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Contents

Protocols

The Notijoves Project: Protocol for a Randomized Controlled Trial About New Communication Technologies and Gamification to Promote Partner Notification of Sexually Transmitted Infections Among Young People ([e12896](#))

Dolors Carnicer-Pont, Eva Loureiro-Varela, Josep Manresa, Montse Martinez, Àngels Avecilla, Laura Montero-Pons, Gemma Falguera-Puig. 5

The Effects of the Digital Platform Support Monitoring and Reminder Technology for Mild Dementia (SMART4MD) for People With Mild Cognitive Impairment and Their Informal Carers: Protocol for a Pilot Randomized Controlled Trial ([e13711](#))

Peter Anderberg, Pilar Barnestein-Fonseca, Jose Guzman-Parra, Maite Garolera, María Quintana, Fermin Mayoral-Cleries, Evi Lemmens, Johan Sanmartin Berglund. 14

Transitional Experiences of Internationally Qualified Midwives Practicing in Australia: Protocol for a Mixed Methods Study ([e13406](#))

Mitra Javanmard, Mary Steen, Rachael Vernon, Megan Cooper. 26

Biological and Functional Changes in Healthy Adult Smokers Who Are Continuously Abstinent From Smoking for One Year: Protocol for a Prospective, Observational, Multicenter Cohort Study ([e12138](#))

Cam Tran, Loyse Felber Medlin, Nicola Lama, Brindusa Taranu, Weeteck Ng, Christelle Haziza, Patrick Picavet, Gizelle Baker, Frank Lüdicke. 3 4

Mobile Messaging Support Versus Usual Care for People With Type 2 Diabetes on Glycemic Control: Protocol for a Multicenter Randomized Controlled Trial ([e12377](#))

Andrew Farmer, Kirsty Bobrow, Natalie Leon, Nicola Williams, Enita Phiri, Hazel Namadingo, Sara Cooper, John Prince, Amelia Crampin, Donela Besada, Emmanuelle Daviaud, Ly-Mee Yu, Jonathan Ngoma, David Springer, Bruno Pauly, Shane Norris, Lionel Tarassenko, Moffat Nyirenda, Naomi Levitt. 45

Comparing Written Versus Pictorial Asthma Action Plans to Improve Asthma Management and Health Outcomes Among Children and Adolescents: Protocol of a Pilot and Feasibility Randomized Controlled Trial ([e11733](#))

Lisa Hynes, Kristine Durkin, Desireé Williford, Hope Smith, David Skoner, Christa Lilly, Viral Kothari, Jenny Mc Sharry, Christina Duncan. . . 5 6

“Smartphone Medication Adherence Saves Kidneys” for Kidney Transplantation Recipients: Protocol for a Randomized Controlled Trial ([e13351](#))

John McGillicuddy, Jessica Chandler, Luke Sox, Martina Mueller, Lynne Nemeth, Prabhakar Baliga, Frank Treiber. 69

Feasibility and Clinical Relevance of a Mobile Intervention Using TrackPAD to Support Supervised Exercise Therapy in Patients With Peripheral Arterial Disease: Study Protocol for a Randomized Controlled Pilot Trial (e13651)	
Katrin Paldán, Jan Simanovski, Greta Ullrich, Martin Steinmetz, Christos Rammos, Rolf Jánosi, Susanne Moebus, Tienush Rassaf, Julia Lortz.	9
Web-Based Self-Management Guide for Kidney Transplant Recipients (The Getting on With Your Life With a Transplanted Kidney Study): Protocol for Development and Preliminary Testing (e13420)	
Daniela Massierer, Ruth Sapir-Pichhadze, Vanessa Bouchard, Kaberi Dasgupta, Nicolas Fernandez, Deborah da Costa, Sara Ahmed, Marie-Chantal Fortin, Rosalie Langevin, Nancy Mayo, Tania Janaudis-Ferreira.	115
Adapting the HIV Infant Tracking System to Support Prevention of Mother-to-Child Transmission of HIV in Kenya: Protocol for an Intervention Development Pilot Study in Two Hospitals (e13268)	
Sarah Finocchiaro-Kessler, May Maloba, Melinda Brown, Brad Gautney, Kathy Goggin, Catherine Wexler, Natabhona Mabachi, Beryne Odeny, Silas Lagat, Sharon Koech, Jacinda Dariotis, Thomas Odeny.	124
Using Temporal Features to Provide Data-Driven Clinical Early Warnings for Chronic Obstructive Pulmonary Disease and Asthma Care Management: Protocol for a Secondary Analysis (e13783)	
Gang Luo, Bryan Stone, Corinna Koebnick, Shan He, David Au, Xiaoming Sheng, Maureen Murtaugh, Katherine Sward, Michael Schatz, Robert Zeiger, Giana Davidson, Flory Nkoy.	135
Older People With Type 2 Diabetes—Individualizing Management With a Specialized (OPTIMISE) Community Team: Protocol for a Safety and Feasibility Mixed Methods Study (e13986)	
Rajna Ogrin, Sandra Neoh, Tracy Aylene, Ralph Audehm, Leonid Churilov, Lorena Thurgood, Georgia Major, Jeffrey Zajac, Elif Ekinici.	154
Protocol for the Development of a Behavioral Family Lifestyle Intervention Supported by Mobile Health to Improve Weight Self-Management in Children With Asthma and Obesity (e13549)	
David Fedele, Robert Lucero, David Janicke, Mutasim Abu-Hasan, Elizabeth McQuaid, Jon Moon, Andrea Fidler, Tanya Wallace-Farquharson, David Lindberg.	174
Understanding Pregnancy and Postpartum Health Using Ecological Momentary Assessment and Mobile Technology: Protocol for the Postpartum Mothers Mobile Study (e13569)	
Dara Mendez, Sarah Sanders, Hassan Karimi, Pedram Gharani, Stephen Rathbun, Tiffany Gary-Webb, Meredith Wallace, John Gianakas, Lora Burke, Esa Davis.	184
Uniform Noting for International Application of the Tumor-Stroma Ratio as an Easy Diagnostic Tool: Protocol for a Multicenter Prospective Cohort Study (e13464)	
Marloes Smit, Gabi van Pelt, Annet Roodvoets, Elma Meershoek-Klein Kranenburg, Hein Putter, Rob Tollenaar, J van Krieken, Wilma Mesker.	2
Integration of Gender-Affirming Primary Care and Peer Navigation With HIV Prevention and Treatment Services to Improve the Health of Transgender Women: Protocol for a Prospective Longitudinal Cohort Study (e14091)	
Javier Lama, Kenneth Mayer, Amaya Perez-Brumer, Leyla Huerta, Hugo Sanchez, Jesse Clark, Jorge Sanchez, Sari Reisner.	209
Enhancing Diabetes Self-Management Through Collection and Visualization of Data From Multiple Mobile Health Technologies: Protocol for a Development and Feasibility Trial (e13517)	
Ryan Shaw, Angel Barnes, Dori Steinberg, Jacqueline Vaughn, Anna Diane, Erica Levine, Allison Vorderstrasse, Matthew Crowley, Eleanor Wood, Daniel Hatch, Allison Lewinski, Meilin Jiang, Jane Stevenson, Qing Yang.	221
An Affirmative Coping Skills Intervention to Improve the Mental and Sexual Health of Sexual and Gender Minority Youth (Project Youth AFFIRM): Protocol for an Implementation Study (e13462)	
Shelley Craig, Lauren McInroy, Andrew Eaton, Gio Iacono, Vivian Leung, Ashley Austin, Cheryl Dobinson.	232

Stimulation of Nucleotide Oligomerization Domain and Toll-Like Receptors 2 to Enhance the Effect of Bacillus Calmette Guerin Immunization for Prevention of Mycobacterium Tuberculosis Infection: Protocol for a Series of Preclinical Randomized Controlled Trials (e13045) 248
 Michael Eisenhut.....

Diet-Induced Alteration of Microbiota and Development of Obesity, Nonalcoholic Fatty Liver Disease, and Diabetes: Study Protocol of a Prospective Study (e11553) 271
 Martine Uittenbogaart, Wouter Leclercq, Danielle Bonouvrie, Marleen Romeijn, Arijan Luijten, Steven Olde Damink, Francois van Dielen, Sander Rensen.....

Preliminary Effectiveness and Safety of High Frequency Oscillation in Addition to Mechanical Insufflation and Exsufflation for Intratracheal Mucus Removal in Patients With Neuromuscular Disease: Protocol for a Prospective Study (e12102) 277
 Hiroyuki Awano, Masashi Nagai, Ryosuke Bo, Mariko Muraio, Yusuke Ishida, Tsukasa Tanaka, Kazumi Tomioka, Masahiro Nishiyama, Hiroaki Nagase, Kazumoto Iijima.....

A Pragmatic Cluster Randomized Trial of an Electronic Clinical Decision Support System to Improve Chronic Kidney Disease Management in Primary Care: Design, Rationale, and Implementation Experience (e14022) 283
 Elaine Khoong, Leah Karliner, Lowell Lo, Marilyn Stebbins, Andrew Robinson, Sarita Pathak, Jasmine Santoyo-Olsson, Rebecca Scherzer, Carmen Peralta.....

Policies and Programs for the Prevention and Control of Breast Cancer in Mexican and Latin American Women: Protocol for a Scoping Review (e12624) 300
 Igor Ramos Herrera.....

Adolescent Male Couples-Based HIV Testing Intervention (We Test): Protocol for a Type 1, Hybrid Implementation-Effectiveness Trial (e11186) 307
 Tyrel Starks, Sarah Feldstein Ewing, Travis Lovejoy, Sitaji Gurung, Demetria Cain, Carolyn Fan, Sylvie Naar, Jeffrey Parsons.....

Testing a Motivational Interviewing Implementation Intervention in Adolescent HIV Clinics: Protocol for a Type 3, Hybrid Implementation-Effectiveness Trial (e11200) 322
 Sylvie Naar, Karen MacDonell, Jason Chapman, Lisa Todd, Sitaji Gurung, Demetria Cain, Rafael Dilones, Jeffrey Parsons.....

An Electronic Pre-Exposure Prophylaxis Initiation and Maintenance Home Care System for Nonurban Young Men Who Have Sex With Men: Protocol for a Randomized Controlled Trial (e13982) 336
 Aaron Siegler, James Brock, Christopher Hurt, Lauren Ahlschlager, Karen Dominguez, Colleen Kelley, Samuel Jenness, Gretchen Wilde, Samuel Jameson, Gina Bailey-Herring, Leandro Mena.....

Pre-Exposure Prophylaxis Integration into Family Planning Services at Title X Clinics in the Southeastern United States: A Geographically-Targeted Mixed Methods Study (Phase 1 ATN 155) (e12774) 348
 Jessica Sales, Cam Escoffery, Sophia Hussen, Lisa Haddad, Ashley Phillips, Teresa Filipowicz, Maria Sanchez, Micah McCumber, Betty Rupp, Evan Kwiatkowski, Matthew Psioda, Anandi Sheth.....

Original Papers

iCanCope With Pain: Cultural Adaptation and Usability Testing of a Self-Management App for Adolescents With Persistent Pain in Norway (e12940) 85
 Erik Grasaas, Liv Fegran, Sølvi Helseth, Jennifer Stinson, Santiago Martinez, Chitra Laloo, Kristin Haraldstad.....

Web-Based Eligibility Quizzes to Verify Opioid Use and County Residence Among Rural Young Adults: Eligibility Screening Results from a Feasibility Study (e12984) 162
 April Ballard, Hannah Cooper, April Young.....

Aims, Study Design, and Enrollment Results From the Assessing Predictors of Infant Respiratory Syncytial Virus Effects and Severity Study ([e12907](#))

Edward Walsh, Thomas Mariani, ChinYi Chu, Alex Grier, Steven Gill, Xing Qiu, Lu Wang, Jeanne Holden-Wiltse, Anthony Corbett, Juilee Thakar, Lauren Benoodt, Matthew McCall, David Topham, Ann Falsey, Mary Caserta. 257

Protocol

The Notijoves Project: Protocol for a Randomized Controlled Trial About New Communication Technologies and Gamification to Promote Partner Notification of Sexually Transmitted Infections Among Young People

Dolors Carnicer-Pont¹, MD, MPH, PhD; Eva Loureiro-Varela², MSc; Josep M^a Manresa^{3,4}, MD, BScB; Montse Martinez⁵, Midwife, RN; Àngels AVECILLA⁶, MD; Laura Montero-Pons⁷, Midwife, RN; Gemma Falguera-Puig⁸, PhD, Midwife, RN[‡]

¹Cancer Prevention and Control Programme, Catalan Institute of Oncology, Hospital Duran i Reynals, L'Hospitalet de Llobregat, Spain

²Informatics Department, Catalan Institute of Oncology, Hospital Duran i Reynals, L'Hospitalet de Llobregat, Spain

³Research Support Unit, Metropolitana Nord, Primary Health Research Institute, Barcelona, Spain, Spain

⁴Nursing Department, Autonomous University of Barcelona, Cerdanyola del Vallès, Spain

⁵ASSIR Cerdanyola del Vallès, Metropolitana Nord, Institut Català de la Salut, Barcelona, Spain

⁶Badalona Assistential Services, Badalona, Spain

⁷ASSIR Santa Coloma de Gramanet, Metropolitana Nord, Institut Català de la Salut, Barcelona, Spain

⁸ASSIR Sabadell, Metropolitana, Metropolitana Nord, Institut Català de la Salut, Barcelona, Spain, Spain

[‡]Sexual and Reproductive Health Consolidated Emerging Group

Corresponding Author:

Dolors Carnicer-Pont, MD, MPH, PhD
Cancer Prevention and Control Programme
Catalan Institute of Oncology
Hospital Duran i Reynals
199-203, Gran Via de L'Hospitalet, Avenue
L'Hospitalet de Llobregat, 08908
Spain
Phone: 34 93 260 73 57 ext 7339
Email: dcarnicer@iconcologia.net

Abstract

Background: An increase in sexually transmitted infections (STIs) as well as an increase in the use of new information and communication technologies among young people in Catalonia is the inspiration behind the idea of designing a smartphone app to promote partner notification of STIs.

Objective: The main objective of this study is to design a Web-based tool adapted to smartphones for partner notification of STIs among youth who are 16 to 24 years old. Additionally, the objective is to evaluate the Web-based tool's role in increasing the *patient referral* partner notification.

Methods: This is a multicenter randomized controlled trial with a proportional stratification of the sample by center and random allocation of participants to the 3 arms of the study (simple Web-based intervention, game Web-based intervention, and control). This study is being conducted by midwives, gynecologists, and physicians in the sexual and reproductive areas of the primary health care centers.

Results: The primary outcome measure is the number and proportion of partner notifications. Additional outcome measures are the yield of early diagnosis and treatment of those exposed and infected, acceptability, barriers, and preferences for partner notification. Expected results include an increase in the yield of partner notification, early diagnosis and treatment among youth using Web-based interventions compared with those receiving the traditional advice to notify, and a description of sexual networks among those participating in the study.

Conclusions: The *Notijoves* is expected to have a sustainable positive impact in the partner notification practice among youth and contribute to increasing the awareness of STI prevention.

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KEYWORDS

mobile apps; sexually transmitted infections; partner notification; youth; games, experimental; game theory; randomized controlled trial

Introduction

Background and Study Rationale

Prevalence of sexually transmitted infections (STIs) among young people has increased over the years. In Catalonia, prevalence of *Chlamydia trachomatis* among those below 25 years increased from 5.8% in 2008 to 8.5% in 2013 [1]. The most affected age group is the 16 to 18 years old.

The main rule to control communicable diseases is guaranteeing an early detection of the infected to treat them and alert the exposed [2]. Therefore, sexual partner notification is crucial to reach awareness of the exposed and facilitate testing for potential diagnosis. Scientific evidence highlights the need to improve partner notification and early testing [3-5], and in the case of *Chlamydia trachomatis*, partner notification is proved to be more cost effective than systematic screening [6,7]. Partner notification is recognized to be crucial for reducing transmission and preventing reinfection at an individual level [3].

In our country, as well as in most of the other European countries, the most frequently used models of partner notification are the ones done by the patient itself (*patient referral*), and the one done by the health professional after obtaining the patient's approval (*provider referral*) [8].

An internet-based system of partner notification allows the anonymous practice through a Web-based notification, an email, or short messaging system. This tool may help in getting in touch with previous sexual partners with whom there is no interest to revisit in person.

In addition, the introduction of a gamified approach of partner notification among youngsters is an innovative way to involve those who otherwise would not be interested in notifying. By discovering through gamification the main aspects of the STI that the youngsters were diagnosed with and the importance of notifying partners for the prevention of further transmission, the youngsters are more likely to notify their partners about a potential infection, and they are more likely to advise them to get tested for the potential infection.

Provided that youngsters are prone to using new technologies and video games and that previous studies prove the utility of gamification as an important tool to promote behavior changes [9-12], we propose to include this gamification as a third arm of the trial.

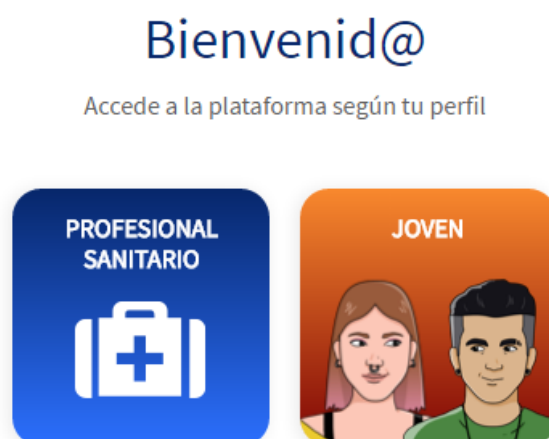
This study also includes the social network analysis that allows for a deep study of the relationships among young people. It is based on the evidence that transmission of sexual infections in a social group is determined by the existence of central members within the social structure [13]. Therefore, we aim to conduct a randomized controlled trial to assess the effectiveness of partner notification through the use of new information and communication technologies (ICTs). Our hypothesis is that the percentage of partners informed by their index cases will be higher when the index cases can use new technologies (personally or anonymously) compared with the use of paper notification card to do a *face-to-face* partner notification, without any specific guidance.

Development of an App to Promote Patient Referral Partner Notification

According to the Report of the Spanish Digital Society, 2017, 86% of the youngsters aged 15 to 24 years own a smartphone, and this has become their main means of communication. It is expected that in 2018, 50% of these youngsters will exclusively use smartphones to be on the Web [14]. In addition, these youngsters are heavy users of smartphone apps. Making available a responsive smartphone app that helps to do partner notification, either personally or anonymously, may increase partner notification practice. New and innovative ways of addressing partner notification in a sustainable way that can benefit youngsters and reduce transmission are a high priority. That is why we proposed the development of a smartphone app in Spanish and in Catalan (see Figure 1 for app icon in Spanish). Experts in gamification and Web app contributed to its development, drawing on the gamification-information-motivation-behavioral skills approach to behavioral change [15].

A total of 3 workshops with youngsters of different social levels were conducted by a psychologist, anthropologists, and nurses to identify the best way to design the game.

The app contains different story games that are sensitive to sexual orientation of youngsters, adapted information to the STI that was diagnosed to the patient, and choice of different methods to do partner notification (short message service, email, WhatsApp, or face to face), either anonymously or by identifying himself or herself. At the end of the game, the youngsters will have learned preventive features of the infection, and they should be motivated to inform all sexual partners exposed to the STI; in addition, they will choose a method to send them the message or inform them personally.

Figure 1. App icon “in Spanish”.

Aims and Objectives

The aim of this study is to describe the protocol for the randomized controlled trial of the *Notijoves* Web-based tool, adapted to smartphones for partner notification of STIs among youngsters aged 16 to 24 years.

The first objective of the study is to design the tool and evaluate its role in increasing partner notification done by the patient (patient referral partner notification) for all eligible sexual partners.

The specific objectives are the following:

- Describe sociodemographic characteristics of index cases and consecutive sexual partners
- Describe coinfections within the group
- Describe acceptability, barriers, and preferences for executing partner notification using ICTs
- Evaluate the utility to apply the game theory (gamification to promote behavior change) in the design of a Web app for partner notification of STIs
- Evaluate the yield of ICTs for partner notification of STIs among sexual partners
- Assess the impact of ICTs in primary transmission of STIs
- Describe the characteristics of the social and sexual network among youngsters

Methods

Design

This is an unblinded 3-armed randomized controlled trial, assigning patients to each arm of the study through the proportionally stratified sample of patients by health center, which will test the primary hypothesis that a greater proportion of partners will be informed about their exposure to STIs (syphilis, chlamydia, or gonococcus) in the intervention groups compared with the control group. We will randomize 416 young and recently diagnosed index cases in 1 of the 7 centers of the study. The researcher responsible for analyzing the data will be blind to group allocation.

Ethical and Research Governance Approval

This trial was approved by the Ethics Committee of the Institute of Research in Primary Care of Catalonia Institut Universitari d'Investigació en Atenció Primària Jordi Gol and given funding through the competitive call: Health Research and Innovation Strategic Plan 2016-2020 of the Catalan Government (ID:SLT002/16/00197).

Participants

This trial is being conducted in 7 public-based primary health care centers for sexual and reproductive health of Catalonia in the cities of Mataró, Badalona, Santa. Coloma de Gramanet, Granollers, Mollet, Cerdanyola-Ripollet, and Sabadell. Participants to the study are being recruited in each of the primary health care centers according to the following *inclusion criteria*: Young people 16 to 24 years old, diagnosed with at least 1 of the curable STIs (syphilis, gonococcus, or chlamydia). Partners who have had sexual contact within the previous 6 months since the diagnosis of index case.

Exclusion criteria are the following: diagnosis of other STIs (trichomonas, HIV, Hepatitis C, and Hepatitis B), which, although partner notification is advisable, will not be included to prevent complexity in the study. Under the diagnosis of 1 of these STIs, health professionals will perform according to the current clinical guidelines.

Study Period

The study will be conducted within a 3-year period. A total of 1 year to prepare the Web app, 18 months for the field work, and 6 months for the evaluation and dissemination of results.

Groups of the Study

Control Group

Those receiving the recommendation to inform their partners about exposure to STIs by the standard procedure currently available in the Catalan guidelines, use of a Partner notification paper card.

