References

1. Yıldırım M, Verloigne M, de Bourdeaudhuij I, Androutsos O, Manios Y, Felso R, et al. Study protocol of physical activity and sedentary behaviour measurement among schoolchildren by accelerometry--cross-sectional survey as part of the ENERGY-project. BMC Public Health 2011 Mar 25;11:182 [FREE Full text] [doi: 10.1186/1471-2458-11-182] [Medline: 21439040]
2. Gerike R, de Nazelle A, Nieuwenhuijsen M, Panis LI, Anaya E, Avila-Palencia I, PASTA Consortium. Physical activity through sustainable transport approaches (PASTA): a study protocol for a multicentre project. BMJ Open 2016 Jan 07;6(1):e009924 [FREE Full text] [doi: 10.1136/bmjopen-2015-009924] [Medline: 26743706]
3. Ritvo P, Obadia M, Santa MD, Alibhai S, Sabiston C, Oh P, et al. Smartphone-enabled health coaching intervention (iMOVE) to promote long-term maintenance of physical activity in breast cancer survivors: protocol for a feasibility pilot randomized controlled trial. JMIR Res Protoc 2017 Aug 24;6(8):e165 [FREE Full text] [doi: 10.2196/resprot.6615] [Medline: 28838886]
4. Hinckson E, Duncan S, Oliver M, Mavoa S, Cerin E, Badland H, et al. Built environment and physical activity in New Zealand adolescents: a protocol for a cross-sectional study. BMJ Open 2014 Apr 15;4(4):e004475 [FREE Full text] [doi: 10.1136/bmjopen-2013-004475] [Medline: 24736036]
5. Wight D, Wimbush E, Jepson R, Doi L. Six steps in quality intervention development (6SQuID). J Epidemiol Community Health 2016 May;70(5):520-525 [FREE Full text] [doi: 10.1136/jech-2015-205952] [Medline: 26573236]
6. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008 Sep 29;337:a1655 [FREE Full text] [Medline: 18824488]
7. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: medical research council guidance. BMJ 2015 Mar 19;350:h1258 [FREE Full text] [Medline: 25791983]
8. Bradshaw P, Tipping S, Marryat L, Corbett J. 2005 Aug 01. GrowingUp in Scotland sweep 1 - 2005 user guide URL: http://doc.ukdataservice.ac.uk/doc/5760/mrdoc/pdf/5760_userguide_cohort1_sweep1.pdf [accessed 2018-03-30] [WebCite Cache ID 6yIkAgeVu]
9. Robusto KM, Trost SG. Comparison of three generations of ActiGraph™ activity monitors in children and adolescents. J Sports Sci 2012;30(13):1429-1435 [FREE Full text] [doi: 10.1080/02640414.2012.710761] [Medline: 22857599]
10. Romanzini M, Petroski EL, Ohara D, Dourado AC, Reichert FF. Calibration of ActiGraph GT3X, Actical and RT3 accelerometers in adolescents. Eur J Sport Sci 2014;14(1):91-99. [doi: 10.1080/17461391.2012.732614] [Medline: 24533499]
11. Cain K, Sallis JF, Conway TL, Van Dyck D, Calhoon L. Using accelerometers in youth physical activity studies: a review of methods. J Phys Act Health 2013 Mar;10(3):437-450. [Medline: 23620392]
12. Schipperijn J, Kerr J, Duncan S, Madsen T, Klinker CD, Troelsen J. Dynamic accuracy of GPS receivers for use in health research: a novel method to assess GPS accuracy in real-world settings. Front Public Health 2014;2:21 [FREE Full text] [doi: 10.3389/fpubh.2014.00021] [Medline: 24653984]
13. Crocker P, Bailey DA, Faulkner RA, Kowalski KC, McGrath R. Measuring general levels of physical activity: preliminary evidence for the physical activity questionnaire for older children. Med Sci Sports Exerc 1997 Oct;29(10):1344-1349. [Medline: 9346166]
14. Pais MB, Bissell S. Overview and implementation of the UN convention on the rights of the child. Lancet 2006 Feb 25;367(9511):689-690. [doi: 10.1016/S0140-6736(06)68267-6] [Medline: 16503467]
15. HRCR. 1986. Gillick v West Norfolk and Wisbech area health authority URL: http://www.hrcr.org/safrica/childrens_rights/Gillick_WestNorfolk.htm [accessed 2018-03-30] [WebCite Cache ID 6yIkzqEt6]
16. Medical Research Council. 2004. MRC ethics guide: medical research involving children URL: https://www.mrc.ac.uk/documents/pdf/medical-research-involving-children/ [accessed 2018-03-30] [WebCite Cache ID 6yIlBwh1P]
17. McDonald H, Adam S. A comparison of online and postal data collection methods in marketing research. Marketing Intelligence & Planning 2003 Apr;21(2):85-95. [doi: 10.1108/02634500310465399]
18. Hurvitz PM. GPS and accelerometer time stamps: proper data handling and avoiding pitfalls. 2015 Nov Presented at: UrbanGIS15: 1st International ACM SIGSPATIAL Workshop on Smart Cities and Urban Analytics; November 3-6, 2015; Bellevue, WA, USA p. 94-100.

Abbreviations

DST: daylight saving time
GPS: global positioning system
GUS: Growing Up in Scotland
ICF: Informed Consent Forms
NHS: National Health Service
PAQ-C: Physical Activity Questionnaire for Children
REC: Research Ethics Committee
SPACES: Studying Physical Activity in Children's Environments across Scotland
SPHSU: Social and Public Health Sciences Unit

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