Game Intervention Group

Those advised to enter the *Notijoves* Web app with a code and follow the steps of the game to finally choose among different ways to notify their partners.

Web App Direct Intervention Group

Those advised to enter the *Notijoves* Web app with a code and directly choose among different ways to notify their partners.

Main Outcome Variable

The main outcome variable of the study is the percentage of partners informed of their exposure to a STI from their index cases, according to the assigned study group.

Sample Size

Young population accessing all centers of study within a year is around 400. They have been randomly distributed in 3 arms, according to the Bonferroni correction, to allow multiple comparisons of outcomes with a significance level of $P=0.016$. The trial is expected to have 10% of withdrawals after recruitment within the intervention groups and 20% of withdrawals after recruitment within the control group. Therefore, to have at least 120 participants in each 1 of the groups, 133 are recruited in each 1 of the intervention groups and 150 are recruited in the control group. The random list ratio is 1:1:1.28. To achieve this sample, participant recruitment is allowed for a period ranging from 13 to 18 months.

Randomization and Informed Consent Procedure

The sample is proportionally being assigned to each of the 7 centers, according to their regular activity (see [Table 1](#)).

The health professional proposes that the young patient index case should participate in the study, and once verbal acceptance is obtained, he gets into the Web app (see [Figure 1](#)) to obtain a random code that assigns the patient to 1 of the 3 arms of the

study. He also prints the informed consent to be signed by the patient and explains all the procedures to him/her, according to the arm assigned (control, direct Web app, and game Web app). A copy of the Informed consent is given to the patient, and the original is kept under the custody of the health professional in the participating center.

Participation Procedure

All the candidates who accept to participate in the study are given information about the study, both verbally and by receiving an Information sheet. The candidates refusing participation are also asked to complete a quick survey (2 questions) to provide reasons for not participating. (see [Figure 2](#))

Control Group

The control group receives usual partner notification advice, and the health professional prints as many partner notification paper cards as the patient index case mentions to be able to provide partner notification paper cards to exposed partners. Therefore, exposed partners are expected to receive a partner notification paper card and a letter that are to be given to their health professional. The letter informs of the potential diagnosis and advised treatment. The card has information of the STI and the list of Sexual and Reproductive Health Centers and primary health care centers for sexual and reproductive health, where the recipient of the notification can go for diagnosis and potential treatment.

The random code given to the index case patient appears in the informed consent and in a short paper questionnaire (12 questions). Each 1 of the partner notification paper cards has a code in line with the study arm of the index case. This means that partners receiving a partner notification paper card from an index case assigned to the control arm are kept in the control arm themselves.

Table 1. Sample size distribution for each primary health care center for sexual and reproductive health.

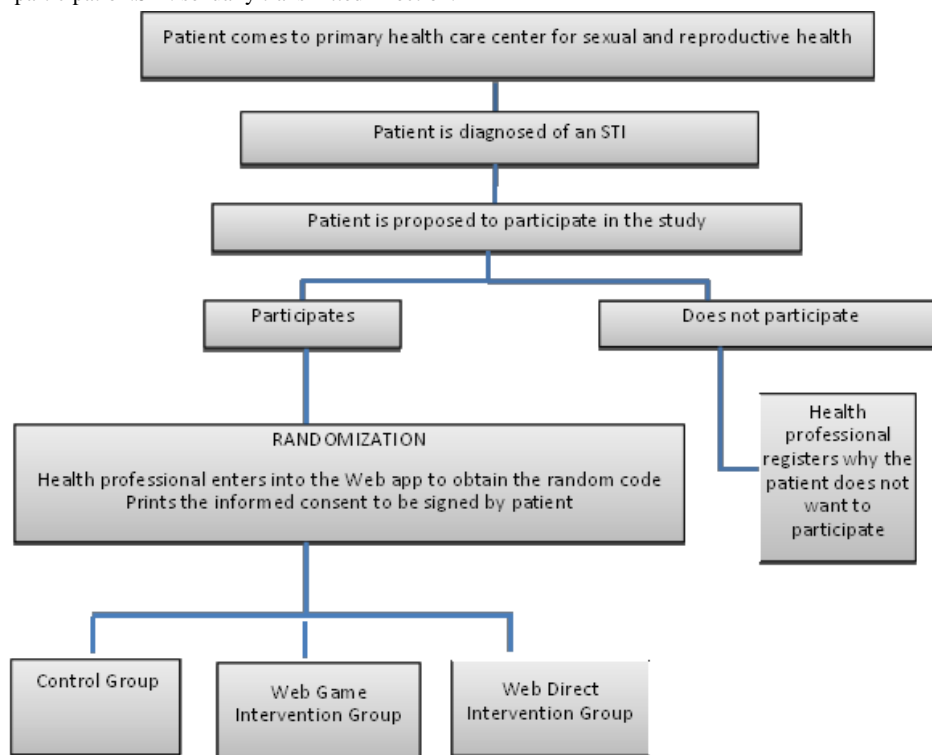
Location of health care centres ^a	Control ^b N1	Intervention game ^c N2	Intervention Web ^d N3	Total N
Badalona	30	26	26	82
Sabadell	27	24	24	76
Granollers	27	24	24	74
Mollet	20	18	18	57
Mataró	20	17	17	55
Santa Coloma	14	13	13	40
Cerdanyola	12	11	11	34
Total	150	133	133	416

^aPrimary Health Care Centres for Sexual and Reproductive Health.

^bControl group.

^cGame intervention group.

^dWeb app direct intervention group.

Figure 2. Algorithm of participation. STI: sexually transmitted infection.

Web App Game Intervention Group

Individuals assigned to this group receive an Information sheet explaining the objectives and procedures of the study. After providing a signature of their informed consent, they receive a paper copy of this informed consent that has a specific code through which they enter the game by connecting to the *Notijoves* Web address. A paper card with the “Notijoves” Web address is given to the patients. Once they enter the Web app, they are asked to feed the given code into the field of Young PANDORA screen.

By entering the code, they start playing the game, and they are directed through different screens and situations. A Web-based questionnaire is inserted in the game. At the end of the game, they are also asked to respond to a satisfaction questionnaire.

The game is expected to motivate the youngster to notify partners of their exposure to an STI. While playing the game, the youngsters are asked to answer questions related to the clinical symptoms, prevention, and control of their recently diagnosed STI. Like this, they *learn by playing*. Another feature of the Web app is the link to advisory videos on how to approach the *face-to-face* notification of exposure to an STI. Finally, the game ends with a screen, where the youngsters can choose from among the different electronic tools to notify (short message service, email, or WhatsApp) either anonymously or by identifying themselves.

The electronic partner notification card has the following: (1) a code automatically assigned by the electronic system that is concordant with the arm where the index case patient entered the study, (2) the informative message advising the partner to visit a health center for diagnosis and potential treatment, and (3) a link to a list of health centers of the study and the Web app address, where the partner could go and where the informed partner could enter and participate in the study by introducing the code. Along with the notification card, the partner receives an electronic letter to be given to the health professional for him to be aware of the STI diagnosed to the sender of this notification and the advised treatment.

Web App Direct Notification Intervention Group

Individuals assigned to this group receive an Information sheet explaining the objectives and procedures of the study. After providing a signature of their informed consent, they receive a paper copy of this informed consent that has a specific code through which they enter the *Notijoves* Web address. A paper card with the *Notijoves* Web address is given to the patients. Once they enter the Web app, they are asked to feed the given code into the field of Young PANDORA screen (see [Figure 3](#)). By entering the code, they are directed to a Web-based questionnaire and are offered an option to choose from among the different electronic tools (short message service, email, or WhatsApp) to notify either anonymously or by identifying themselves. Finally, they are also asked to respond to a satisfaction questionnaire.

Figure 3. Entrance to game “in Catalan”.

What Happens to the Partners Receiving the Notification Card?

Partners visiting participating centers are easily linked to the study by their code, and they are also offered participation to the study. Once accepted, they also sign the informed consent, and they are asked to respond to a recipients' questionnaire. After receiving the test results, if they are infected, they initiate the same procedure as an index case, with their given code, in concordance with the branch of the study that their index case was assigned. If they are not infected, the health professional registers results linked to the receptors questionnaire.

There may be partners visiting participating centers but not bringing the letter for the health professional and not having the code. These partners cannot be linked to any partner notification card, and therefore they are lost to follow-up for the system. Nevertheless, if they turn out to be infected, they are recruited as new index cases, with a new randomly assigned code. Moreover, those partners visiting a center out of the study area are lost to follow-up for the study.

Data Collection

The Web app has 2 entries: the entry of health professional and the entry of the youngster.

The health professional entering the Web system activates the random assignment of the code to 1 of the 3 arms of the study and registers the information on the diagnosed STI.

The involvement of the youngsters with the study gives rise to different situations among candidates:

1. The index case wanting to participate
2. The recipient of the notification wanting to participate
3. The index case or the recipient not wanting to participate

4. Participants assigned to 1 of the intervention groups who finalized the experience of partner notification after using the Web app

For each 1 of the situations, there is a specific questionnaire:

1. The questionnaire given to index cases collects data on the recruiting health care center, date of interview, date of birth, sex (boy, girl, transgender born as man, and transgender born as woman), country of birth, mother's country of birth, education (without studies, primary studies, secondary studies, and university), with whom they have sex (boys, girls, or indistinctly boys or girls), number of sexual partners 6 months before the diagnosis, whether they look at webpages to obtain information about STIs (yes, no), whether they look for partners on the Web (yes, no), currently diagnosed with STI, positioning toward partner notification (will inform all partners, only some, none, and do not know), and reasons for not notifying.
2. The questionnaire given to recipients of a partner notification card collects the same data as above and substitutes the last 3 questions with to which STI have you been exposed? How did you get to know your exposure (face to face, partner notification card, WhatsApp, short message service, email, and other)? Did you receive the notification anonymously (yes, no)?
3. Those not wanting to participate are asked about their reasons in an open question. They are also recorded as index case or recipient of a notification.
4. The opinion or satisfaction questionnaire collects data on whether the Web app helped its users to solve doubts related to STIs (not at all, a few, normal, quite a lot, and a lot), usefulness of the Web app to notify partners (not at all, a few, normal, quite a lot, and a lot), use of the anonymous option to notify (yes, no), easiness to choose from among

the options to notify (yes, no, and if not, why not?), wish to recommend the Web app to friends (yes, no, and if not, why not?), and how can we improve the Web app? (open question)

Data Analysis

Descriptive analysis of index cases visiting health centers will be baselined to further assess differences in yield by groups. Chi-square test and Student *t* test for categorical and continuous variables will be used to assess differences in baseline characteristics among groups. Regression analysis and adjusting for confounding variables will be used to evaluate the primary outcome and relative risk, and its 95% CIs will be calculated. Significance will be set at .05. The multiple imputation method will be used to generate possible values for missing values. This is considered the gold standard for dealing with missing values. Data will be analyzed in Stata v12 (StataCorp LLC).

The methodology of analysis of the social and sexual networks will be used from an egocentric perspective. Structural measures of the network will be calculated, such as the size of the network, number of direct links, density, the geodesic average distance, diameter of ego's network, and measures of centrality, such as the degree of intermediation of a contact or index case. Furthermore, we will compare social network, density, and structure. Network measurements will be done using the R statistical package.

Confidentiality, Storage, and Archiving

Data will be archived in a safe environment, according to the European Data protection law.

Ethical Aspects

The investigators are committed to respect the prevailing norms of Good Clinical Practice, the requisites of the Declaration of Helsinki, and the clauses of general and particular ethical conditions related to the right to privacy, anonymity, and confidentiality. Neither the first name nor surname or any other type of data indicating the identification of the young population will be registered. Therefore, identification will be made by alphanumeric codes. Youngsters participating in the study will sign an Informed Consent by paper, and when they are enrolled through the Web, they will confirm acceptance to participate by clicking on the confirmatory cell.

Results

The Web app was available to the health professional to initiate recruitment by early April 2018. From April 1 to May 30, we expected to recruit 83 index cases, but difficulties on accreditation of new health professionals and on entry to the study environment in the Web prevented recruitment. In early June 2018, there were 32 young people who accepted to

participate in the study. They were assigned randomly to control group (n=15), game intervention group (n=9), and Web direct intervention group (n=8).

The project is currently recruiting with a rate of approximately 6 recruitments per month. Recruitment is slower than expected. Mainly because of the difficulties in the implementation of the Web app. Our confidence is that within the last 6 months of the field study, recruitment pace will be doubled, and the expected sample size will be achieved. To improve recruitment, since September 2018, we have allocated 3 more professionals to the task.

Discussion

Summary

During the trial period, the Web app is only available to research participants; therefore, source coding and App content have been preserved.

Limitations

First, the study relies on an assumed independence of the groups. This means that young participants randomly assigned to 1 of the intervention groups will not share information with those falling in the control group. However, it can happen that some controls have friends assigned to the game or Web app directly and that they visit it with them. This can generate a classification bias, underestimating the real effect of the intervention. Second, information bias to assess primary transmission can occur when not all expected partners to be notified are the ones who visit health centers for testing. Third, those partners receiving a notification but visiting a health center out of the study area will be lost to follow-up if they are assigned to the control group. This will generate a participation bias, overestimating the partner notification yield of the other arms of the study. Fourth, a malicious use of the Web app could occur, when anonymous partner notification is sent by some youngsters to other youngsters who were not even exposed. This may generate overestimation of the partner notification yield. Finally, we cannot fully ascertain the network across experimental conditions because of the anonymous condition of our experiment. It may happen, although very rarely, that partners receive a notification from 2 index cases assigned to different arms of the trial. In that case, the system assumes that the first notification received by the youngster is the one that will be followed-up and the one that will contribute to network analysis.

Conclusions

Few studies have examined the yield of partner notification among young people, especially by the use of Web apps. The *Notijoves* smartphone app is an intervention that, if shown to be effective, may be implemented for all of Catalonia.

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Conflicts of Interest

None declared.

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Abbreviations

ICT: information and communication technology

STI: sexually transmitted infection

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Protocol

The Effects of the Digital Platform Support Monitoring and Reminder Technology for Mild Dementia (SMART4MD) for People With Mild Cognitive Impairment and Their Informal Carers: Protocol for a Pilot Randomized Controlled Trial

Peter Anderberg¹, PhD; Pilar Barnestein-Fonseca², PhD; Jose Guzman-Parra², PhD; Maite Garolera³, PhD; María Quintana³, PhD; Fermin Mayoral-Cleries², MD, PhD; Evi Lemmens⁴, PhD; Johan Sanmartin Berglund¹, MD, PhD

¹Department of Health, Blekinge Institute of Technology, Karlskrona, Sweden

²Research Unit, La Unidad de Gestión Clínica de Mental Health, Instituto de Investigación Biomédica de Málaga, Hospital Regional Universitario Málaga, Málaga, Spain

³Brain, Cognition and Behavior - Clinical Research, Consorci Sanitari de Terrassa, Barcelona, Spain

⁴University Colleges Leuven-Limburg, Genk, Belgium

Corresponding Author:

Peter Anderberg, PhD

Department of Health

Blekinge Institute of Technology

Valhallavägen 1

Karlskrona, 37179

Sweden

Phone: 46 734223736

Email: pan@bth.se

Abstract

Background: Many countries are witnessing a trend of growth in the number and proportion of older adults within the total population. In Europe, population aging has had and will continue to have major social and economic consequences. This is a fundamentally positive development where the added life span is of great benefit for both the individual and the society. Yet, the risk for the individual to contract noncommunicable diseases and disability increases with age. This may adversely affect the individual's ability to live his or her life in the way that is desired. Cognitive conditions constitute a group of chronic diseases that predominantly affects older people. Recent technology advancements can help support the day-to-day living activities at home for people with cognitive impairments.

Objective: A digital platform (Support Monitoring and Reminder for Mild Dementia; SMART4MD) is created to improve or maintain the quality of life for people with mild cognitive impairment (PwMCI) and their carers. The platform will provide reminders, information, and memory support in everyday life, with the purpose of giving structure and lowering stress. In the trial, we will include participants with a diagnosed neurocognitive disorder as well as persons with an undiagnosed subjective memory problem and cognitive impairment, that is, 20 to 28 points on the Mini-Mental State Examination.

Methods: A pragmatic, multicenter RCT is being conducted in Spain, Sweden, and Belgium. The targets for recruitment are 1200 dyads—split into an intervention group and a control group that are in usual care. Intervention group participants will be provided with a data-enabled computer tablet with the SMART4MD app. Its core functionalities, intended to be used daily at home, are based on reminders, cognitive supporting activities, and sharing health information.

Results: Inclusion of participants started in December 2017, and recruitment is expected to end in February 2019. Furthermore, there will be 3 follow-up visits at 6, 12, and 18 months after the baseline visit.

Conclusions: This RCT is expected to offer benefits at several levels including in-depth knowledge of the possibilities of introducing a holistic multilayered information and communication technology solution for this group. SMART4MD has been developed in a process involving the structured participation of PwMCI, their informal carers, and clinicians. The adoption of SMART4MD faces the challenge of this age group's relative unfamiliarity with digital devices and services. However, this challenge can also be an opportunity for developing a digital device tailored to a group at risk of digital exclusion. This research

responds to the wider call for the development of digital devices which are accessible and affordable to older people and this full scale RCT can hopefully serve as a model for further studies in this field.

Trial Registration: ClinicalTrials.gov NCT03325699; <https://clinicaltrials.gov/ct2/show/NCT03325699>

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KEYWORDS

dementia; mild cognitive impairment; tablet; app; carer; eHealth; mHealth

Introduction

Background

The number of older adults in the population as well as their proportion within the total population are increasing in many parts of the world. In Europe, population aging has had and will continue to have major social and economic consequences. This is a fundamentally positive development where the added life span is of great benefit for both the individual and the society. Many older people are able to support themselves and continue to make important contributions to society. Yet, the risk for the individual to contract noncommunicable diseases and disability increases with age. This may impair the ability of the individual to live his/her life in the way that is desired. It also exerts pressure on health services and support systems for older people.

Cognitive conditions such as mild cognitive impairment (MCI) and dementia constitute a group of chronic diseases that predominantly affects older people [1]. The general increase in life span causes the number of people with MCI [2] to increase; people with dementia in Europe alone is estimated to reach 13.4 million by 2030. The challenge of ensuring a good life for all is likely to remain formidable [3]. Health care policies are focused on extending the ability of older people to continue to live independently as one way of meeting these challenges. As medical treatment options currently remain centered on symptomatic treatment, the use of technology [4] and specifically information and communication technologies (ICTs) is suggested as a way to support function and maintain a good life [5,6]. For people with neurocognitive disorders, a good quality of life (QoL) means that they experience a certain level of independence and self-management of daily-life activities, which may be promoted by using technology.

It is important to be aware of the heterogeneity in technology use abilities [7-9]. Involving end users in design and development of technology is especially important for the development of usable technology [10-12].

Cognitive problems affect both the individual as well as their surroundings [13,14]. Living together with and/or caring for a PwMCI or dementia can compromise the informal carer's own well-being and health because of a feeling of being overloaded in the caregiving role [15-17].

The central role the informal carers play also accentuates the importance of the well-being of the informal carers themselves, and provision of support to the informal carers is therefore essential [18]. This is also an important target for the development of new supportive technologies. For example,

people with dementia often experience disorientation and thus tend to get lost while they are outside on their own, causing stress for the caregiver. According to a pilot study by Pot et al [19], global positioning system tracking reduces feelings of worry when being alone outside, both in people with dementia as well as their caregivers. The Rosetta system integrated 3 ICT systems to support daily functioning (eg, social contact, memory, and activities) and to detect changes in daily behavior and identify emergency situations. Using this system, feelings of safety and security improved QoL in people with dementia and their carers [12].

Many devices and digital apps to support the day-to-day living activities at home for people with neurocognitive disorders have been developed during the recent years. However, most solutions focused on cognitive impairment training or support and safety for people living alone. Most of them are single apps or devices, but few were integrated into a single solution or product [20,21].

A recent study by Yousaf et al [22] categorized mobile health apps for dementia into apps for cognitive training and daily living (eg, word games, videos, and music), screening (eg, clock drawing), health and safety monitoring (eg, fall detection using installed cameras, alarms, and emergency help), leisure and socialization (eg, media for reminiscence therapy), and navigation (eg, tracking). Similarly, Meiland et al [11] looked at 3 fields of technologies for this group: (1) support with managing everyday life, (2) support with participating in pleasurable and meaningful activities, and (3) support with dementia health and social care provision. The study highlighted the importance of both inclusion of the group in the development of technology as well as the need for more comprehensive studies and higher quality evaluation of technology usability. Furthermore, the early introduction of technology in a degenerative cognitive process, or preferably before, may be an important factor [23,24].

The importance of including QoL as an outcome measure in dementia trials has been identified by the World Federation of Biological Psychiatry's Old Age Taskforce [25] as well as others in the field. QoL is multifactorial; therefore, besides "the individual's perception of their position in life in the context of culture and value systems in which they live, and in relation to their goals, standards, and concerns" [26,27], QoL also encompasses physical and mental health, social relationships, and participating in activities. In this trial, we therefore aim to analyze QoL in a broad sense.

Few systematic reviews are available that investigate the effectiveness of interventions on the QoL of people with dementia [11]. Among those available, 1 systematic review

found preliminary evidence that nonpharmacological interventions targeting both patients and their carers improved the QoL of persons with dementia living at home [28]. In contrast, a systematic review of pharmacological interventions to improve QoL and well-being in persons with dementia found that these interventions failed to show positive results in these domains [25]. Other relevant systematic reviews focused on the use of assistive technologies to improve QoL in older people in general [29,30]. These covered technologies, including the computer and the internet (ie, general ICT), robotics, sensors, telemedicine, medication management apps, mobile tracking devices, and video games. Regarding QoL in older people with dementia specifically, the review [29] identified 3 studies investigating general ICT and sensors. These studies suggested that the investigated technologies have the capacity to enhance QoL not only in people with dementia but also in those caring for them. It is important to note that most studies included in these reviews were small, not randomized, did not include or report QoL as a primary outcome measure, or did not include a valid QoL measure [29]. Altogether, they state a current lack of high-quality evidence that these interventions improve the QoL of persons with neurocognitive disorders and underline the need of large randomized controlled trials (RCTs).

Results from a randomized controlled pilot study were published using a computerized platform entitled “A technology platform for the Assisted living of Dementia elderly Individuals and their informal carers” (ALADDIN) [31]. The authors demonstrated that the use of ALADDIN enhanced the carers’ ability to care for a person with dementia by improving the QoL and reducing distress and carer burden.

MCI and dementia are used mostly as terms in this text. Today, these conditions are more correctly referred to as neurocognitive disorders, classified according to diagnostic criteria in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders. However, as the earlier concepts, to a large extent, are still used in the literature, we have chosen not to continually change terms at all instances in this paper.

Aim

In this trial, we aim to create a digital platform (Support Monitoring and Reminder for Mild Dementia, SMART4MD) to improve or maintain the QoL for people with mild neurocognitive disorders and their carers. The platform will provide the individual with reminders, information, and memory support in everyday life with the purpose of giving structure and lowering stress. In the trial, we will include participants with a diagnosed neurocognitive disorder as well as persons with an undiagnosed subjective memory problem and cognitive impairment, that is, 20 to 28 points on the Mini-Mental State Examination (MMSE). We will refer to this group as persons with mild cognitive impairment (PwMCI) in the following text.

Primary Objective

The research hypothesis is that use of the SMART4MD app over a period of 18 months can result in an improvement in the QoL of PwMCI.

The statistical null hypothesis is that the use of the SMART4MD platform produces no change in the mean total Health-related

quality of life Alzheimer's disease QoL-AD score of PwMCI over 18 months.

The statistical alternative hypothesis is that the use of the SMART4MD platform produces a change in the mean total QoL-AD score of PwMCI over 18 months.

Secondary Objectives

The secondary objectives also apply to the intervention group using the app over a period of 18 months. The objectives are as follows:

- To increase adherence to prescribed medication by 10% (all documented prescriptions)
- To reduce functional decline in PwMCI by 10% (as measured by Instrumental Activities of Daily Living)
- To monitor PwMCI's attendance at health care appointments and admission to health care institutions
- To monitor the informal carers' mental well-being as a strong determinant of caregiver burden and in turn of QoL of informal carers in the control and intervention group

Methods

Study Design

This is a pragmatic, multicenter RCT, and the Consolidated Standards of Reporting Trials (CONSORT) [32] guidelines will be followed. The ClinicalTrials.gov identifier is NCT03325699.

Setting

This study will be performed in 3 European countries: Spain, Sweden, and Belgium and 4 participant centers, which are as follows: Consorci Sanitari de Terrassa (Catalonia, Spain), Servicio Andaluz de Salud (Andalusia, Spain), Blekinge Institute of Technology (Sweden), and University College Leuven-Limburg (Belgium).

Participants

In total, 1200 participant dyads in 3 European countries (Spain, Sweden, and Belgium) will be included in the study. The participant dyads will comprise the PwMCI and his/her informal carer, with the PwMCI being the main participant. The participant will be selected by a nonprobabilistic consecutive sampling method. All participants will receive their treatment as usual (TAU) in their respective site, but the care of the intervention group will be improved with the support of the SMART4MD app.

Sample Size

A total of 1200 dyads (PwMCI+carers) is the target for recruitment, divided over 2 groups: an intervention group, using the SMART4MD app, and a control group, not using the SMART4MD app. In this clinical trial, QoL is the primary outcome measure, measured by the QoL-AD total score [33]. This score is based on 13 four-point (1 to 4) items on a discrete visual analog scale. Recent papers [34] show the standard deviation (SD) of the total QoL-AD score approaches 7.

To detect a small effect size of 0.2 comparing 2 groups (intervention and control), using a 2-sided *t* test with a 5% statistical significance level, with a power of 80%, the minimum

number of PwMCI required in each group is 394 (788 overall). If there would be a dropout rate of 20%, the number of PwMCI registered on the study would need to be 493 in each group (thus 986 overall).

On the other hand, one of our secondary objectives is to increase adherence to prescribed medication by 10% in the intervention group. If we consider that in people with dementia, the treatment adherence is between 44% and 99% [35,36], and assuming the less prevalence (44%), which we want to increase by 10%, with a power of 0.8 and a significance level of .05, we need 1174 subjects (20% dropouts included). Therefore, the sample size of this study is adequate to detect statistical and clinical differences between groups for the QoL-AD (primary outcome) and treatment adherence (a secondary outcome).

Inclusion Criteria

A participant will be eligible for inclusion in this trial only if all of the following criteria are met:

- Participants score 20 to 28 points on the MMSE whether or not a diagnosed neurodegenerative disease is present;
- A professional assessment of the patient's own experience of memory problems over a substantial period of time (more than 6 months);
- Participants are older than 55 years;
- Participants are home care recipients;
- Participants have an informal carer;
- Participants take prescribed medication and are in charge of their own medication use;
- Participants have no specific conditions reducing their physical ability to use the app, for example, visual, hearing, or motor impairments.

Exclusion Criteria (Persons With Mild Cognitive Impairment Only)

A participant will not be eligible for inclusion in this trial if any of the following criteria apply:

- Participants have a terminal illness with less than 3 years of expected survival;
- Participants score above 11 on the Geriatric Depression Scale (GDS-15) [37] or have another known significant cause of disease as an explanation for cognitive impairment such as abuse and other psychiatric diagnoses such as bipolar disorders, schizophrenia, and developmental disorders.

Recruitment

Participants will be identified from a cohort of people with cognitive impairment that has been present for more than 6 months and who meet all the study eligibility criteria. Participants can be under primary care services as well as secondary care services, such as those who are being followed up in memory clinics, outpatient clinics, day hospitals or other components of specialist mental health care, geriatric medicine, and neurology services. Participants will also be identified from patient databases such as those integrated in the centers' networks. The identification process will consist of screening using information gathered from medical notes, clinic records,

and/or clinical consultations for initial eligibility based on inclusion criteria.

Each country will have a country specific recruitment plan that will be revised by the trial steering committee.

After a brief explanation of the study design and research goals, participants will be invited to participate in the study, and an appointment with the researchers will be made. Participants will be provided with all the information they need to make an informed decision via a participant information sheet. They will be given a cooling-off period of at least 24 hours between informally agreeing to participate in the study and being invited to formally consent in a meeting with the research team.

At the first visit, the researcher will explain the study in detail and answer any questions the patient or caregiver may have. The patient's eligibility will be confirmed and their ability to consent will be assessed. Once consent is officially given by signing an informed consent form by all parties, the dyad will be randomized into either the intervention or the control group.

Randomization

Enrolled dyads will undergo 1:1 block randomization by each study clinic performed by the Anglia Ruskin Clinical Trials Unit (ARCTU) to assign them to the intervention group or the control group. Randomization will be undertaken using an internet-based randomization system setup by ARCTU on the TENALEA system provided by FormsVision BV. The system stores the predetermined sequence of randomization; this list is not available to the investigators.

Intervention: the Support Monitoring and Reminder Technology for Mild Dementia Platform

Our intervention strategy, which aims to improve the QoL of PwMCI, is based on the use of a single or multiple function that the SMART4MD app enables. The rationale behind and description of the functionalities of the SMART4MD app are presented in detail in a separate document ([Multimedia Appendix 1](#)). Briefly, participants in the intervention group will be provided with a data-enabled computer tablet preinstalled with the SMART4MD app. The tablet will be configured in such a way that it is not possible for participants to download any other app or software onto the tablet.

SMART4MD is a general electronic health app that has been adapted specifically for MCI through a structured process involving the participation of PwMCI and their informal carers and health care professionals. Focus groups were conducted with PwMCI and their informal carers, and interviews were conducted with health care professionals. The app can run both on tablet and mobile phone devices adopting the Android operating system but is specifically optimized for tablet devices as opposed to smaller screen mobile phone devices.

The core functionalities of the app are based on reminders (medication, appointments with health care providers, and meeting up with family and friends), cognitive supporting activities (clock, calendar, brain games, and photos) and optional status and health information sharing with family and informal carers (including mood and specific health problems such as headaches).

The app allows the participant to share health information to other people of their choice (relatives or research team) by email. The participant can select what kind of information he/she can share and to whom he/she wants to send this information.

An important feature of SMART4MD is its personalization facility: main users (PwMCI and informal carers) will be able to switch on/off or change various features and information-sharing possibilities.

The app is intended to be used daily at home, mainly by the PwMCI themselves, with the help of their informal carers when needed.

Training and Support for App Users

The SMART4MD user training across the trial sites will be delivered in the most uniform way possible, minimizing bias. Support during the trial regarding the use of the app will be provided, and each center will nominate 1 individual to lead the support for participants recruited and assigned to the intervention group, helping users in their own language. On the day of delivery of the tablet, a training session is held for both the subject and the caregiver, with explanations of how the tablet and the app works.

In addition, a paper-based manual is delivered on the introductory meeting as a complement to the verbal introduction. The manual has been developed with an emphasis on the parts of the tablet and app, where users in the feasibility study experienced difficulties.

Finally, throughout the clinical trial, participants have a contact person in each site with whom they can consult regarding their doubts and technical problems.

The hours and limits of responsibility of this support will be standardized across trial sites. The support will be delivered at clinical visits or via email or phone calls.

Control Group

The control group will only receive their TAU. There are different conditions and diseases and the treatment can vary widely among the participants. In addition, there are different health care systems among study centers. In any case, the participants in the control group will receive the TAU that they would receive at their care center regardless of the study.

Outcomes in Persons With Mild Cognitive Impairment

Primary Outcome

Health Related Quality of Life

Health related quality of life of PwMCI will be measured using the total score of the QoL-AD questionnaire [33,38,39]. This is a 13-item measure, which has been specifically designed to measure QoL in individuals with dementia from the perspective of both the PwMCI and the informal carer. It includes questions related to the interpersonal, environmental, functional, physical, and psychological status of the person with dementia, and thus, it is a global measure for QoL. QoL-AD will be assessed via an interview with PwMCI and via self-completion by informal carers.

Secondary Outcomes:

Adherence to Prescribed Medication: Doses and Pill Count

Adherence to prescribed medication will be assessed by comparing the PwMCI's documented prescription for medications with the number of pills taken (or if medication is not in pill form, pill equivalents) in the 30 days before the assessment day.

This assessment will be undertaken by a Principal Investigator PI or delegate at the 6-, 12- and 18-month visits. PwMCI and informal carer dyads will be asked to bring any documentation related to their prescription history for all medications and all the remaining pills (or pill equivalents) and empty medication packaging they have from the previous 30 days so that the researcher can undertake the medication count.

The dose/pill count is the number of pills or doses taken divided by the number of pills or doses prescribed, multiplied by 100 (expressed as a percentage) [40,41]. According to Haynes et al recommendations, a good adherence is considered when the result of counting is between 80% (a 20% of doses/pills missed) and 110% (the patient takes 10% more doses/pills) of doses/pills prescribed. We will select a maximum of 2 drugs for each participant in the pill count.

Cognitive Function

It will be measured by the MMSE [42]. It is also used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time. To be included in the trial, individuals must score between 20 and 28 points on the scale. The use of an MMSE cutoff value of 28 is not common and has some risks but has been used in other studies [43]. O'Bryant et al [44] showed that an MMSE cutoff score of 28 gave the best sensitivity and specificity for detecting mild dementia in a population with self-reported memory complaints.

Functional Decline

The EuroQoL-5D (EQ-5D) is a self-completion questionnaire that consists of 5 questions plus a scale where the participant rates their health state on a scale of 0 to 100. EQ-5D has been shown to correlate well with QoL-AD, indicating that the 2 measures are compatible and can be used side by side [38].

Service Utilization

Attendance at health care appointments and admissions to health care institutions will be collected from health management systems in the participating regions.

Independent Variables-Covariables

Sociodemographic Data

Age, gender, education, whether participant lives alone, marital status, and relationship with the informal carer are the sociodemographic variables.

Medical History of Persons With Mild Cognitive Impairment

These include family antecedents such as Alzheimer disease, Parkinson disease, other dementing illness; Comorbidity International Classification of Diseases-10; Current Treatment according to The Anatomical Therapeutic Chemical

Classification System Information about dementia: diagnosis of dementia, type of dementia, if they have undergone a magnetic resonance imaging scan, and if they are using any pharmacological treatment for their dementia.

Depression

The GDS-15 [37] will be used as an exclusion criterion, screening for depression. If participants score above 11, they will be excluded from the trial.

The GDS is commonly used as a routine part of a comprehensive geriatric assessment. The grid sets a range of 0 to 4 as “normal,” 5 to 8 as “mildly depressed,” 9 to 11 as “moderately depressed,” and 12 to 15 as “severely depressed.”

Familiarity With Comparable Technological Devices

This will be assessed via a questionnaire of 6 questions tailored to this study, covering both prior and current experience of using internet and mobile technology in general and, specifically, apps with particular relevance to SMART4MD functionality (Multimedia Appendix 2). It will also include an instrument to measure general attitudes and feelings toward technology [45].

User Behavior

In the intervention group, the following data will be collected from the platform: date and time of any interaction with the SMART4MD app, length of interaction, and the functions used during the interaction.

Outcomes in Carers

Secondary Outcomes

Carer Burden

The Zarit Caregiver Burden Interview (ZBI-12) [46,47] will be used to evaluate informal carers' burden. The ZBI-12 is a 12-item scale with each answer chosen from a 5-point Likert scale. It is a shortened version of the original scale that was developed specifically for informal carers of PwMCI and covers issues such as carer stress and the degree to which caring is affecting their health and social life. It will be administered via interview with the informal carer.

Independent Variables-Covariables

Sociodemographic Data

Age, gender, education, whether participant lives alone, marital status, and familiarity with comparable technological devices are the sociodemographic variables.

Follow-Up Visits

There will be 3 follow-up visits at 6, 12, and 18 months after baseline interview. A summary of visits' assessments is shown in Table 1. In addition, to measure medication adherence, there will be a preadherence phone call in each follow-up visit (30 days before the visit).

Table 1. Schedule of events.

Events, assessments, and data collection	Screening	Baseline	Tablet delivery	Month 6 ±18 days	Month 12 ±18 days	Month 18 ±18 days
Informed consent (PwMCI ^a and informal carer)	X ^b	— ^c	—	—	—	—
Review of inclusion and exclusion criteria (PwMCI)	X	—	—	—	—	—
Demography (PwMCI and informal carer) and medical history (PwMCI)	—	X	—	—	—	—
Introduction and training for Support Monitoring and Reminder for Mild Dementia (intervention group only, PwMCI and informal carer)	—	—	X	—	—	—
Geriatric Depression Scale (PwMCI)	X	—	—	X	X	X
Mini-Mental State Examination (PwMCI)	X	—	—	X	X	X
Quality of Life in Alzheimer's Disease scale (PwMCI)	—	X	—	X	X	X
Instrumental Activities of Daily Living (PwMCI)	—	X	—	X	X	X
Adherence to prescribed medication (PwMCI)	—	X	—	X	X	X
EuroQoL-5D (PwMCI and informal carer)	—	X	—	X	X	X
Attendance at appointments and admissions (PwMCI)	—	X	—	X	X	X
Familiarity with tech survey (PwMCI and informal carer)	—	—	X	—	—	—
QoL-AD on behalf of PwMCI (informal carer)	—	X	—	X	X	X
Zarit Caregiver Burden Interview (informal carer)	—	X	—	X	X	X
User satisfaction survey (intervention group only, PwMCI, and informal carer)	—	—	—	X	X	X
User behavior (intervention group only, informal carer, and PwMCI)	—	—	—	X	X	X

^aPwMCI: persons with mild cognitive impairment.

^bThe instrument is used at this time point.

^cThe instrument is not used at this time point.

Statistical Analysis

All analyses will be performed with the SPSS 25+ program (IBM Corp) [48].

Summary of Baseline Data and Persons With Mild Cognitive Impairment Progress Through the Trial

For continuous variables we will collect the mean, median, minima and maxima, lower and upper quartiles, and SD. Categorical variables will be summarized using counts and percentages. The progress of the PwMCI will be shown schematically with counts and percentages in a CONSORT diagram. The analysis will adopt the intention-to-treat principle.

Primary Outcome Analysis

The primary analysis will be the comparison of total QoL-AD score mean changes (at 18 months) between intervention group and control group using a 2-sample, 2-sided Monte Carlo permutation *t* test. The use of a permutation test will avoid the need for strong assumptions about the distribution of the data. Similarly, a bootstrap approach will be used to obtain the 95% confidence limits for the difference between the group means.

Secondary Outcome Analyses

The comparison between intervention group and control group for continuous variables will be analyzed with the same method described above, and categorical variables will be analyzed using Fisher exact test.

Regression analysis will be used to assess the relationship between the primary and secondary outcome measures and the Technology Familiarity Score to analyze whether prior experience of technology has an effect on the outcomes. Furthermore, a regression analysis will be used to assess the relationship between the primary and secondary outcome variables and the usage variables to indicate which aspects of the computer tablet use most affected the outcomes.

A user-behavior analysis will be performed to assess how users interact with the platform and how their behavior affects its efficacy. Specifically, we will assess and analyze the frequency of access to the SMART4MD app, the length of this interaction, and the quality of the inputs provided. These data will be correlated with users' reminder schedules to explore differences between proactive and reactive use of the platform and will be followed over time to understand how increasing familiarity with the platform affects user behavior. In addition, the data will be used to improve the SMART4MD app, if necessary, to optimize user interaction. The results of the usability tests will be analyzed using statistical methods to quantify the error rate, effectiveness, and learning curve of the SMART4MD app and functions. For this, the intervention group will be asked to perform specific tasks with the app, and different interaction parameters will be measured such as number of taps, reaction time, time to target, time to accomplish, etc.

Subgroup Outcome Analyses

Checks for the consistency of the intervention effects across sites will be done using a 2-way analysis of variance with the 2 factors being group (intervention/control) and site. Similarly, a subgroup analysis will be carried out according to the severity

of cognitive impairment. These subgroups will be formed based on the MMSE score corrected by educational level and age.

Adjusted Analyses

A secondary analysis will be an analysis of covariance to compare the 18-month total QoL-AD score means, where the response variable will be the 18-month total QoL-AD score and the covariate will be the baseline total QoL-AD score. This analysis will provide a comparison of the 18-month total QoL-AD score means adjusted for the baseline total QoL-AD score. Again, the *P* value will be obtained using a Monte Carlo permutation method, and the 95% confidence limits for the adjusted difference between the means will be obtained using a bootstrap approach.

Procedures to Account for Missing or Spurious Data

For analyses involving multiple regression analysis, a multiple imputation approach will be considered and used, if statistically sound, depending on the proportion and pattern of missing values.

Methods to Ensure Validity and Quality of Data

Accurate and reliable data collection will be assured by verification and cross-check of the electronic case report form (eCRF) against the investigator's records (source document verification). Source document verification will be conducted for 5% of data in subjects.

A comprehensive validation check program using front-end checks in the eCRF will verify these data. Discrepancies and queries will be generated accordingly in the eCRF for Web-based resolution by the investigator at the site. In addition, the eCRF data will be reviewed on an ongoing basis for medical and scientific plausibility.

Ethical Considerations

This study will conform to the principles of the declaration of Helsinki. Ethical approval for this trial was granted by the regional ethical review boards at each participating site ensuring full compliance with all research and legislative regulations in the respective countries. The major ethical considerations for this study with respect to the group with PwMCI have been analyzed in depth ([Multimedia Appendix 3](#)).

The database used for the unidentified clinical data is located physically at Blekinge Institute of Technology and is used for several other clinical studies including the Swedish National Study of Aging and Care following all relevant protocols for data security and integrity. The code key containing the identifier are kept in a locked cupboard on a computer/Universal Serial Bus memory not connected to the internet.

Results

Inclusion of participants started in December 2017, and recruitment is expected to end in February 2019. Furthermore, there will be 3 follow-up visits at 6, 12, and 18 months after the baseline visit.

Discussion

The benefits of this RCT will be at several levels including in-depth knowledge of the possibilities of introducing a holistic multilayered ICT solution for this particular group. Support for the hypothesis that particular SMART4MD functions may improve QoL in PwMCI can be found in other studies. For example, SMART4MD enables users to record a list of their medication, to receive reminders to take their medication, and to record that they have done so. In this way, it encourages treatment adherence. An association between treatment adherence in Alzheimer disease and improved QoL for persons with dementia is claimed in a nonsystematic review of literature on factors affecting adherence to cholinesterase inhibitors, the main class of therapeutic drugs [35]. More specifically, 1 study [49] (the first to address this specific issue) found that people taking acetylcholinesterase inhibitors rated their QoL (using the total QoL-AD score) more highly than those who did not. Similarly, the control of dementia risk factors has consistent evidence for dementia prevention, especially in those at risk of developing dementia because of memory claims and/or MCI. Therefore, the adequate control of chronic diseases, such as hypertension, diabetes, and hypercholesterolemia, for which an adequate adherence to pharmacological treatment is necessary, could imply an improvement in the QoL [50].

SMART4MD also enables users to access information about dementia and MCI. A systematic review of literature on information services for persons with dementia and informal carers [51] found that 2 out of the 3 RCTs measuring the QoL of the person with dementia under these circumstances indicated benefit. A systematic review of literature on social support group interventions for person with dementia identified 2 studies, 1 of which showed the QoL benefit of a support group providing educational seminars and supportive discussion on medical causes and treatments and future planning and strategies for enhancing communication and daily living [52,53].

The secondary objectives of the trial comprise establishing possible improvements in medication adherence, functional status, and informal carers' well-being as a result of using SMART4MD.

The proposition that particular SMART4MD functions may promote these outcomes is also supported in literature. Reviews demonstrating that oral acetylcholinesterase inhibitors improve performance in activities of daily living [54,55] mean that the medication reminder function is well placed to support functional status. Other studies have shown that digital games

can support communication and a sense of well-being in persons with dementia [56] and that multimedia memory aids can promote recall [57]. A recent systematic review has also shown some positive results for computerized cognitive training in population with MCI or dementia [58]. Providing information about dementia to informal carers as well as supporting them in mobilizing social support networks have been shown to reduce informal carers' burden [59]. There is also a significant burden in informal caregivers of individuals with MCI [60]. Assistance with medication regimes not only has the capacity to improve QoL in person with dementia's or MCI but also that of informal carers [61].

SMART4MD has been developed from an existing general health management app in a process involving the structured participation of PwMCI, their informal carers, and clinicians. The adoption of SMART4MD by older people faces the challenge of this age group's relative unfamiliarity with digital devices and services. However, this challenge can also be seen as an opportunity. This research entails developing a digital device, which is specifically tailored to a group of people who are particularly at risk of digital exclusion. In this respect, the research responds to the wider call for the development of digital devices that are accessible and affordable to older people, rather than a source of anxiety [62].

SMART4MD's combination of a number of functions distinguishes it from other comparable products and services, making it the kind of innovative nonpharmacological intervention that experts in the field have called for [56].

The occurrence of dementia and MCI is a common problem across Europe, but its management varies between countries and even regions. Variations in the commitment of member states to national dementia strategies naturally translates into variations in clinical practice through differences in both funding and priority given to dementia in different countries. More generally, health care systems vary widely between member states and regions, with differing emphasis placed on home, community, primary, and secondary care. These differences are further amplified by varying practice in reimbursement of health care costs between private health care insurers and public authorities; and by different levels of funding available for health care. As a result, the support and treatment available for PwMCI across the European Union varies widely. By including PwMCI, informal carers, and health care professionals from various European countries in this study, we can ascertain whether SMART4MD can support PwMCI and informal carers irrespective of these differences in services and treatments.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

The intervention strategy for Support Monitoring and Reminder for Mild Dementia.

[[PDF File \(Adobe PDF File\), 201KB - resprot_v8i6e13711_app1.pdf](#)]

Multimedia Appendix 2

Support Monitoring and Reminder for Mild Dementia questions on experience of and familiarity with technology.

[[PDF File \(Adobe PDF File\), 71KB - resprot_v8i6e13711_app2.pdf](#)]

Multimedia Appendix 3

Additional brief clarification for the potential ethics issues associated with longer-term trials involving older persons with mild cognitive impairment.

[[PDF File \(Adobe PDF File\), 124KB - resprot_v8i6e13711_app3.pdf](#)]

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Abbreviations

ARCTU: Anglia Ruskin Clinical Trials Unit

CONSORT: Consolidated Standards of Reporting Trials

eCRF: electronic case report form

EQ-5D: EuroQoL-5D

GDS-15: Geriatric Depression Scale

ICTs: information and communication technologies

MCI: mild cognitive impairment

MMSE: Mini-Mental State Examination

PwMCI: persons with mild cognitive impairment

QoL: quality of life

RCT: randomized controlled trial

SMART4MD: Support Monitoring and Reminder for Mild Dementia

TAU: treatment as usual

ZBI-12: Zarit Caregiver Burden Interview

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Protocol

Transitional Experiences of Internationally Qualified Midwives Practicing in Australia: Protocol for a Mixed Methods Study

Mitra Javanmard^{1*}, BM, RM, BHSc (Hons); Mary Steen^{1*}, BHSc, RN, RM, DipClinHypn, PGDipHE, MCGI, PhD; Rachael Vernon^{1*}, BN, RN, MPhil (Distinction), PhD; Megan Cooper^{1*}, BM, RM, BHSc (Hons), PhD

School of Nursing and Midwifery, Division of Health Sciences, University of South Australia, Adelaide, Australia

* all authors contributed equally

Corresponding Author:

Mitra Javanmard, BM, RM, BHSc (Hons)

School of Nursing and Midwifery

Division of Health Sciences

University of South Australia

108 North Terrace

Adelaide, 5000

Australia

Phone: 61 425477771

Email: mitra.javanmard@mymail.unisa.edu.au

Abstract

Background: Approximately 13% of the total Australian midwifery workforce is internationally qualified. Although the internationally qualified midwives (IQMs) play a significant role in the Australian midwifery system, there is limited understanding of their transitional experiences.

Objective: The objective of this study protocol is to explore the transitional experiences and views of IQMs practicing in Australia, through the investigation of demographic profiles and key challenges that influence a smooth transition.

Methods: This paper presents an explanatory sequential mixed methods study protocol. This protocol incorporates an e-survey and individual interviews. The e-survey in the first phase will be distributed to IQMs in Australia via the website e-bulletins of the Australian Nursing and Midwifery Federation and the Australian College of Midwives. Additionally, potential respondents will be recruited via social media (ie, Twitter and Facebook) and associated snowball sampling. Data from the e-survey will be statistically analyzed. At the end of the e-survey, respondents will be asked whether they are willing to take part in an interview. The results of the e-survey and relevant literature review will help to develop a guideline for interview questions for the second phase. In phase two, a purposeful sample of participants will be recruited using the same selection criteria as for the e-survey. Semistructured interviews will provide a deeper insight into the transitional experiences of IQMs. Data from the interviews will then be thematically analyzed.

Results: An integration of the e-survey results (phase one) and interview findings (phase two) will be synthesized to explore and better understand the transitional experiences of this group of midwives. It is anticipated that data collection and analysis will be completed by June 2019 and results will be disseminated through peer-reviewed publications in late 2019.

Conclusions: This research protocol may generate new knowledge about the transition of IQMs in Australia. These findings could be used to formulate recommendations to inform the transition of future IQMs in Australia.

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KEYWORDS

internationally qualified midwives; experiences; views; adjustment; transition; integration

Introduction

Background

Australia is a multicultural country with 49% of the Australian population (24.77 million) either born overseas or having at least one parent who was born overseas [1]. As in many other fields, multiculturalism affects the health professional workforce [2]. For example, the 4244 internationally qualified midwives (IQMs) who received their midwifery qualification in countries other than Australia and are currently practicing in Australia represent 12.99% of all registered midwives (4244/32,669) in the country [3]. Globally, there has been increasing reliance on IQMs and internationally qualified nurses (IQNs) within the health workforce of some developed countries [4-6]. A shortage of nurses and midwives, coupled with increased demands for health care, may be two of the factors driving this increase [7,8]. However, the transition of this group of health professionals into the Australian health care system has been accompanied by various challenges [8-11]. Pilette [12] explains that the process of adjustment into a foreign health care system may take about one year and is comprised of four different phases, including acquaintance, indignation, conflict resolution, and integration. He noted that each phase is associated with unique challenges [12]. Furthermore, it is possible that IQNs from culturally and linguistically diverse backgrounds may find it takes longer to adjust [13].

Differences in nursing practices, along with a lack of familiarity with local technologies, policies, and guidelines, are reported as major challenges for IQNs [11,14,15]. IQNs from different educational backgrounds may face stressful situations due to different ways of undertaking clinical procedures [16], which can result in frustration and anxiety [17]. Deskillling and lack of recognition of IQNs' capabilities, skills, and experiences can cultivate feelings of invisibility and marginalization, which may have a negative effect on self-esteem, confidence, and well-being [14,18]. These factors are important to consider and acknowledge as these may be similar for IQMs. The literature also highlighted multidimensional discrimination and cultural impositions experienced by IQNs in some health care systems of destination countries [11,15]. Diversity in race, color, culture, or language can be a trigger of inequality of opportunities and racism in the form of bullying by staff or rejection of care by some patients [13]. For IQMs and IQNs, racial discrimination can lead to intimidation, public humiliation, social exclusion, and loss of confidence and professional authority [6,15,19].

Proceeding on the basis of Cooper's Taxonomy [20], a structured literature search was conducted by the authors [21]. The five steps that guided the literature review included *formulate the problem, search the literature and gather information, evaluate study quality, analyze, and interpret the data* [20]. Only two studies reported the experiences of midwives practicing in a foreign country; one study examined UK midwives' experiences of working in Australia [6] and another in New Zealand [10]. The literature appears to focus mainly on internationally qualified nurses and doctors, with midwives usually included within the broader category of nurse migration. However, the International Confederation of Midwives has stated that

“midwifery should be recognised as an autonomous profession globally” [22].

Although midwifery is an internationally mobile profession, there appears to be a global gap in literature that explores the transition experiences of IQMs moving between countries [23]. Hence, this lack of research, as well as the need to investigate and explore the transitional experiences of IQMs as they transition into Australian maternity services, is clear justification for undertaking this doctoral study. Understanding the transitional experiences of this group of midwives into the Australian midwifery system, as well as disseminating the findings, will increase awareness of challenges that IQMs may experience.

Study Aim and Objectives

Given the identified gap in the literature, this study aims to explore the transitional experiences and views of IQMs practicing in Australia. The objectives of this study are to investigate demographic profiles of IQMs in Australia and to explore the key challenges that promote or hinder a smooth transition into this workforce. The research questions for this study are as follows:

1. What are the demographic characteristics of IQMs practicing midwifery in Australia?
2. What challenges do IQMs face during their transitional process into the Australian midwifery workforce?
3. How do IQMs practicing midwifery in Australia perceive the level of:
 - a. peer support?
 - b. peer respect?
 - c. peer acceptance?

Methods

Study Design

The researchers will use an explanatory, sequential, mixed methods design, incorporating two phases to provide valid and credible outcomes [24]. This mixed methods design is underpinned by the philosophical assumptions of *pragmatism*, which guides both phases [24-26]. The research emphasizes the use of the pluralistic approaches in order to achieve a deeper understanding of the transitional experiences of individual IQMs, as well as the challenges they confront during their transition into the Australian midwifery workforce [24-27]. Regarding pragmatism, the criterion of “what works?” will be used to select the best methodologies to address the research questions and, ultimately, to find some strategies to solve any challenges, as required [26].

This research protocol incorporates an e-survey and individual interviews. Phase one includes an e-survey study that is currently being undertaken to capture IQMs' demographic profiles, their transitional experiences, and positive and negative factors contributing to their transition during the first year of their practice in Australia. The exploratory nature of the second phase requires a qualitative approach to identify and describe the transitional experiences and views of individual IQMs. Hence, qualitative descriptive design based on semistructured interviews

will be used for phase two to provide a detailed description of the experiences and views of IQMs in language similar to their own forms of expression [28,29].

The results from the e-survey will assist in determining questions for the interviews to explore, clarify, and affirm the experiences and perspectives of IQMs [26]. The findings of the interviews will provide further explanations for unexpected results that may emerge during the e-survey study [24-26]. The final inferences will be presented on the basis of integrated data from both phases of the study [27].

Study Population

The target population for this study is a sample of midwives who obtained their midwifery qualifications outside of Australia, who practiced for a minimum of 12 months in the countries in which they obtained their midwifery qualifications, and who are presently practicing as midwives in Australia. In order to maximize recruitment opportunities, a specific length of time of employment in Australia will not be specified. It is beyond the scope of this research to consider the experiences of midwives who obtained their midwifery qualifications within Australia.

Data Collection and Setting

IQMs will be invited to participate in this study nationally within Australia.

E-Survey

IQMs practicing in Australia are being accessed via a nonprobability sample design, which also incorporates factors such as convenience and snowball sampling. The Nursing and Midwifery Board of Australia was approached at the beginning of respondent recruitment, with a request made to access the contact details of all registered IQMs in Australia. This request was denied due to the Board's privacy policy. There are no other official organizations or bodies that collect contact details of IQMs in Australia. A nonprobability sampling framework and an opt-in e-survey are being used, as a random sample cannot be accessed.

As such, the most effective method to recruit as many IQM respondents as possible is via the Australian Nursing and Midwifery Federation and Australian College of Midwives websites. The e-bulletins of these midwifery professional bodies are advertising and distributing the e-survey, which is linked to SurveyMonkey, a Web-based survey platform. Other approaches being used to recruit potential respondents include snowball sampling and social media platforms, such as Facebook and Twitter.

Calculation of the potential sample size is not feasible for this e-survey study, due to using a nonprobability sampling framework and undertaking an opt-in e-survey, and this is acknowledged as a current limitation of the study. Furthermore, a response rate cannot be calculated due to the inability to identify the contact details of IQMs and the associated absence of a sampling frame [30,31]. Finally, a power calculation is not appropriate for this descriptive e-survey study, as a hypothesis is not being tested [32].

The data collection tool was developed by adapting pre-existing and relevant questionnaires used by Giegerich [33] and the Australian Midwifery Workforce Survey [34].

The adapted descriptive questionnaire is comprised of the following elements:

1. A total of 26 closed-ended questions designed to collect IQMs' demographic characteristics and their current working arrangements in Australia.
2. A total of 12 7-point Likert-scale questions to capture the multidimensional perspectives of the IQMs' transitioning experiences during their first 12 months of working in Australia.
3. Two open-ended questions to offer IQMs the opportunity to further share their experiences.

Prior to administration of the e-survey, the adapted questionnaire was assessed for content and face validity by a panel of three experts who had survey development expertise or experience of working with IQMs in Australia. The e-survey is hosted via SurveyMonkey and presented over 10 pages; it will allow respondents to review and change their answers prior to completion. Once the e-survey has been completed, respondents will not be able to change their responses nor will they be able to complete the e-survey again. The e-survey will be administered in English; the estimated time to complete the questionnaire is approximately 15-20 minutes (see [Multimedia Appendix 1](#)).

Interviews

The consolidated criteria for reporting qualitative studies (COREQ), a 32-item checklist, will be followed in this phase to ensure all aspects of the study methods, analysis, findings, and interpretations are considered [35]. Participants will be recruited nationally within Australia. To recruit participants, a purposeful sample using the same selection criteria as for the e-survey study will be used [36]. Therefore, the sample will be a subset of the e-survey study. At the end of the e-survey, respondents will be asked whether they are willing to take part in an interview and, if so, they will be encouraged to contact the primary researcher voluntarily.

The interview guidelines will be developed based on the e-survey results and relevant literature and will then be reviewed by all authors, three of whom are experienced researchers (MS, RV, and MC). Questions will be open-ended with a broad focus to explore the transitional experiences of IQMs. Semistructured interviews—face-to-face or telephone interviews—will be digitally audio recorded with the prior consent of the participants and each will last approximately 30-45 minutes. All interviews will be professionally transcribed for analysis by using a consistent template to obtain consistency between the transcripts.

Although we are not able to specify the sample size needed to reach data saturation, it is estimated that we will need to interview approximately 6-12 participants, based on evidence published by Guest et al [37]; however, it may depend on the richness and depth of gathered data [38]. Data collection will continue until saturation is achieved: that is, when we no longer identify new data or when confirming or disconfirming data can be reached with respect to the research questions [37-39].

Transcripts will be returned to all participants and they will be invited to review them for accuracy.

Data Analysis

E-Survey

The aim of this e-survey study is to provide descriptive results for the research questions by analyzing the e-survey responses [40]. All responses will be analyzed even where they are incomplete. Statistical analysis will be conducted using SPSS Statistics for Windows, version 22.0 (IBM Corp). Descriptive statistics will be used to determine sample characteristics, such as frequencies, percentages, means, and standard deviations of the total sample of ordinal outcomes [26]. Ordinal outcomes from Likert scales will be analyzed using the nonparametric Mann-Whitney U test to compare the transitioning experiences of IQMs from English-speaking backgrounds and non-English-speaking backgrounds, if required. Statistical significance will be identified as $P < .05$, if necessitated.

Qualitative analysis of the two open-ended questions in the e-survey will be conducted manually. Summative content analysis [41] will be used to identify categories that best describe the respondents' views. This will involve counting of common words or phrases to analyze similarities and differences between participants' responses [41]. Significant phrases will be identified and findings will be formulated. The final analysis will be agreed upon by consensus to assure consistency and confirmation of results.

Interviews

Interviews will be analyzed thematically, following the six-step approach explained by Braun and Clarke [42]. This systematic approach includes data familiarization, generation of initial codes, thematic search, thematic review, thematic definition, and reporting. Analysis will commence by first entering the transcribed interviews into a Microsoft Excel worksheet to manage and summarize the corpus of data and to generate columns consisting of all comments. Multiple readings of the transcripts will be undertaken to understand participants' meanings and to find similarities and differences of their experiences. Words or phrases relevant to the research questions will be coded and relevant data will be collated to each code. Codes will then be sorted into potential themes, while the relevant coded data extracts will be collated within these identified themes. Once coding is complete, all researchers will compare findings. Codes that express similar meanings will be highlighted with the same color. The concepts and categories will be reviewed multiple times to ensure a coherent pattern. Following this, the validity of individual themes will be considered. Finally, as part of the refinement process, themes containing subthemes will be identified. The final analysis will be agreed upon by consensus to assure consistency and confirmation of findings.

Results

Overview

Findings from the e-survey study and interviews will be drawn together and compared in order to synthesize the final results

and to reach an overall interpretation. To integrate data, *triangulation protocol* will be followed, a technique that has been explained by O'Cathain et al [43]. For this technique, findings from each phase of the study will be listed on the same page, helping to identify findings that are potentially convergent, complementary, or discrepant. In order to interpret the data from a multidimensional perspective, the datasets will first be separately analyzed deductively and inductively; we will then move back and forth between the datasets, with knowledge produced by each one, and will finally bring them together [44]. It is anticipated that data collection and analysis will be completed by June 2019 and results will be disseminated through peer-reviewed publications in late 2019.

Rigor

To promote integrity and quality in this mixed methods study, appropriate strategies will be applied during each phase of the study as follows [24,26]. Regarding the e-survey, content and face validity were conducted for the adapted questionnaire prior to administration of the e-survey. Regarding the interviews, credibility, transferability, dependability, and confirmability will be considered to ensure trustworthiness of the study [45,46]. Consistent use of interview guidelines will ensure consistent data collection [39]. Participants' views will be accurately reflected via the use of audio recording; to maintain consistency between the transcripts, a consistent template will be used for each transcript [35]. Moreover, participant validation will occur in which participants will review and verify the interpretations [47]. Confirmability will be ensured through the use of an audit trail, where the activities exercised in the study, both in the collection of data and its analysis, will be accurately detailed and recorded [46]. Furthermore, the researchers will achieve confirmability through the use of participant quotes to support the findings. A reflexive process will be documented to reduce subjectivity bias. This will be supported by a clear audit trail of decision making throughout the study [48]. Publication and presentation of findings for target readers, such as the study participants, researchers, and other IQMs, will provide opportunities to enhance credibility [46]. In addition, a mixed methods design has been employed for this study, which will enable data triangulation to take place [24-26].

Ethical Considerations

This study has obtained ethical approval from the University of South Australia Human Research Ethics Committee on July 4, 2017 (protocol number: 0000036397). All information about the nature and aim of the study, confidentiality, anonymity, voluntary nature of participation and withdrawal, potential benefits and risks of the study, contact details of a person designated to receive complaints, and contact details of the research team will be provided to participants of this study, according to ethical guidelines [49,50]. Consent to participate in the e-survey is implied by the respondent's voluntary completion of the SurveyMonkey questionnaire. Written consent will be obtained from all participants who agree to be involved in phase two interviews. Phase one responses will be collected anonymously in SurveyMonkey. Participants who agree to be involved in phase two will be interviewed, either face-to-face or by telephone, at a mutually convenient date, time, and place.

All data collected will be stored securely for 5 years. Participants will not receive any incentive for agreeing to be involved in this study.

Discussion

Motivational factors underpinning the migration of internationally qualified health professionals (IQHPs) to developed nations have been highlighted in the literature, with these factors including the desire for an increased standard of living, higher education, professional experiences, and opportunities to achieve better pay [4,8,17]. However, the literature also highlights contradictions between the expectations of IQHPs before commencing work in their host countries and their actual experiences [13,18].

Migrating to a new country with differences in midwifery and nursing practices, different workplace cultures, and the presence of bullying and discrimination may be confronting for IQMs and IQNs. This could create further challenges during the process of their integration into a foreign midwifery and nursing clinical workforce [21]. Different educational backgrounds, different ways of undertaking clinical procedures, and different guidelines and policies may negatively influence the adjustment of IQMs and IQNs into a new health care workforce [16]. Consequently, the experience of such stressful situations may lead to frustration and anxiety [17]. Lack of recognition of the capabilities, skills, and experiences of IQNs may result in feelings of invisibility and marginalization. This, in turn, may negatively affect their confidence, self-esteem, and well-being [14,18,51,52].

An intrinsic barrier for IQNs attempting to adjust to a new health care system is a lack of familiarity with the culture of local health practice [14,16,52-54]. The literature broadly discusses the culture clash experienced due to feelings of not fitting in and isolation [52-54]. Moreover, migrants from culturally and linguistically diverse backgrounds can find these challenges more problematic [55].

The literature highlights that IQNs face cultural impositions and multidimensional discrimination in some health care systems of their host countries [11,15,56] and, markedly, that bullying may stem from racism towards IQNs and IQMs [21]. Racial discrimination may give rise to intimidation, social exclusion, and public humiliation, resulting in IQMs and IQNs experiencing a loss of professional authority [6,15,19,57].

The process of migrating to Australia and working as a midwife can be a complex and challenging one [14,58]. To gain insight into how to best support the needs of IQMs, such challenges need to be explored and understood [13,18]. Midwives have long migrated and worked across borders, but their needs and perspectives have been paid relatively minimal attention, especially during their adjustment into the Australian midwifery workforce. With a prediction of continuing recruitment of IQMs and the lack of studies undertaken on this cohort, the challenges of their professional integration need to be explored. This is an area essential to advancing research and practice. Currently the first of its kind in Australia, this study protocol has been designed to address this priority through exploring the experiences and views of IQMs practicing in Australia. The insight gained from the understanding of IQMs' enablers, as well as their barriers, may be of great value.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

The adapted questionnaire.

[PDF File (Adobe PDF File), 76KB - [resprot_v8i6e13406_app1.pdf](#)]

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Abbreviations

COREQ: consolidated criteria for reporting qualitative studies

IQHP: internationally qualified health professional

IQM: internationally qualified midwife

IQN: internationally qualified nurse

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Protocol

Biological and Functional Changes in Healthy Adult Smokers Who Are Continuously Abstinent From Smoking for One Year: Protocol for a Prospective, Observational, Multicenter Cohort Study

Cam Tuan Tran¹, MSc, MD; Loyse Felber Medlin¹, PhD; Nicola Lama¹, PhD; Brindusa Taranu¹, MD; Weeteck Ng¹, PhD; Christelle Haziza¹, PhD; Patrick Picavet¹, MD; Gizelle Baker¹, PhD; Frank Lüdicke¹, MD

Philip Morris International Science and Innovation, Philip Morris Products SA, Neuchâtel, Switzerland

Corresponding Author:

Cam Tuan Tran, MSc, MD

Philip Morris International Science and Innovation

Philip Morris Products SA

Quai Jeanrenaud 5

Neuchâtel, 2000

Switzerland

Phone: 41 58 242 1111

Email: CamTuan.Tran@pmi.com

Abstract

Background: The harm of smoking results mainly from long-term exposure to harmful and potentially harmful constituents (HPHCs) generated by tobacco combustion. Smoking cessation (SC) engenders favorable changes of clinical signs, pathomechanisms, and metabolic processes that together could reduce the harm of smoking-related diseases to a relative risk level approximating that of never-smokers over time. In most SC studies, the main focus is on the quitting rate of the SC program being tested. As there is limited information in the literature on short to multiple long-term functional or biological changes following SC, more data on short to mid-term favorable impacts of SC are needed.

Objective: The overall aim of the study was to assess the reversibility of the harm related to smoking over 1 year of continuous smoking abstinence (SA). This has been verified by assessing a set of biomarkers of exposure to HPHCs and a set of biomarkers of effect indicative of multiple pathophysiological pathways underlying the development of smoking-related diseases.

Methods: This multiregional (United States, Japan, and Europe), multicenter (42 sites) cohort study consisting of a 1-year SA period in an ambulatory setting was conducted from May 2015 to May 2017. A total of 1184 male and female adult healthy smokers, willing to quit smoking, were enrolled in the study. Nicotine replacement therapy (NRT) was provided for up to 3 months upon the subject's request. SC counseling and behavioral support were continuously provided. Biomarkers of exposure to HPHCs and biomarkers of effect were assessed in urine and blood at baseline, Month 3, Month 6, and Month 12. Cardiovascular biomarkers of effect included parameters reflecting inflammation (white blood cell), lipid metabolism (high-density lipoprotein cholesterol), endothelial function (soluble intercellular adhesion molecule-1), platelet function (11-dehydrothromboxane B2), oxidative stress (8-epi-prostaglandin F2 alpha), and carbon monoxide exposure (carboxyhemoglobin). Respiratory biomarkers of effect included lung function parameters and cough symptoms. The biomarkers of effect to evaluate genotoxicity (total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) and xenobiotic metabolism (cytochrome P450 2A6 activity) were also assessed. Continuous SA was verified at each visit following the actual quit date using self-reporting and chemical verification. Safety assessments included adverse events and serious adverse events, body weight, vital signs, spirometry, electrocardiogram, clinical chemistry, hematology and urine analysis safety panel, physical examination, and concomitant medications.

Results: In total, 1184 subjects (50.1% male) were enrolled; 30% of them quit smoking successfully for 1 year. Data analyses of the study results are ongoing and will be published after study completion.

Conclusions: This study provides insights into biological and functional changes and health effects, after continuous SA over 1 year. Study results will be instrumental in assessing novel alternative products to cigarettes considered for tobacco harm reduction strategies.

Trial Registration: ClinicalTrials.gov NCT02432729; <http://clinicaltrials.gov/ct2/show/NCT02432729> (Archived by WebCite at <http://www.webcitation.org/78QxovZrr>)

International Registered Report Identifier (IRRID): DERR1-10.2196/12138

KEYWORDS

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

Introduction

Cigarette smoking is the leading cause of preventable deaths worldwide and is associated with increased risk of pulmonary disease, cardiovascular disease (CVD), and other serious diseases, such as cancer [1]. The World Health Organization (WHO) has estimated that there will be 1.5 billion smokers globally by 2050 [2]. Preventing smoking initiation and increasing smoking cessation (SC) can reduce the number of deaths and is a public health priority. However, complete and permanent SC is challenging for many current smokers. Most smokers (55%) do not try to quit, and those who do try often relapse to smoking. Only about 5% are able to quit smoking for 1 year or longer [1].

It is widely recognized that the harm associated with smoking results mainly from long-term exposure to the harmful and potentially harmful constituents (HPHCs) contained in cigarette smoke, generated by combustion of tobacco and not from nicotine itself [3], as stated by the Royal College of Physicians “most of the harm caused by smoking arises not from nicotine but from other components of tobacco smoke” [4]. Exposure to HPHCs leads to molecular changes causing perturbations in biological mechanisms, which in turn cause cell and tissue damage, physiological changes, and disease manifestation to the individual, ultimately leading to population burden. Smoking affects multiple organ systems, disease pathways, and mechanisms, such as inflammation, oxidative stress, platelet activation, and lipid metabolism, simultaneously [5].

Owing to the abundant concurrent processes in disease pathways, there is no single biomarker that is considered as a validated surrogate measure reflecting the biological processes, physiological system, and/or a mechanism of action that is associated with, or actually known to contribute to, smoking-related diseases. Numerous epidemiological studies have shown that most of the smokers who quit smoking benefit from a gradual and significant reduction of harm and risk of smoking-related diseases over time, as SC favorably reverses many of the adverse functional and biological changes associated with smoking [6-8]. It has been demonstrated that long-term smoking abstinence (SA) results in reduced blood levels of hemostatic and inflammatory markers, such as white blood cell (WBC) or fibrinogen, which are important determinants in the subsequent development of cardiovascular or chronic obstructive pulmonary disease, reverting to levels of never-smokers [9]. Furthermore, SC curtails the decline in forced expiratory volume in 1 second (FEV₁) predicted and improves respiratory function [5,10]. Additional health benefits have also been described, including favorable changes in oxidative stress (eg, 8-epi-prostaglandin F₂ alpha [8-epi-PGF_{2α}]) [11], lipid metabolism (high-density lipoprotein [HDL] cholesterol) [12], endothelial function (eg, soluble intercellular adhesion molecule-1 [sICAM-1]) [13], and platelet function (eg, 11-dehydrothromboxane B₂ [11-dehydro-TXB₂]) [14].

Despite the substantial amount of SC studies in the literature, the main focus of these studies has been the successful quitting rates as a result of SC treatment rather than on evaluating short- and long-term (up to 1 year and beyond) functional and biological changes in the body upon continuous SA. Given the need for additional data to bridge this evidence gap, providing broader and deeper insights into the clinical benefits upon SC, we conducted a study in adult healthy smokers who were continuously abstinent from smoking for 1 year. The overall aim of our study was to assess the reversibility of smoking-related harm after continuous SA.

Using available epidemiological data reporting quantitative estimates of the association with CVD, respiratory diseases and cancer in smokers and reversibility upon SC within a 1-year time frame, a set of biological and functional parameters, identified as biomarkers of effect and biomarkers of exposure to HPHCs, were selected based on predefined criteria and assessed in this study. Covering multiple pathways involved in the pathogenesis of smoking-related diseases, the selected parameters will provide an overall understanding of how SC triggers favorable changes and the time frame of reversibility from mechanistic pathways that are commonly involved in the onset and progression of smoking-related diseases.

Offering smokers nicotine delivery products, with the potential to reduce the risk of smoking-related diseases, as a replacement for cigarettes is an emerging approach for smoking harm reduction strategy [15].

To assess reduced risk potential, the Institute of Medicine of the National Academies recommends the use of appropriately designed studies to establish whether the use of novel alternatives to cigarettes, such as heat-not-burn tobacco products or nicotine-containing e-vapor products, reduces exposure to toxicants or induces positive changes in surrogate markers [16]. If the magnitude and time frame of positive changes in surrogate markers approximate those observed of SC, then that would provide pivotal scientific evidence to demonstrate the reduced risk potential of the alternative products. This study will provide a comprehensive assessment of the favorable health effects of SC on multiple short- and long-term biological and functional endpoints evaluated over 1 year and could serve as a benchmark to assess novel alternatives to cigarettes considered for tobacco harm reduction strategies for smokers who would otherwise continue to smoke.

Methods

Study Design

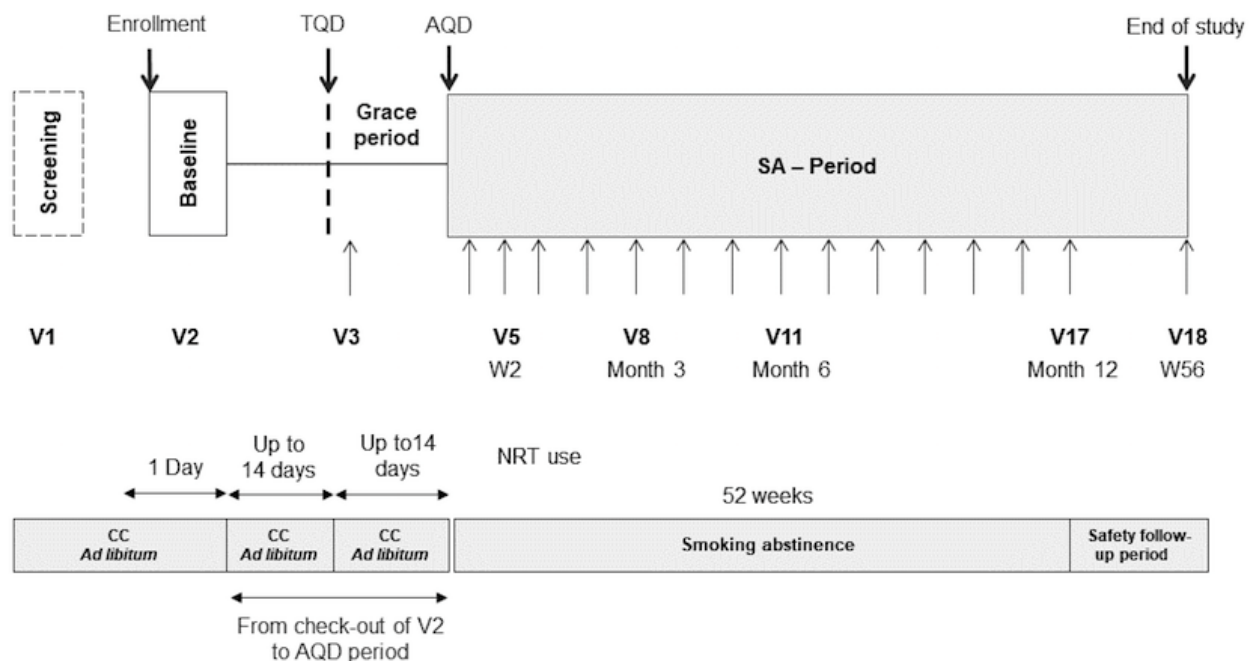
This 56-week, multiregional, multicenter, ambulatory study was conducted at 42 sites in the United States, Japan, and Europe, and it is registered at ClinicalTrials.gov (identifier NCT02432729). The institutional review boards or independent ethics committees for each participating institution granted ethical approval. The study followed the principles defined by

the International Conference on Harmonization Good Clinical Practice, the Declaration of Helsinki, and other applicable regulations [17,18]. No smoking control arm was included, as the endpoints were analyzed before and after SC and numerous studies have already documented such aspects in smokers [19-21]. The first subject was enrolled in the study on May 5, 2015, and the last subject completed the study on May 30, 2017. The study design is illustrated in Figure 1. Samples were collected during the baseline visit for baseline biomarker analysis. During this visit, participants were asked to define their target quit date, the date from which they would stop smoking. The target quit date had to be within 14 days after the baseline visit. The next visit, scheduled 24 to 48 hours after the target quit date, was used to determine whether the subject had stopped smoking and to provide SC support. A grace period of up to 14 days was allowed after the target quit date, during which occasional use of nicotine and/or tobacco-containing products was tolerated. Starting from the actual quit date, participants had to abstain completely from smoking and from

using any nicotine or tobacco-based products other than nicotine replacement therapy (NRT; allowed for up to 3 months and 2 weeks). The period from baseline visit to the actual quit date has been established to identify participants with a higher likelihood of successful SA for 1 year.

Participants recorded their own actual quit date and provided the information to their study clinic. Visits were scheduled on a monthly basis for the duration of the 52-week study (1 year), with biomarker sample collections scheduled for the Month 3, Month 6, and Month 12 visits. The study ended after a 28-day safety follow-up period. SC support, including counseling and behavioral support, was provided throughout the study at scheduled visits and between visits as requested by the subject. Participants were allowed to use NRT to support SC if requested by the subjects. NRT was started any time between the target quit date and 1 week after the actual quit date and was permitted for up to 3 months and 2 weeks. Adverse events were collected at each visit. Participants who smoked after the actual quit date were discontinued from the study.

Figure 1. Study design and timeline. Target quit date (TQD) was within 1-14 days after check out of Visit 2; actual quit date (AQD) was within 14 days after the TQD (grace period with occasional tobacco/nicotine use). Nicotine replacement therapy (NRT) was only permitted for up to three months + two weeks after the start date of NRT, which occurred at any time between the TQD and one week after the AQD. CC: cigarettes; SA: smoking abstinence; V: visit; W: week.



Participants

All participants provided written informed consent. The study enrolled healthy adult smokers who were motivated to quit smoking within the next 30 days. Their motivation was assessed using a questionnaire based on the Prochaska stages of change [22]. The main inclusion and exclusion criteria are summarized in Textbox 1. Participants had at least 10 years of smoking history and had smoked at least 10 cigarettes per day over the last 12 months. Participants with FEV₁ and forced vital capacity (FVC) <0.7 and FEV₁ <80% predicted value at

postbronchodilator spirometry and those with FEV₁ and FVC <0.75 (postbronchodilator) and reversibility in FEV₁ (both >12% and >200 mL from pre- to postbronchodilator values) were excluded from the study. There were no limitations on race or ethnicity. Stratified sampling was used to ensure adequate representation of genders (at least 40% of each sex at enrollment).

A total of 1035 participants who successfully abstained from smoking for at least 2 weeks after the actual quit date were remaining in the study, meaning the study was completed with at least 190 successful quitters.

Textbox 1. Inclusion and exclusion criteria of participants.

<p>Inclusion criteria</p> <ul style="list-style-type: none">• Informed consent form(s) signed• Age 30 to 65 years (inclusive)• Positive urine cotinine test at both screening and Visit 2 (cut-off ≥ 200 ng/mL)• Smoking history of at least 10 years before screening• Smoking history of at least 10 cigarettes/day on average in the 12 months preceding screening (as reported by the subject)• Willingness to quit smoking within the next 30 days <p>Exclusion criteria</p> <ul style="list-style-type: none">• Clinically relevant gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, pulmonary, immunological, psychiatric, or cardiovascular disorders or any other conditions that would jeopardize the safety of the participant or affect the validity of the study results• Abnormal findings on physical examination, in the medical history, or in clinical laboratory results deemed clinically relevant by investigators (as per the common terminology criteria for adverse events)• Acute illness (eg, upper-respiratory tract infection and viral infection) requiring treatment within 42 days before enrollment in the study• Use of any prohibited, prescribed, or over-the-counter systemic medications within 42 days of enrollment (except for vitamins, hormonal contraceptives, and hormone replacement therapy)• Forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) < 0.7 and FEV₁ $< 80\%$ predicted value at postbronchodilator spirometry• FEV₁/FVC < 0.75 (postbronchodilator) and reversibility in FEV₁ $> 12\%$ and > 200 mL from pre- to postbronchodilator values• Pregnancy or breastfeeding
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Study Objectives and Endpoints

The main objective of the study was to describe the biological and functional changes in smokers who are continuously abstinent from smoking. The biomarkers of effect, including those associated with CVD, respiratory diseases, xenobiotic metabolism, and genotoxicity, are provided in [Table 1](#). This broad range of biomarkers of effect were selected based on the predefined criteria according to the epidemiological evidence that the biomarkers of effect were associated with smoking-related diseases, sensitive to smoking status, and reversible upon SC over a period of time that was compatible with the study duration.

The biomarkers of exposure to HPHCs in smokers who continuously abstained from smoking ([Table 2](#)) were derived from published guidelines from the WHO and the US Food and Drug Administration [[23,24](#)] and according to predefined criteria, as reported previously [[25](#)].

The rate of continuous SA was determined at each visit following the actual quit date.

Safety was established by monitoring adverse events, body weight, vital signs, spirometry, electrocardiogram, hematology and clinical chemistry marker panels, urine analysis, physical examination, and concomitant medications. Adverse events were coded according to MedDRA terminology.

Table 1. Biomarkers of effect.

Variable, effect category	Effect
Associated with cardiovascular disease	
Lipid metabolism	<ul style="list-style-type: none"> • High-density lipoprotein cholesterol • Low-density lipoprotein cholesterol • Apolipoprotein A1 (Apo A1) • Apolipoprotein B (Apo B) • Apo B/Apo A1
Inflammation	<ul style="list-style-type: none"> • White blood cell count • High-sensitivity C-reactive protein • Homocysteine
Platelet function	<ul style="list-style-type: none"> • Platelet cell count • Fibrinogen • 11-dehydrothromboxane B2 (urine)
Oxidative stress	<ul style="list-style-type: none"> • 8-epi-prostaglandin F2 alpha (urine) • Myeloperoxidase
Endothelial dysfunction	<ul style="list-style-type: none"> • Soluble intercellular adhesion molecule-1 • Albumin (urine)
Acute cardiovascular effect	<ul style="list-style-type: none"> • Carboxyhemoglobin
Metabolic syndrome	<ul style="list-style-type: none"> • Glycosylated hemoglobin
Associated with respiratory diseases	
Spirometry	<ul style="list-style-type: none"> • Forced expiratory volume in one second (FEV₁) • Forced vital capacity (FVC) • FEV₁/FVC • Forced expiratory flow at 25–75% of the pulmonary volume (FEF₂₅₋₇₅)
Lung volume	<ul style="list-style-type: none"> • Vital capacity • Total lung capacity • Functional residual capacity • Inspiratory capacity • Residual volume
Cough	<ul style="list-style-type: none"> • Cough symptoms (intensity and frequency) • Sputum production and bothersome cough symptoms reported in cough questionnaire
Lung sounds analysis	<ul style="list-style-type: none"> • Computerized multichannel Stethographics and Stethos
Gas transfer	<ul style="list-style-type: none"> • Carbon monoxide lung diffusion capacity and rate constant
Associated with xenobiotic metabolism	
— ^a	<ul style="list-style-type: none"> • Cytochrome P450 2A6 activity
Associated with genotoxicity	
—	<ul style="list-style-type: none"> • Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL; urine)

^aNot applicable.

Table 2. Biomarkers of exposure endpoints.

Harmful and potentially harmful constituents	Biomarkers of exposure
Carbon monoxide	Carbon monoxide in exhaled breath
Nicotine	Cotinine and nicotine in plasma and nicotine equivalents in urine
1,3-butadiene	Monohydroxybutenylmercapturic acid
Acrolein	3-hydroxypropylmercapturic acid
Acrylonitrile	2-cyanoethylmercapturic acid
Benzo(a)pyrene	3-hydroxybenzo(a)pyrene
Pyrene	Total 1-hydroxypyrene
Crotonaldehyde	3-hydroxy-1-methylpropylmercapturic acid
N-nitrosornicotine	N-nitrosornicotine
4-aminobiphenyl	4-aminobiphenyl
Benzene	S-phenylmercapturic acid
1-aminonaphthalene	1-aminonaphthalene
2-aminonaphthalene	2-aminonaphthalene
o-toluidine	o-toluidine
Ethylene oxide	2-hydroxyethylmercapturic acid
Toluene	S-benzylmercapturic acid

Study Measurements

Full lung function assessments, blood and urine samples for biomarkers of effect, and biomarkers of exposure analyses were conducted at baseline (Visit 2) and at 3 time points during the study (Month 3, Month 6, and Month 12 visits). Cough assessment by visual analog scale and Likert scales (intensity of cough, frequency of cough, and amount of sputum collection) were conducted at baseline (Visit 2) and at 3 time points during the study (Month 3, Month 6, and Month 12 visits). Noncompliance with continuous SA was verified as follows:

- At each visit, participants were asked to confirm their continued abstinence from smoking from the actual quit date onward (ie, free from tobacco product use [eg, cigarettes, pipes, cigars, and snus] or any nicotine-containing products [including electronic cigarettes] other than NRT) or continued NRT use after the allowed time frame (ie, 3 months and 2 weeks after the NRT start date).
- CO breath test (>10 pm) from Visit 4 onward.
- Urine cotinine test at each visit from Visit 10 onward (cotinine test ≥ 100 ng/ml).
- Free cotinine concentration (part of nicotine equivalents) in 24-h urine collected at Visit 11 (free cotinine ≥ 50 ng/mL).

Socioeconomic status, lifestyle, stage of change [22], and nicotine dependence [26] were assessed as baseline characteristics. One central laboratory was used for sample management and several laboratories were used for the blood and urine analyses (Covance Central Laboratory Services Inc; Celerion, Lincoln, United States; and Celerion Switzerland AG, Switzerland) using validated and fit-for-purpose methods.

Statistical Considerations

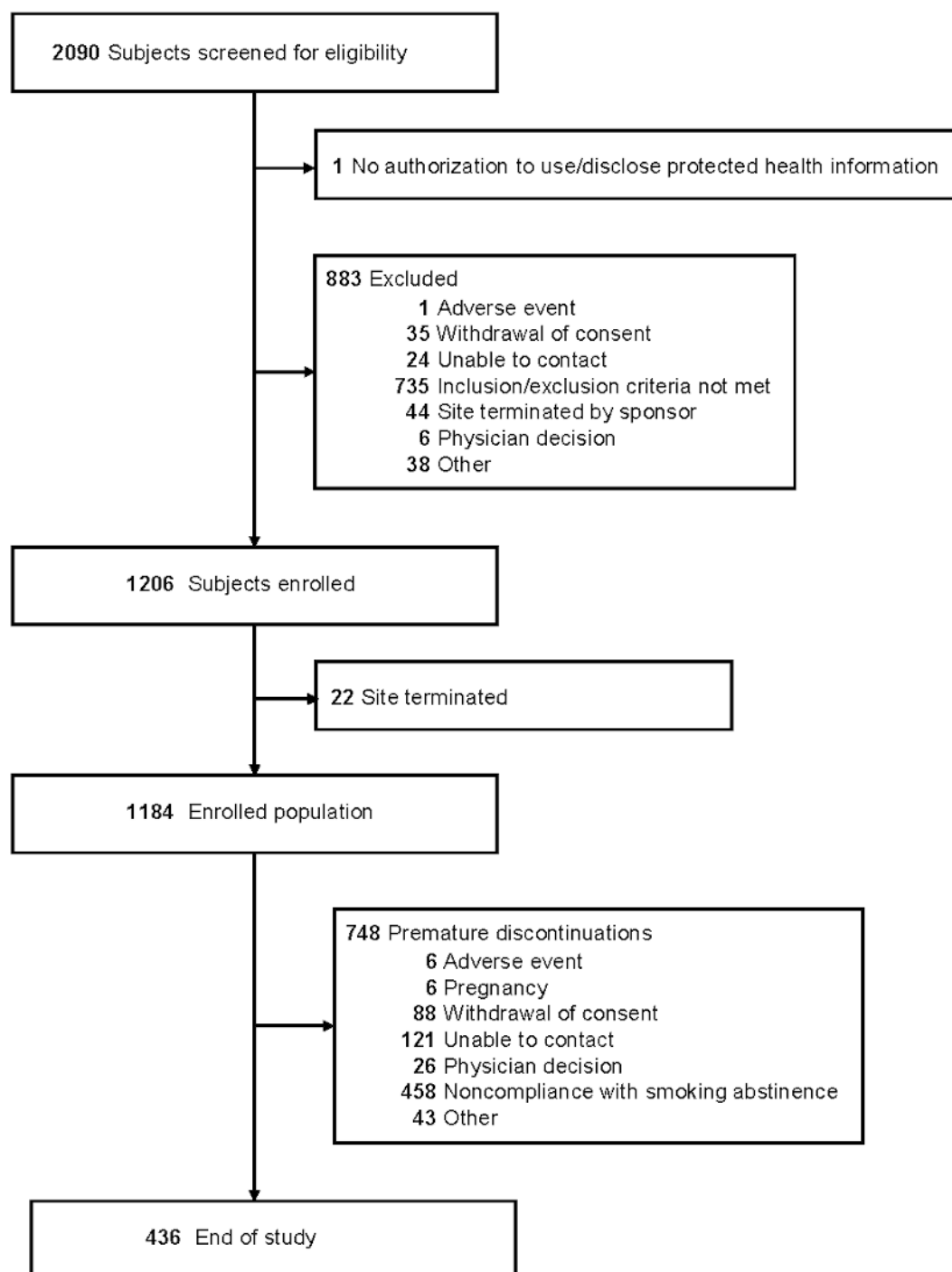
On the basis of the results of the Lung Health Study and on the 1-year abstinence rates from English smoking treatment services [27], at least 950 smokers were required to have approximately 190 participants who successfully abstain from smoking for the duration of the study [28]. Sample size was driven by FEV₁, which is expected to have the lowest effect size. Approximately 190 participants were needed to estimate the mean increase from baseline of 1.98 (% predicted) in FEV₁ at Month 12, with a 90% probability of obtaining a margin of error (95% CI) of at most ± 1 (% predicted). Enrolled participants who failed to abstain for at least 2 weeks were discontinued from the study.

Changes from baseline were summarized for the main analysis population, defined by quitters with no major protocol deviations impacting subject availability. Data collected after evidence of noncompliance with continuous abstinence were not included in the analysis. For analysis purposes, the concentrations of free cotinine (≥ 50 ng/mL) [29] and total NNAL (≥ 75.9 pg/mL) [30] in 24-hour urine collected at Visit 11 were included in the list of tools for continuous SA verification. This study had no formal prespecified hypotheses to be tested for statistical significance. However, a 95% CI accompanied all effect estimates.

Results

A total of 2090 subjects were screened for the study (Figure 2); 1206 subjects were included in the Full Safety Population, 1184 subjects were enrolled, and of these, 358 subjects were abstinent from smoking for 1 year. The mean age of the enrolled subjects was 43.8 years, and 50.1% were male.

The study was completed in May 2017. The results of this study are under evaluation and will be published upon completion of analysis.

Figure 2. Flow chart of study participants.

Discussion

Overview

The approach of our study is unlike other SC studies whose primary objective was to test the efficacy of an SC treatment (ie, drug or behavioral cessation support) [31-33]. This dataset will supplement the existing literature data on the effects of SC while providing prospective and comprehensive perspective on

favorable health effects that occur following SC. Although several papers report favorable changes in biomarkers of effect with SC [34,35], there are very little data on 1-year observations and none with such an extensive set of endpoints for clinical risk and exposure. Changes in inflammatory markers with SC have been evaluated in previous studies. SC is reported to reduce oxidant stress and inflammation. This is evidenced by an improved urinary F₂ isoprostane:creatinine [F₂:Cr] ratio and decreases in WBC counts [36]. Time-dependent changes in

LDL levels have been reported with cessation. LDL levels were measured in 50 smokers before cessation and at 3 months and 1 year after cessation. At 1 year after cessation, LDL levels were reported by Komiyama et al to decrease significantly, although levels did not change at 3 months [37]. For a long time, it has also been known that smokers have lower HDL levels than nonsmokers. Past studies have shown that HDL levels increase following cessation, and that this increase occurs rapidly, in less than 3 weeks, but with no clear pattern of change thereafter [6]. SC is also reported to be accompanied by a rapid reduction in tobacco smoke carcinogen and toxicant biomarkers. After 3 days of cessation, an >80% reduction has been reported for monohydroxybutyl mercapturic acid, 3-hydroxypropyl mercapturic acid, 4-hydroxybut-2-yl mercapturic acid, S-phenyl mercapturic acid, and 2-hydroxyethyl mercapturic acid. Gradual reduction has been reported for some biomarkers, including a 92% reduction in total NNAL after 42 days [38]. Variable dose-response change in biomarkers of exposure following a reduction in cigarettes smoked per day has also been reported. Some biomarkers, such as plasma nicotine, show a strong dose-response reduction, whereas others, such as plasma thiocyanate, show weaker dose-response reductions [39].

In this study, the list of biological and functional parameters and biomarkers of exposure to be tested was extensive. This list was carefully selected to provide high-quality evidence for the effect of SA on a variety of HPHCs and the health-related effects of smoking that are reversible upon SC. These endpoints will provide further insights into the risk profile of a smoker following abstinence from smoking within a short time frame by examining a collection of logical, empirically coherent, and mutually supportive data from multiple clinical risk components across several biological processes, physiological systems, and mechanisms that are known to contribute to the pathogenesis of smoking-related diseases.

The results of this study may offer a valuable point of reference for future assessments of alternative products in the context of

tobacco harm reduction, providing scientific evidence of the potential of alternative products to reduce the risk of harm in smokers within a 1-year time frame when compared with continuing to smoke cigarettes. With this aim, cross-study analyses need to be designed carefully to ensure baseline comparability of quitters with the population of smokers switching to the alternative product. Such a comparative approach is valuable for obtaining data on the risk reduction potential of a product alternative to cigarettes earlier than epidemiological studies, which require long-term assessment to provide data.

Limitations

The design and approach used in the present study should be considered in light of its limitations. One limitation was related to the difficulty of recruiting smokers who were both willing and motivated to quit smoking, completely and continuously, for 1 year. In addition, the uncontrolled before and after study design and the lack of a control arm with no intervention might require careful interpretation of the outcomes of this study. The results of this study should be interpreted with caution owing to the lack of control of potential confounding factors. Factors such as concomitant medications, lifestyle, and weight increase can cause changes in lipid metabolism and other biochemical processes following SC [40].

Conclusions

This study was designed to provide an extensive dataset on changes in biomarkers of effect and biomarkers of exposure after 12 months of continuous SA. Therefore, it will provide a comprehensive overview of the beneficial short-term health effects that occur over the course of 1 year in a smoker who ceases smoking. The results from this study will complement existing evidence for the benefits of cessation. In the context of smoking harm reduction, these results may be used as a benchmark for the future evaluation of alternative products to cigarettes and to supplement the existing literature on the biological and functional health effects of SC.

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Conflicts of Interest

The study reported in this publication was solely funded by PMI. All authors are (or were) employees of PMI Research & Development (R&D) or worked for PMI R&D under contractual agreements.

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Abbreviations

- CVD:** cardiovascular disease
- FEV1:** forced expiratory volume in one second
- FVC:** forced vital capacity
- HPHC:** harmful and potentially harmful constituent
- NRT:** nicotine replacement therapy
- PMI:** Philip Morris International
- PMI R&D:** Philip Morris International Research & Development
- SA:** smoking abstinence
- SC:** smoking cessation
- WBC:** white blood cell
- WHO:** World Health Organization

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Protocol

Mobile Messaging Support Versus Usual Care for People With Type 2 Diabetes on Glycemic Control: Protocol for a Multicenter Randomized Controlled Trial

Andrew Farmer^{1*}, DM, FRCGP; Kirsty Bobrow^{2*}, MBChB, MSc, DPhil; Natalie Leon³, MA (ClinPsych), MA (Public Health), PhD; Nicola Williams¹, MSc; Enita Phiri⁴, BA, MSc; Hazel Namadingo⁴, MSc; Sara Cooper³, PhD; John Prince⁵, BEng; Amelia Crampin⁶, MBChB, MSc, FFPHM; Donela Besada³, MPH; Emmanuelle Daviaud³, MSc; Ly-Mee Yu¹, MSc, DPhil; Jonathan Ngoma⁷, MBBS, FCP (SA), FCP (ECSA); David Springer⁸, DPhil; Bruno Pauly⁹, MBChB; Shane Norris¹⁰, PhD; Lionel Tarassenko⁵, FEng, FMedSci; Moffat Nyirenda⁶, PhD, FRCP; Naomi Levitt², MD, FCP (SA)

¹Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, United Kingdom

²Chronic Disease Initiative for Africa, University of Cape Town, Cape Town, South Africa

³South African Medical Research Council, Cape Town, South Africa

⁴Malawi Epidemiology and Intervention Research Unit, Lilongwe, Malawi

⁵Institute of Biomedical Engineering, Oxford, United Kingdom

⁶Malawi Epidemiology and Intervention Research Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom

⁷Kamuzu Central Hospital, Lilongwe, Malawi

⁸The Boston Consulting Group, London, United Kingdom

⁹Department of Diabetes and Endocrinology, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa

¹⁰South African Medical Research Council, Developmental Pathways for Health Research Unit, University of Witwatersrand, Johannesburg, South Africa

*these authors contributed equally

Corresponding Author:

Andrew Farmer, DM, FRCGP
Nuffield Department of Primary Care Health Sciences
University of Oxford
Primary Care Building
Woodstock Road
Oxford, OX2 6GG
United Kingdom
Phone: 44 1865 289280
Email: andrew.farmer@phc.ox.ac.uk

Abstract

Background: Health outcomes for people treated for type 2 diabetes could be substantially improved in sub-Saharan Africa. Failure to take medicine regularly to treat diabetes has been identified as a major problem. Resources to identify and support patients who are not making the best use of medicine in low- and middle-income settings are scarce. Mobile phones are widely available in these settings, including among people with diabetes; linked technologies, such as short message service (SMS) text messaging, have shown promise in delivering low-cost interventions efficiently. However, evidence showing that these interventions will work when carried out at a larger scale and measuring the extent to which they will improve health outcomes when added to usual care is limited.

Objective: The objective of this trial is to test the effectiveness of sending brief, automated SMS text messages for improving health outcomes and medication adherence in patients with type 2 diabetes compared to an active control.

Methods: We will carry out a randomized trial recruiting from clinics in two contrasting settings in sub-Saharan Africa: Cape Town, South Africa, and Lilongwe, Malawi. Intervention messages will advise people about the benefits of their diabetes treatment and offer motivation and encouragement around lifestyle and use of medication. We allocated patients, using randomization with a minimization algorithm, to receive either three to four intervention messages per week or non-health-related messages every 6

weeks. We will follow up with participants for 12 months, measuring important risk factors for poor health outcomes and complications in diabetes. This will enable us to estimate potential health benefits, including the primary outcome of hemoglobin A_{1c} (HbA_{1c}) levels as a marker for long-term blood glucose control and a secondary outcome of blood pressure control. We will record the costs of performing these activities and estimate cost-effectiveness. We will also use process evaluation to capture the collection of medication and assess the reception of the intervention by participants and health care workers.

Results: Recruitment to the trial began in September 2016 and follow-up of participants was completed in October 2018. Data collection from electronic health records and other routinely collected sources is continuing. The database lock is anticipated in June 2019, followed by analysis and disclosing of group allocation.

Conclusions: The knowledge gained from this study will have wide applications and advance the evidence base for effectiveness of mobile phone-based, brief text messaging on clinical outcomes and in large-scale, operational settings. It will provide evidence for cost-effectiveness and acceptability that will further inform policy development and decision making. We will work with a wide network that includes patients, clinicians, academics, industry, and policy makers to help us identify opportunities for informing people about the work and raise awareness of what is being developed and studied.

Trial Registration: ISRCTN Registry ISRCTN70768808; <http://www.isrctn.com/ISRCTN70768808> (Archived by WebCite at <http://www.webcitation.org/786316Zqk>)

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KEYWORDS

randomized controlled trial; diabetes mellitus; type 2 diabetes; mobile health; treatment adherence

Introduction

The Global Health Importance of Diabetes Mellitus

Diabetes mellitus, specifically type 2 diabetes, is a major burden to individuals and health care systems globally, including in low-resource settings. Estimates of the prevalence of diabetes in Southern Africa vary. A 2009 survey across South Africa placed the incidence at 9% [1], but a survey in Cape Town identified a rising prevalence with an age-adjusted prevalence of 13.1% [2] in black Africans. The prevalence of diabetes is also rising in Malawi with an incidence of 6% [3]. As the prevalence of diabetes is rising, it is likely that the impact of the associated premature mortality and morbidity through, for example, visual impairment, renal dysfunction, neuropathy, and cardiovascular disease will increase. However, failure to take medicine as prescribed, often referred to as nonadherence, can result in a failure to deliver the benefits of effective medical treatments into better outcomes for individual patients. For example, there is an association between better adherence to treatment and better control and fewer complications for people with type 2 diabetes [4,5].

The Need for Further Research and Interventions to Improve Regular and Sustained Use of Medication

Reasons for not collecting or taking medications as intended are well documented and include psychological factors, lack of social support, low levels of health literacy, and interactions with the health care system that do not support self-management [6]. Medication adherence in sub-Saharan Africa is estimated at around 64% [7]. Better understanding of treatments and helping people deal with day-to-day challenges can improve the collection and taking of medicines [8]. Interventions delivered by short message service (SMS) text messaging have been effective in increasing adherence to antiretroviral therapy and other conditions [9,10]. More research is needed to develop

and test better ways to leverage widely used new technologies to help people to improve their use of medicine.

Mobile Health-Based Support for People With Long-Term Conditions

In a primary care setting in the Western Cape [11], we developed a low-cost system of registering patients and regularly sending health messages via SMS text messages. A randomized trial of the intervention for people with high blood pressure—the SMS-Text Adherence Support-Blood Pressure (StAR-BP) trial [12]—showed better adherence and improved blood pressure control for people receiving the SMS text messages compared to those who received active control messages (ie, usual care supplemented by noninformational text messaging). Our system of sending text messages complies with the principles of the information and communications technology policy frameworks now being established in sub-Saharan countries, including the South African mHealth Strategy [13]. For example, our system aims to be integrated into routine care and simple in design. As part of our work to understand the broader applicability of the intervention for people with other chronic diseases, we are now exploring its use for people with type 2 diabetes.

Our own recent focus group work and interviews alongside the StAR-BP trial [14] confirm the importance of offering evidence-based information to help with self-management of long-term conditions. For example, lack of knowledge and mixed feelings toward regular use of medicine to treat chronic conditions, as well as difficulty in remembering to take them, can lead to missing clinic appointments for medicine collection and missing out on taking the tablets. Participants in the StAR-BP trial told us how helpful the system was in reminding them to collect and use their medication. They also told us it encouraged them to make greater efforts to maintain their general health [14].

A systematic review of SMS text messaging in supporting medication use in type 2 diabetes suggested significant benefits, but there was substantial heterogeneity. A recent study in New Zealand that included people with type 1 diabetes and type 2 diabetes with insulin treatment also suggested a benefit in glycemic control. Other work has been carried out to evaluate diabetes-focused SMS systems in low-resource settings where very low rates of medication use offer potential for substantial benefit. In a two-center comparison study in Senegal, text messages were sent to people with diabetes over 3 months. A 6-month randomized trial in Bangladesh consisting of 256 patients identified a small but significant fall in hemoglobin A_{1c} (HbA_{1c}) [15]. However, a longer study duration, the use of structured message development, and studies in sub-Saharan Africa are needed to reduce uncertainty.

We therefore adapted the message content for the StAR-BP system to be appropriate for people with type 2 diabetes in two sub-Saharan settings. Content was based on development work to identify messages that could provide support through behavior-change techniques as proposed by the Capability, Opportunity, Motivation-Behavior (COM-B) framework, which focuses on capability, opportunity, and motivation factors for changing behavior [16-18]. We followed recommended guidelines on SMS text message development, including testing and adapting for local applicability as well as usefulness and field-testing the intervention. Feedback was elicited from a range of stakeholders, including diabetes patients, diabetes health care staff, and experts, concerning promotion of a healthy lifestyle, diet, and exercise in order to understand relevance, usefulness, and acceptability of message content. The system offers a new approach to improving access to care through providing support to patients with diabetes alongside usual care.

In doing this development work, we followed the Medical Research Council framework for developing and evaluating complex interventions [16]. We have also used theory- and evidence-informed behavior-change constructs to guide the content and delivery mechanisms of the SMS text message intervention in this setting [19]. The explicit use of this approach

for diabetes messaging in this context is novel [20]. We planned to test effectiveness and cost-effectiveness of the system in improving glycemic control using an individually randomized controlled design with an embedded process evaluation.

Methods

Trial Aims and Objectives

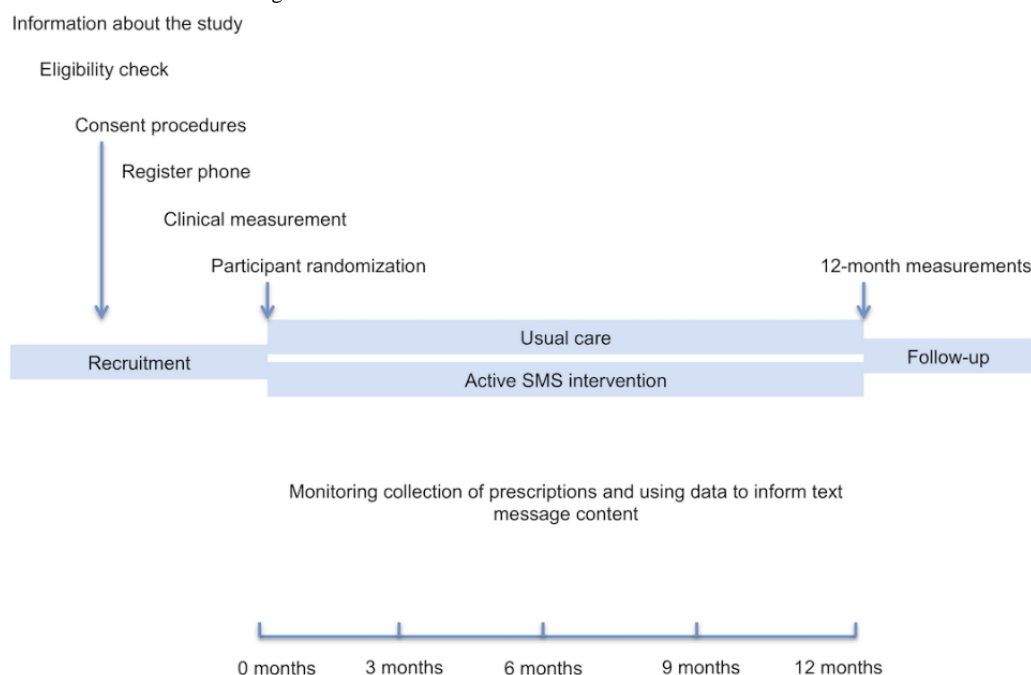
The overall aim of the SMS-Text Adherence Support for Type 2 Diabetes (StAR2D) trial is to test the effectiveness of sending SMS text messages in improving health outcomes and medication adherence in patients with type 2 diabetes compared to an active control. A secondary aim is to examine the incremental cost and cost-effectiveness of the intervention. A process evaluation using qualitative research methods will be carried out alongside the trial to investigate participant responses and acceptability.

Ethical Issues

The University of Oxford Tropical Research Ethics Committee (OXTREC) approved the research protocol (reference number 22-15). Additionally, the University of Cape Town Human Research Ethics Committee (UCT HREC) (reference number 126/2015) and the Malawi National Health Services Research Committee (NHSRC) (reference number 15/7/1425) also approved the protocol. The sponsor of this study—University of Oxford—has put in place insurance in the event that any participant suffers harm as a result of their involvement in the research. This protocol refers to version 2.0 of the StAR2D trial protocol, dated September 16, 2016, that was submitted following formative work but before recruitment to the trial began.

Trial Design

The trial is a 12-month, multicenter, two-parallel-arm, individually randomized controlled trial. A flowchart showing the sequence of recruitment, assessment, and intervention is shown in Figure 1. A checklist of trial procedures is given in Table 1.

Figure 1. Trial flowchart. SMS: short message service.**Table 1.** Visits and procedures to be performed during the trial.

Procedures	Visits			
	Eligibility check	Baseline	Follow-up session with routine data and nonscheduled research contacts	12-month visit
Eligibility assessment	X			
Duration of diabetes				
Demographics: age, gender, language preference, and work status		X		
Medical history: comorbid conditions and duration of diabetes		X		
Current medication, including current oral glucose medication, doses, use of insulin, and other medications	X	X		X
Tobacco use		X		X
Changes in medication			X	X
Physical examination: height and weight		X		X
Hemoglobin A _{1c} measurement		X		X
Total and HDL ^a cholesterol		X		X
Blood pressure measurement		X		X
Medication pickup		X	X	X
Adherence score		X		X
Purchase of drugs during stock-out (ie, out of stock at clinic)				X
EuroQol 5-Dimension 3-Level		X		X
Satisfaction with care		X		X
Self-reported measures of eating and physical activity		X		
Nonscheduled research contact			X	
Adverse event assessment			X	X
Failure to receive message			X	

^aHDL: high-density lipoprotein.

Setting

Participants were recruited from publicly funded outpatient facilities that treat people with type 2 diabetes. We identified sites in Cape Town, South Africa, and Lilongwe, Malawi, serving patients living in low- and middle-income settings. Both are urban sites with a high burden of type 2 diabetes. In Cape Town, recruitment was from two clinics serving townships to the north of the city, and Lilongwe is the capital city of Malawi. A high proportion of the population live in low-income informal settlements where one clinic was involved in recruitment. In both settings, patients received health care and medication from a locally appropriate health care facility. Care is provided free of charge and a limited range of essential medicines are available at no cost to patients to reduce blood glucose and blood pressure.

Participant Eligibility, Recruitment, and Screening

Eligible patients were those with type 2 diabetes, aged 18 years or greater, and taking an oral glucose-lowering medication. Other inclusion criteria included the following: ability to communicate in one of the predominant official languages spoken in the Western Cape province in South Africa (English, Afrikaans, or isiXhosa) and in Malawi (English or Chichewa language); access to a mobile phone, where shared access is allowed with permission of the phone owner; ability to use, or be helped to use, the SMS text messaging feature on a mobile phone, including knowing that a text message had been received and reading it; and current and planned future residence in the communities served by the participating clinics. The following patients were ineligible for recruitment: patients who have been admitted to hospital for hyperglycemia or hypoglycemia within the previous 3 months; patients who are pregnant or within 3 months postpartum by self-report or with plans to become pregnant in the next 12 months; patients with a terminal medical condition; patients with another member of the household already recruited to the trial; or patients who participated in formative work for the intervention development.

Patients attending the clinic for their regular diabetes care were provided with information about the trial at the regular education sessions, on posters, and in leaflets. Clinic patients who attended for routine diabetes care or to pick up diabetes medicine and who have received information about the trial were asked if they were interested in joining the trial.

Potential trial participants received verbal and written information about the trial in their preferred language and had the opportunity to speak to trained study research staff and ask them questions. If they agreed to participate, they provided verbal assent to screening procedures. If eligible, they then provided written consent for enrolment and to enter the trial. Copies of the consent forms were given to participants and randomization was not carried out until confirmation that a “welcome” text message had been received.

Data were transmitted using a low-cost, advanced-feature mobile phone (ie, smartphone) acting as the trial data collection system. A secure implementation of Sana (MIT), which ran on the mobile phone, was linked to a secure server running Open Medical Records System (OpenMRS) [21] using secure information exchange protocols. This allowed errors in data

entry to be checked and enabled immediate upload of data to the trial server.

Randomization

We used a remote Web-based randomization program, Sortition (Oxford), minimizing for time since diagnosis, age, sex, and trial site. Adults with type 2 diabetes were allocated in a 1:1 ratio to receive automated text message support or usual care supplemented by active control. Allocations were directly uploaded into the OpenMRS database to avoid creation of locally held records. Randomization was carried out remotely and independently of the clinic and local research staff. No arrangements for unblinding during the trial were made.

Trial Outcomes and Other Measures

The primary outcome of the trial is the change in HbA_{1c} from baseline to 1 year. Secondary clinical outcomes are the proportion of patients collecting 80% or more of their agreed-upon, diabetes-related medication derived from routine clinic data [22]; change in systolic blood pressure; change in lipids; a combined measure of cardiovascular risk based on HbA_{1c}, lipids, and systolic blood pressure [23]; and the proportion of the participants reaching treatment goals (ie, HbA_{1c} <8% and systolic blood pressure <140 mmHg).

The EuroQol 5-Dimension 3-Level (EQ-5D-3L) instrument [24] and a locally adapted questionnaire to establish satisfaction with treatment and delivery of treatment [25,26] were used and available in all of the study languages. In addition, self-reported medication-taking was recorded [27]. Basic demographic data collected included age, sex, language preference, and work status. Anthropometric measures were collected, including measurement of height and weight using standard procedures and self-reports of eating and physical activity, with a 7-day recall.

Measurement and collection of data were carried out by a team of research assistants trained and supervised to ensure consistency between and within study sites with standard operating procedures for clinical measurement.

Follow-Up Assessment

Annual follow-up is integrated with routine health care review. At 12 months, a reminder text will be sent to invite participants to attend their annual health care review and a final trial assessment. Participants who do not attend the 12-month follow-up clinic appointment will be followed up using the mobile phone and other contact details; if the cause of nonattendance is hospital admission or death, then hospital records will be obtained.

Intervention

Trial participants allocated to the intervention group received specifically designed text messages, including motivational and educational messages. They also received prompts (ie, reminders) about medication collection with timing personalized by the information collected about all participants at the baseline visit, from the clinic and pharmacy attendance. Messages were sent three to four times a week for a period of 1 year. A message was sent giving options to change the delivery time or language

of messages. Messages were randomly selected from a library, using rules that ensured individual messages were not repeated. Messages were also personalized by information given about smoking and use of alcohol. Full details of the intervention are given in [Multimedia Appendix 1](#). The intervention included information intended to encourage people to take their medicine regularly as prescribed. The intervention also prompted participants when an anticipated attendance has not occurred and informed them when an out-of-stock medicine was received in the pharmacy and patients needed to return to obtain it. The intervention is summarized in the Template for Intervention Description and Replication (TIDieR) statement uploaded as [Multimedia Appendix 2](#).

Trial participants allocated to the usual care group received an active control protocol: only noninformational text messages were sent (eg, messages thanking the participant for taking part in the study and a message on their birthday), alongside usual care every 6 weeks. At both study sites, usual care consisted of attendance to collect medication supplies at 2-monthly intervals with review appointments where clinically indicated. Health material on type 2 diabetes were available at all sites, which included information about the importance of taking medicine regularly, alongside other health information. Attendance at all appointments by trial participants was tracked through routinely implemented electronic and manual registers. Messages were stopped at participant request.

Sample Size Estimation

We consider a minimum reduction in HbA_{1c}, from baseline to 12 months, of 0.5% in this population clinically important and feasible. A total of 814 participants (407 per group) across all sites would be required to show a 0.5% reduction—assuming, conservatively, a standard deviation of 2.2%—in this population with 5%, two-sided significance level and power of 90% using PASS software version 12 (NCSS). We have increased the number to account for potential clustering between sites and loss to follow-up of up to 20% to a total of 1066 (ie, 533 per group). We will also have 90% power to detect a 10%-point increase in adherence rate in the intervention group (ie, from 50% to 60%), including adjustment for clustering effects. We plan to recruit half of the participants in each setting.

Analyses

The primary analysis will be carried out on the basis of intention-to-treat (ITT) analysis. We will endeavor to obtain full follow-up data on every participant to allow full ITT analysis, but we expect missing data due to withdrawal, loss to follow-up, or failure to attend clinic visits. The results from the trial will be prepared as comparative summary statistics with 95% confidence intervals. All the tests will be done at a 5%, two-sided significance level. The study results will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement. A full, detailed, statistical analysis plan will be prepared and finalized before participant follow-up is completed.

A linear regression model will be used to compare the primary outcome (ie, change in HbA_{1c} from baseline to 1 year) between groups, adjusting for baseline HbA_{1c} and minimizing variables.

Similar methods will be used to analyze blood pressure data and other continuous outcomes. The proportion of people with more than 80% proportion of days covered with medication will be compared using adjusted logistic regression. We will carry out a prespecified secondary analysis to compare outcomes in individuals with uncontrolled diabetes (ie, HbA_{1c} >8%) at baseline.

Missing data will be reported with reasons given where available and the missing data pattern and mechanism will be explored. We will also carry out various sensitivity analyses using alternative imputation methods to examine the robustness of the results. Finally, we will use the regression method to determine the factors influencing the impact of the intervention.

We will carry out subgroup analyses of the primary outcome and adherence outcomes for the following subgroups: age (<55 years or ≥55 years); site (Cape Town or Lilongwe); sex (male or female); number of years with type 2 diabetes (<7 years or ≥7 years); presence of one or more comorbidity (none, one, or more); diabetes control at baseline (HbA_{1c} ≤8% or >8%); and self-reported adherence rating score at baseline (25 or <25).

Economic Analysis

The costing study will be based on data collected during the trial and by using the trial findings. The costing study will provide a descriptive account of the different cost components annualized to take into account development and capital costs in the form of a percentage increase in costs; the cost-effectiveness study will model the system in terms of cost per disability-adjusted life year (DALY) averted.

To assess the added cost per patient-year, the one-off design costs will be excluded. Setup costs will be annualized over a period of 10 years to reflect their potential for use in scale-up and other applications and added to 1-year delivery costs. Capital costs will be calculated by the replacement value of each item and the estimated useful life and then annualized with a discount rate of 3%. Costs will be adjusted for time using the consumer price index. We will carry out a descriptive analysis of the observed costs using standard methodologies. To assess additional costs as a proportion of nonintervention delivery costs per patient-year, total costs per treatment per patient-year will be calculated.

Economic costs will include provider and patient costs. Facility-level expenditure will include clinical staff, supplies, and overhead (ie, capital, support staff, utilities, administration, and management). Overhead will be calculated based on the level of diabetes clinical activity as a share of the facility activity. Number of visits, laboratory tests, and medication will be collected from the project database. Besides facility costs, costs associated with the SMS text messaging will be included. One-off costs of the initial design of the system (ie, equipment capital costs, staff, and supplies) will be identified. Research costs, apart from that component of the formative research that would be required if the intervention were rolled out to new districts, will be excluded. Data sources will include interviews with staff, facilities' financial records (ie, staff packages and unit costs of drugs, laboratory tests and other supplies, and overheads), and financial records of the SMS organization.

Patient costs will include recording the time spent in clinic and asking about time spent travelling and costs of transport to the clinic. These questions will only be asked once. The study project manager and local coordinators will be interviewed to validate the information.

The costing outcome will be the cost per patient-year and the cost-effectiveness outcome will be incremental cost per DALY averted [28,29].

Process Evaluation

The process evaluation is aimed at understanding implementation of the intervention and contextual factors that may explain the effects and applicability of the intervention. In particular, we will explore the reach of and patient responses to the intervention, including acceptability, in order to enhance our understanding of why and how the intervention worked or not and how it can be optimized in the future. Process measures on the intervention reach and fidelity will be collected from the SMS text message system where numbers of participants and numbers of text messages sent and received are stored. At each site, sources of data will be used to measure activity in the clinic (eg, numbers attending the clinic) and the pharmacy. We will also use these measures during the period of the study to identify where problems might develop and to explore differences between sites.

To explore how the intervention was received and responded to, we will use semistructured interviews and focus groups with purposive and convenience sampling of stakeholders, mainly patient participants, but also clinic staff and representatives from the relevant department of health involved with the study. We will also conduct document reviews relating to the implementation of the trial. Purposive sampling aims to explore variation in response by variables, including age, gender, and language group of patient participants. Patient participant interviews will explore their experiences and views of receiving SMS text messages; their responses (ie, thoughts, feeling, and behaviors, especially in relation to the COM-B behavior-change constructs); and other patient, environmental, and contextual factors that may help us understand the trial outcomes and the experience of participants.

The patient perception and experience component of the process evaluation will be conducted at baseline, after enrolment and before a participant is randomized, and at the end of the trial, but before trial outcomes are known. We aim to interview the same participants at baseline and at the end of the trial. Allocation status of participants will be made known to only the process evaluation researchers, with measures to avoid unblinding the trial staff to individual allocation status. We will also conduct two focus groups per site—one male and one female—with a convenience sample of trial participants. Focus groups will be used to achieve a better understanding of experience by allowing a moderated exchange of views among participants. A trained qualitative researcher using a topic guide will carry out the in-depth interviews and focus groups; data will be captured with field notes and through digital voice recording and will be transcribed with anonymization. Notes or transcripts will be coded and themes developed. Standard approaches to ensuring the quality of the methodology will be

used, including dual review of transcripts, use of a coding framework, and assessment of samples of dual-coded data.

Laboratory Measurement

HbA_{1c} was measured using International Federation of Clinical Chemistry calibrated analyzers linked to an international quality assurance scheme at both sites. Total and high-density lipoprotein (HDL) cholesterol was analyzed using an enzymatic colorimetric method, again with an international quality assurance scheme.

Data Management

Electronic data capture was carried out using Sana (MIT) utilizing low-cost Android mobile phones and a real-time, mobile Internet connection to a server where the data will be stored using OpenMRS [21]. Final locked versions of deidentified data will be stored in SPSS Statistics for Windows, version 25.0 (IBM Corp). Data records will be available for the 1066 patients recruited to the trial and, we estimate, a further 200 records containing data relating to assessed but ineligible patients. All eligible patients will have two study visits. Data management procedures will follow the detailed data management plan submitted to the funders.

Quality Assurance Procedures: Bias, Concealment of Allocation, and Attrition

A standardized presentation was delivered to participants emphasizing the importance of lifestyle modification and medicine in treating diabetes. We asked participants not to share the content of their text messages and we did not recruit more than one participant from the same household. Clinic staff do not have access to information about allocated groups and will not have the facility to send text messages to individuals through the study system. Study procedures will be carried out by trained research staff blinded to participant allocation group. Medication dispensing data were collected blind to participant allocation. Study outcomes will be assessed by laboratory staff with no knowledge of treatment allocation or will be assessed by research staff trained not to ask questions that would elicit group allocation.

The study may be monitored or audited in accordance with the current approved protocol—the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use—Good Clinical Practice (ICH GCP)—relevant regulations, and standard operating procedures by the sponsor or funder. The StAR2D Trial Steering Committee and Data Monitoring Committee members are listed in the [Multimedia Appendix 3](#). The sponsor and funder will have no role in interpretation of data or reporting of the trial.

Publication

The investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases, and any other publications arising from the study. Authors will acknowledge that the study was funded by the UK Medical Research Council and the Global Alliance for Chronic Disease. Authorship will be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines and other contributors will be acknowledged.

Availability of Data and Materials

There are no data relating to this protocol publication; however, following completion, datasets generated during the trial will be available upon reasonable request.

Results

Recruitment to the trial began in September 2016 and follow-up of participants was completed in October 2018. Data collection from electronic health records and other routinely collected sources is continuing. The database lock is anticipated in June 2019, followed by analysis and disclosing of group allocation. Follow-up of participants at 1 year is complete and data collection from routine sources is continuing. The database has not been locked and trial allocation concealment remains intact.

Discussion

Type 2 diabetes is a major global health problem, including in sub-Saharan Africa. This is putting additional strain on health services that are often ill-equipped to deal with people with diabetes and other noncommunicable diseases. Thus, there is a need for novel approaches to support health services for people in managing this and other chronic, lifestyle-associated conditions. Digital technology has the potential to deliver interventions at a low cost and at a wide scale. Small effects have been observed in previous work [20,30]. Since this trial was originally funded, further studies have confirmed the potential for using SMS text messaging. A trial among people with type 1 and type 2 diabetes in New Zealand has demonstrated efficacy in reducing HbA_{1c} [31]; in addition, a study using a before-and-after design has demonstrated the feasibility of text messaging in Senegal [32]. However, another study in three countries did not identify a benefit from using SMS text messages in its intervention [33].

This study allows us to explore the impact of SMS text messaging for people with type 2 diabetes in two sub-Saharan sites. The evaluation of effectiveness will provide information about the potential impact of this strategy and its wider cost-effectiveness. The formative work for this trial, along with the process evaluation, will be published separately from the effectiveness and cost-effectiveness evaluations. This study builds on previous work [12], with an increased frequency of messages and a message library utilizing a wide range of behavior-change techniques and an increased number of content domains [18]. SMS text messaging to deliver brief health-related messages is a technology that is already expanding, as access to Internet-based messaging becomes more widely adopted. Nevertheless, the principle of sending brief messages has the potential to be integrated, using a wide range of messaging platforms, into routine care or implemented as *add-on* programs; these could be particularly helpful for between-clinic visit communication and support from health services.

This study focuses on the use of brief messages that could, if necessary, be read by a friend or relative. We have, therefore, not focused on literacy as a potential mediator of impact of the intervention. Future work may need to be carried out to explore the extent to which literacy is needed for this type of brief intervention, although it will clearly be of importance where more extensive use of digital devices is made.

Although this study targets people with type 2 diabetes, the inclusion criteria are wide and do not exclude either participants with comorbid conditions or those with a varied degree of glycemic control. This study provides a further opportunity to explore the potential for delivering care to people with a wider range of cardiometabolic conditions [34], to look at the extent to which the messages meet the different needs of individuals, [35] and the extent to which this technology could be integrated with other aspects of self-management and care delivery.

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Authors' Contributions

AF, KB, and NL were responsible for the study conception and design. AF, KB, NL, NaL, LT, SN, MN, AC, DB, ED, and L-MY were responsible for drafting the protocol. NL, SC, HN, JP, DS, KB, AF, EP, BP, and JN were responsible for the intervention development. L-MY, NW, JP, DS, AF, and KB were responsible for data management and statistics.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Participant information sheet.

[[DOCX File, 36KB - resprot_v8i6e12377_app1.docx](#)]

Multimedia Appendix 2

Template for Intervention Description and Replication (TIDieR) checklist.

[[PDF File \(Adobe PDF File\), 69KB - resprot_v8i6e12377_app2.pdf](#)]

Multimedia Appendix 3

SMS-Text Adherence Support for Type 2 Diabetes (StAR2D) Trial Steering Committee and Data Monitoring Committee members.

[[DOCX File, 25KB - resprot_v8i6e12377_app3.docx](#)]

Multimedia Appendix 4

Peer-reviewer report from the Medical Research Council.

[[PDF File \(Adobe PDF File\), 300KB - researchprotocols_v8i5e12377_fig.pdf](#)]

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Abbreviations

COM-B: Capability, Opportunity, Motivation-Behavior

CONSORT: Consolidated Standards of Reporting Trials

DALY: disability-adjusted life year

EQ-5D-3L: EuroQol 5-Dimension 3-Level

HbA_{1c}: hemoglobin A_{1c}

HDL: high-density lipoprotein

ICH GCP: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice

ICMJE: International Committee of Medical Journal Editors

ITT: intention-to-treat

NHSRC: National Health Services Research Committee

OpenMRS: Open Medical Records System

EXTREC: University of Oxford Tropical Research Ethics Committee

SMS: short message service

StAR2D: SMS-Text Adherence Support for Type 2 Diabetes

StAR-BP: SMS-Text Adherence Support-Blood Pressure

TIDieR: Template for Intervention Description and Replication

UCT HREC: University of Cape Town Human Research Ethics Committee

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Protocol

Comparing Written Versus Pictorial Asthma Action Plans to Improve Asthma Management and Health Outcomes Among Children and Adolescents: Protocol of a Pilot and Feasibility Randomized Controlled Trial

Lisa Hynes¹, PhD; Kristine Durkin¹, MS; Desireé N Williford¹, MS; Hope Smith¹, BA; David Skoner², MD; Christa Lilly³, PhD; Viral Dilip Kothari², MD; Jenny Mc Sharry⁴, PhD; Christina L Duncan¹, PhD

¹Department of Psychology, West Virginia University, Morgantown, WV, United States

²Department of Pediatrics, School of Medicine, West Virginia University, Morgantown, WV, United States

³Department of Biostatistics, School of Public Health, West Virginia University, Morgantown, WV, United States

⁴School of Psychology, National University of Ireland, Galway, Galway, Ireland

Corresponding Author:

Lisa Hynes, PhD

Department of Psychology

West Virginia University

1124 Life Sciences Building

Morgantown, WV, 26506-6040

United States

Phone: 1 3042161953

Email: lisa.hynes@nuigalway.ie

Abstract

Background: Asthma is an important focus for pediatric health research as management of asthma symptoms is a significant challenge, and morbidity and mortality among youths with asthma remain prevalent. Treatment guidelines for asthma recommend a written asthma action plan (WAAP) that summarizes individualized instructions for daily medication use. However, WAAPs are typically written at a seventh- to ninth-grade reading level, which can be a barrier to young people in understanding their treatment, having confidence in using a WAAP, and engaging with asthma education.

Objective: Utilizing a feasibility and pilot randomized controlled trial (RCT) design, the objective of the *Take Action for Asthma Control* study is to test a symptom-based, computer-generated pictorial asthma action plan (PAAP) in comparison with a standard WAAP and assess the feasibility and acceptability of the asthma action plan (AAP) intervention and study procedures. The study has 3 aims: (1) estimate the effect sizes of PAAPs compared with WAAPs on outcomes (eg, AAP knowledge and medication adherence), (2) evaluate feasibility and acceptability of AAP intervention and RCT procedures from the perspectives of key stakeholders, and (3) establish whether parent and youth literacy levels are associated with treatment outcomes.

Methods: This feasibility and pilot RCT is a block randomized, 2-arm, parallel-group clinical trial, lasting 6 months in duration. At baseline, participants will be randomly assigned to receive a PAAP or WAAP generated for them and reviewed with them by their asthma physician. Study procedures will take place over 4 separate time points: a baseline clinic appointment, 1-month telephone follow-up, and 3- and 6-month clinic-based follow-ups. At each time point, data will be collected related to the main outcomes: AAP knowledge, AAP satisfaction, asthma control, pulmonary function, and adherence to daily asthma medication. A sample size of up to 60 participants (aged 8-17 years) will be recruited. Feasibility and acceptability data will be collected via one-to-one qualitative interviews with providers involved in the study and a subgroup of families that participate in the study.

Results: Recruitment and data collection began in May 2017 and were completed in October 2018.

Conclusions: This pilot and feasibility study will test the potential efficacy, feasibility, and acceptability of an AAP intervention and study procedures. The findings will inform the design and delivery of a future definitive trial to assess the efficacy of PAAPs versus WAAPs in supporting asthma self-management among children and adolescents.

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KEYWORDS

asthma; child; adolescent; education; self-management

Introduction

Background

Asthma affects over 10 million children and adolescents in the United States [1]. Suboptimal asthma management is associated with morbidity (eg, school absences and asthma attacks) [2] and even mortality [1]. Effective asthma management requires that both preventive and rescue medications are taken at the appropriate times and a clear understanding of when to seek emergency care. Current best practices for asthma management include administration of an asthma action plan (AAP), and providing specific, individualized instruction to people with asthma and caregivers regarding their daily treatment regimen [3]. The use of written asthma action plans (WAAPs) can be associated with a number of improved health outcomes, including fewer hospitalizations and improved adherence to medications [4,5]. However, possible literacy deficits [6], lack of self-efficacy in relation to using an AAP [7], and insufficient asthma education [8,9] are important and significant barriers to both providers and families accepting and using AAPs effectively.

Given that most WAAPs consist of densely presented text typically written at a seventh- to ninth-grade reading level [10], their utility could be reduced for people with literacy concerns. Low parental literacy, which is often reported in rural populations [11-13], is associated with significantly poorer outcomes in children with asthma, such as an increased number of emergency department visits and school absences [13]. Moreover, although children as young as 9 years old are principally responsible for their asthma medication use [14], young people may not be engaged in asthma education during clinic visits, negatively impacting the development of their asthma literacy and self-management skills [8]. A recent report found that in the United States, only 50.8% of young people under the age of 18 years receive an AAP [7]. Concerns related to the accessibility of AAPs, the literacy levels, and the responsibility placed on young people to manage their asthma provide a rationale for developing a simplified and individualized AAP that can facilitate engaging young people and families in asthma education and in daily asthma management.

Visual tools for communicating health-related information (eg, details about a diagnosis and instructions for treatment) can improve comprehension, satisfaction with information, self-management, and provider-patient engagement [15-17]. Recent AAP research has integrated the use of images with different amounts of supporting text [18,19] or mobile apps [20] to communicate asthma treatment plans. However, the focus of this AAP research has been to develop pictorial asthma action plans (PAAPs) and electronic AAPs [21,22] and to evaluate the feasibility and acceptability of their use [20,23]. Existing research has focused on the perspectives and behaviors of parents with little integration of the perspectives of young people

[19]. The impact of PAAPs or electronic AAPs on the comprehension of asthma treatment among children has not been investigated to date, nor has the impact of PAAPs on parent or youth asthma management behavior.

Study Objective

This protocol describes the final phase in a 2-phase study, called the *Take Action for Asthma Control* (TAAC) study, which aims to assess the feasibility, acceptability, and preliminary efficacy of a symptom-based, computer-generated PAAP for supporting pediatric asthma management relative to a standard text-based WAAP. In the first phase, PAAP software was developed in consultation with young people with asthma, their parents and asthma providers, and a health technology company [24]. This software enables providers to generate simplified and tailored PAAPs that reflect the patient's asthma treatment regimen. PAAPs primarily comprise graphics and images, with minimal words or phrases.

Assessing feasibility and acceptability of interventions in health care settings will ensure that important factors related to intervention design and study procedures are explored and optimized before implementing a definitive randomized controlled trial (RCT) [25]. Moreover, this focus during the intervention development and pilot testing phases is now generally considered a prerequisite for successful implementation of interventions into clinical practice [26]. On the basis of guidance for conducting pilot and feasibility studies [27,25], the approach to data collection in this study was designed to answer pertinent questions ahead of a future definitive trial. Thus, feasibility-related questions are concerned with understanding whether or not a future trial and routine use of PAAPs in practice may be possible. For example, fit of the study activities within the flow of asthma clinics is one of our feasibility outcomes. Acceptability-related questions will address the asthma education preferences of providers and families, and the appeal and usability of PAAPs from the perspectives of families are among the acceptability outcomes in this study.

A mixed-methods approach to data collection and analysis will be used based on the current guidelines for the development of effective behavior change interventions [28]. Using a pilot RCT design, the aims of this study are threefold: (1) assess initial evidence for the efficacy of PAAPs in comparison with WAAPs for improving pediatric asthma management and outcomes (ie, child and caregiver knowledge of treatment plan, AAP satisfaction, adherence to daily controller medication, symptom control, and lung function), resulting in robust effect size estimates ahead of a future definitive RCT; (2) evaluate the feasibility and acceptability of the PAAP software, PAAPs, and study procedures; and (3) identify whether parent health literacy and youth literacy levels are associated with outcomes.

Methods

The study protocol, personnel, and materials have been reviewed and approved by the Institutional Review Board at West Virginia University (WVU).

Study Design and Sample

This study is taking place in subspecialty clinics (asthma/allergy/pulmonology) across 3 locations affiliated with WVU Medicine, Department of Pediatrics. A sample of 60 children and adolescents with asthma (aged 8-17 years) and parents or caregivers or legal guardian (hereon referred to as *parent*) will be recruited. Participants will be block randomized (age: 8-12 and 13-17 years; physician-determined asthma severity: mild or moderate to severe) to 1 of the 2 groups: a PAAP group or a WAAP group. Random group assignment is identified through selection of an envelope from sets of envelopes arranged into the randomization blocks. Group assignment is concealed until the family has completed the informed consent process. Data will be collected at baseline (enrollment and intervention), with follow-up 1, 3, and 6 months later.

The inclusion criteria for the participants are as follows: (1) aged 8-17 years, (2) have a clinical diagnosis of persistent asthma, (3) have a prescription for a daily controller inhaler compatible with an adherence monitoring electronic sensor (ie, Qvar HFA (TEVA), Dulera HFA (Merck), Advair [HFA and Diskus] (GSK), or Flovent [HFA and Diskus] (GSK)), (4) have never received an AAP in the past, and (5) do not have a disability or cognitive impairment that would prevent them from completing the study procedures. Eligible participants must also match at least one of the following supplemental criteria: (1) newly diagnosed with persistent asthma, (2) asthma control is suboptimal (eg, child is using his or her rescue inhaler often), or (3) physician plans to make a change to the patient's asthma treatment plan.

Potentially eligible families will be identified through 2 pathways: (1) clinic staff will identify potential participants through the electronic medical record (EMR) system and share clinic appointment details with the research team or (2) through a filter based on eligibility criteria applied to EMR lists associated with clinics. Families identified this way will receive a brief email message through the EMR system, introducing them to the study and providing contact details for the research team. Families who do not have an active email account as part of the EMR system will receive a phone call. Interested families who are not already receiving care in one of the study's allergy or asthma specialty clinics can be referred by their physician if a referral is deemed appropriate.

A research team member will call all families in advance of their clinic appointment to introduce or reintroduce the study so that they can plan to have enough time to stay to complete the baseline appointment, which lasts approximately 90 min.

Study Intervention

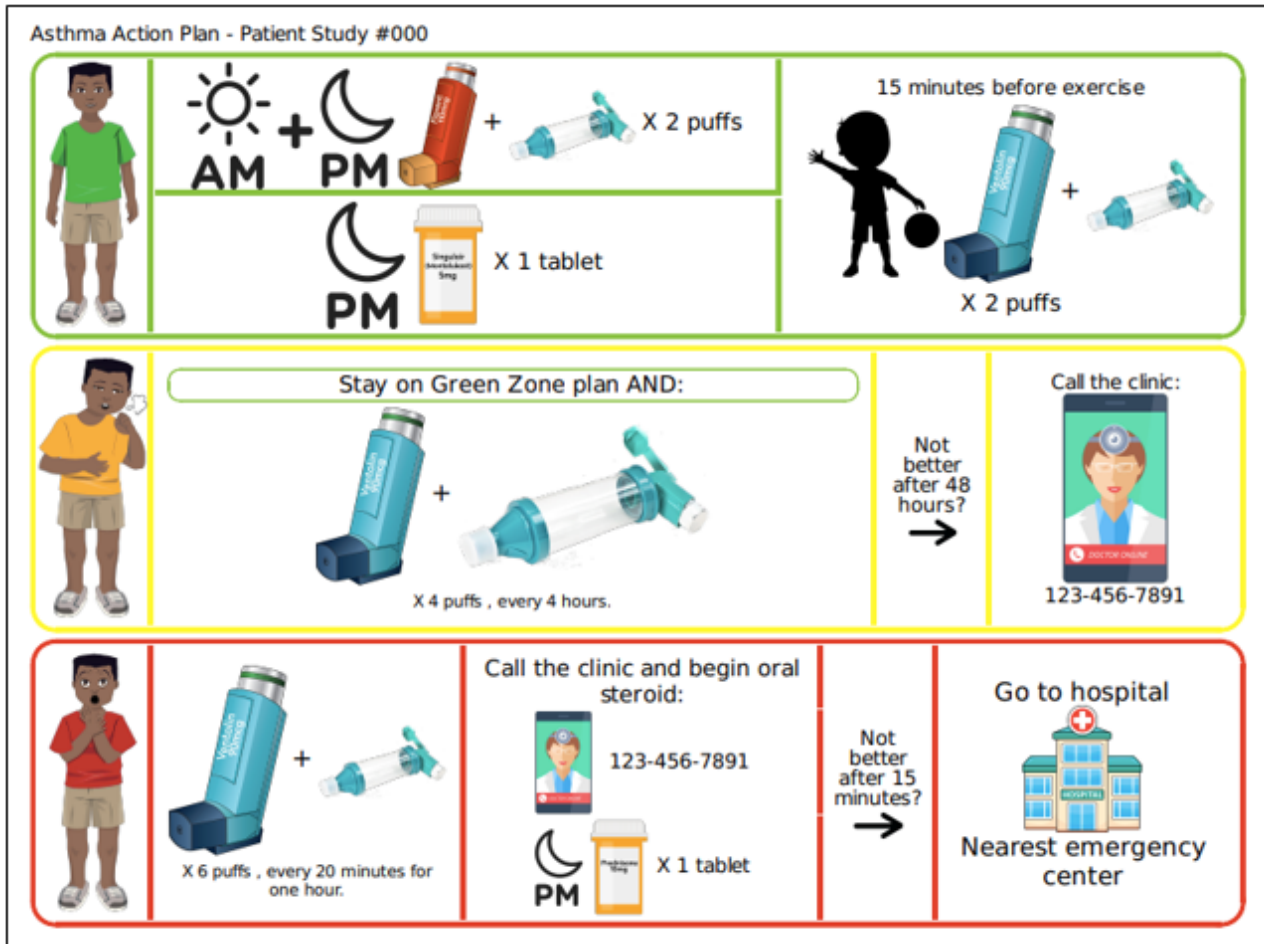
The TAAC intervention involves an individually tailored AAP (WAAP or PAAP) summarizing each participant's asthma

treatment plan. On the basis of the National Health, Lung & Blood Institute (NHLBI) guidelines for managing persistent asthma [3] and the patient's prescribed asthma treatment, physicians will populate AAPs according to 3 colored zones that describe treatment instructions in response to asthma symptoms characteristic of each zone: (1) green zone comprises daily management options when no symptoms are present; (2) yellow zone presents options for managing distressing asthma symptoms, including wheezing and chest tightness; and (3) red zone outlines options for managing highly distressing, even life-threatening asthma symptoms, such as severe shortness of breath. PAAPs will be generated using the PAAP software and printed onto a single page with a color printer, whereas the NHLBI WAAP template [29] will be completed by hand and photocopied for participants. Multiple copies of the AAP will be given to each family, and families will be encouraged to place the copies in convenient locations (eg, refrigerator) for prompting asthma management. The same individually tailored asthma management guidance (via AAP) is delivered to participants, regardless of the assigned intervention group. To ensure AAP review sessions are uniform across participants, physicians are encouraged to maintain consistency in reviewing details of asthma care plans, regardless of participant group assignment, thereby delivering sessions that are equivalent in length. All AAP review sessions are audio recorded, and 20% (approximately 12 recordings) of them will be randomly selected for evaluation by an independent researcher to assess intervention fidelity and uniformity across groups.

The PAAP software is designed to enable providers to quickly and easily generate a PAAP that is tailored to the characteristics (ie, gender and ethnicity) and asthma treatment plans (eg, daily controller inhaler type) of each participant. Physicians will generate the PAAP by responding to questions organized by zone (green, yellow, and red), and each question is followed by a drop-down menu of options. PAAPs comprise 3 horizontal banners for the green, yellow, and red zone treatment instructions (see Figure 1). Each zone begins with an avatar representing the particular child (ie, gender and race and ethnicity) and provides a visual cue for the level of distress and types of symptoms associated with each zone. A child's favorite sport or physical activity is incorporated into the PAAP to communicate a pre-exercise prescription, if relevant. PAAPs contain various images (eg, inhalers, a spacer, and a cell phone) and symbols (eg, sun to denote the time of day) for prompts as well as a small amount of basic text and numerical information to communicate treatment instructions. The PAAP software program was designed so that it does not have the capability to store any Protected Health Information data related to individual participants.

Physician training to generate AAPs using the PAAP software will occur over a 30-minute session with the project coordinator. During these sessions, a written step-by-step guide will be provided to the physicians and they will be introduced to the software, several sample PAAPs will be generated, and issues or questions will be discussed.

Figure 1. Example of personalized pictorial asthma action plan.



The NHLBI WAAP template [30] was chosen because the NHLBI is the principal source of up-to-date and evidence-based guidelines related to asthma management in the United States. The treatment options available to providers in the PAAP software were selected based on the NHLBI guidelines [3]. In addition, the horizontal format of the NHLBI WAAP mirrors the format of the PAAP. The WAAP template enables providers to communicate the same information as that provided through

the PAAP software. However, the WAAP consists of text and numerical content only, with no images included.

Intervention Components

The TAAC intervention comprises 5 behavior change techniques (BCTs), as defined in the BCT Taxonomy version 1 [31]. Table 1 lists the BCTs that are delivered to participants in both the PAAP and WAAP groups, the definition of each BCT according to the BCT Taxonomy, and the operationalization of each BCT in the intervention.

Table 1. Behavior change techniques within the Take Action for Asthma Control intervention (pictorial asthma action plan and written asthma action plan).

Behavior change techniques	Definition	Operationalization
Action planning	To prompt detailed planning of performance of the behavior (must include at least one of the following: context, frequency, duration, and intensity)	The AAP ^a provides step-by step details of prescription for asthma medications (eg, 2 puffs twice a day) and help-seeking steps (eg, call physician).
Habit formation	To prompt rehearsal and repetition of the behavior in the same context repeatedly so that the context elicits the behavior	The AAP prompts taking medication in the morning and evening, before exercise (green zone), or in response to certain symptoms in the yellow and red zones. It also prompts to call the clinic or hospital or 911 in response to lack of symptom improvement.
Adding objects to the environment	To add objects to the environment to facilitate performance of the behavior (more than an information booklet)	The intervention adds an AAP to the family's home environment. Families are encouraged to place the AAP somewhere easily visible.
Goal setting (behavior)	To set or agree on a goal defined in terms of the behavior to be achieved	The AAP provides step-by step details of prescription for asthma medication and help-seeking steps to follow for daily asthma management.
Credible source	To present verbal or visual communication from a credible source in favor of or against the behavior	In both the written asthma action plan and pictorial asthma action plan groups, the physician reviews the AAP during the clinic appointment.

^aAAP: asthma action plan.

Procedure

Baseline Visit

Physicians will assess families for study eligibility during their consultation and invite a researcher to discuss the study further with interested families. Families who agree to participate will provide informed consent (parent) and assent (child) and be randomized to the PAAP or WAAP groups. Group assignment will then be communicated to the physician, who will generate a WAAP or a PAAP and deliver the AAP review session with the family.

Following the AAP review session, the participant and parent will separately complete brief structured interviews to assess their comprehension of the new AAP. Participants and parents will complete a number of questionnaires (see Table 2), and questions and response options will be read aloud to individuals, if preferred. Trained researchers will also administer a standardized measure of reading comprehension and a pulmonary function test with the participant. All study documents, including the PAAP and WAAP, will be coded with the participant's study ID number to omit identifying information.

Table 2. Summary of study appointment procedures.

Appointment information	Baseline	1 month	3 month	6 month
Location	Clinic	Telephone	Clinic	Clinic
Duration (min)	90	30	45	60
Gift card value	US \$30	US \$20	US \$30	US \$45
Participant information	✓ ^a	— ^b	—	—
Asthma Control Test	✓	✓	✓	✓
Spirometry	✓	—	✓	✓
Reading comprehension and health literacy	✓	—	—	—
AAP ^c knowledge	✓	—	✓	✓
AAP satisfaction	—	✓	—	✓
Daily controller adherence ^d	✓	✓	✓	✓

^aIndicates time points at which data were collected.

^bIndicates time points at which data were not collected in relation to a variable, eg, spirometry was not measured at 1 month follow-up as that appointment was conducted by phone.

^cAAP: asthma action plan.

^dDaily controller inhaler adherence is monitored continuously through the sensor attached to each participant's inhaler. Syncing of adherence data with the sensor dashboard will be checked at 4 time points, but the data will only be discussed with families at the 6-month follow-up appointment.

To enable the collection of objective adherence data for daily controller medication, a small electronic sensor will be fitted to the participant's inhaler. The sensor is connected to an app that is downloaded to the participant's or their parent's cell phone or to a device called a hub that can be plugged in at the family's home, with individual participant data transferred to a Web-based dashboard that will be monitored by the research team. A complimentary canister or diskus (circular, rather than cylindrical inhaler device) of their daily controller inhaler will be provided to each participant to allow the research team to fit the sensor onto the inhaler and to show the family how this is done for refill medication.

Follow-Up Visits

Table 2 summarizes the procedure and measures at each of the 1-, 3-, and 6-month follow-up visits. In addition to the procedures outlined in Table 2, during the final study visit, the data gathered by the adherence sensor will be discussed with the family. Sensors and hubs will be collected from families,

and each participant will be entered into a lottery for 1 of 6 US \$50 gift cards if the sensor is in working order. See Table 2 for participant payment information. Finally, families will be invited to take part in a qualitative interview to provide feedback on being part of the study and on their AAP.

Measures

To address aims 1 and 3 of this study, validated measures of health literacy (Short Test of Functional Health Literacy in Adults [S-TOFHLA]) and numeracy (Asthma Numeracy Questionnaire [ANQ]), reading comprehension (Wechsler Individual Achievement Test-III [WIAT-III]), and asthma symptom control (Asthma Control Test [ACT]) will be used. Details of the quantitative measurement tools that will be used are summarized in Table 3. AAP knowledge and AAP satisfaction will be assessed using a participant and parent structured interview developed for this study. Asthma symptom control and adherence to daily controller inhaler will be measured using objective methods, as described below.

Table 3. Overview of quantitative measures.

Measure	Length	Validation status	Cronbach alpha according to previous re-search	Response options	Range possible	Respondents
Literacy assessments						
Short Test of Functional Health Literacy in Adults	36 items	Validated for use with young people and adults aged 13+	Youth=.90-.92; adults=.97	Fill in the blanks to complete sentences	0-36	Parents and participants aged 13-17 years
Asthma Numeracy Questionnaire	4 items	Validated for use with adults	.57 ^a	Question-specific; free text or list of possible answers	0-4	Parents
Wechsler Individual Achievement Test-III	Varies by grade	Validated for use based on current grade	>.08	— ^b	Varies by grade	Youth
Asthma control						
Asthma Control Test	—	Validated for use with ages 4-11 years and >12	—	Version and question specific, for example, 4-point Likert scale from very bad to very good	—	—
Age 4-11 years version	7 items	—	.76	—	0-27	Parent and youth
Age >12 years version	5 items	—	.84	—	5-25	Youth

^aFor measures with less than 10 items, an alpha value greater than .05 indicates satisfactory reliability.

^b—: not applicable.

Literacy Assessment

Short Test of Functional Health Literacy in Adults

The S-TOFHLA [32] is a measure of a respondent's ability to read and understand health-related information. Total raw scores <16 are reflective of *inadequate* literacy. The measure will only be administered to parents and participants aged 13 to 17 years, as the measure has been validated in this age group but not with younger children [29].

Asthma Numeracy Questionnaire

The ANQ [33] is a validated measure assessing understanding of numerical concepts including risk and percentages in asthma self-management instructions. This 4-item measure will be completed by parents at baseline.

Wechsler Individual Achievement Test-III Reading Comprehension Subtest

The Wechsler Individual Achievement Test-III [34]—Reading Comprehension Subtest is a measure of reading comprehension that is widely validated for use in children and adolescents. It

will be used as a proxy for health literacy with the full sample of young people in this study because there are no comprehension-based health literacy measures for youth aged less than 13 years. Participants' raw score on the WIAT-III will be converted to age-based and grade-based standard scores for data analyses, and age-based and grade-based percentile rank.

Asthma Symptom Control

The ACT [35] is a measure of asthma health status, including asthma symptom activity. Both versions of the ACT (aged 4-11 years and >12 years) use the same cutoff score of 19, with lower scores indicating problems with asthma symptoms. An average item score will be computed for statistical analyses. Total scores will be reported for descriptive purposes only.

Asthma Action Plan Knowledge

A structured interview (*AAP Knowledge Interview*) was designed for this study and will assess participants' and parents' understanding of prescribed AAPs at 3 time points, face-to-face (baseline and 3 and 6 months). Two versions of this interview have been created (parent and participant), with 3 parallel forms of each version (A, B, and C) to reduce practice effects across assessments. Respondents can refer to their AAP to answer questions. The first 7 items describe different scenarios involving asthma symptoms commonly experienced by young people, and respondents are asked to identify the relevant zone for each scenario. Each of these items are scored for accuracy (1=correct, 0=incorrect). The final 3 items ask about details of the child's green, yellow, and red zone instructions. Responses to these final 3 questions are coded for accuracy using the following categories: 2=correct, 1=correct but vague, 0=incorrect. A total of 3 scores are calculated: (1) zone identification, (2) treatment plan knowledge, and (3) total score.

Asthma Action Plan Satisfaction

Devised for this study, the *AAP Satisfaction Interview* consists of parallel forms (parent and young person), each consisting of 11 items to assess the perception of the content, clarity, appeal, and utility of AAPs. For example, "How clearly does your (your child's) asthma action plan explain medicines that you (your child) need(s) to take every day?". Respondents will answer items using 4-point Likert scales relevant to the wording of each item (eg, *Very helpful* to *Not helpful at all* or *Very clear* to *Not clear at all*), and items are summed to yield a total score. After each question, respondents will be invited to share feedback or experiences related to that question.

Pulmonary Function

Pulmonary function will be assessed using spirometry, administered by a trained member of the research team during clinic-based appointments. After maximal inhalation, spirometry measures the volume of air exhaled during a forceful and complete exhalation, as well as the flow of air at different time points. The 4 primary endpoints derived and focused on for the purposes of this study will be (1) the total exhaled volume known as forced vital capacity (FVC; both absolute and percentage of predicted values), (2) the volume exhaled in the first second known as forced expiratory volume in 1 second (FEV1; both absolute and percentage of predicted values), (3) their ratio (FEV1/FVC), and (4) the forced expiratory flow

between 25% and 75% of the forced vital capacity (FEF 25-75; percentage of predicted values), which may provide information regarding the small airways.

Medication Adherence

Objective adherence data will be collected using an electronic sensor provided by Propeller Health (Madison, WI), a company specializing in mobile self-management technology for respiratory conditions, including asthma. The Propeller Health sensor provides a reliable and objective record of each actuated dose from participants' inhaler [36,37]. During enrollment, the participant's treatment plan information will be entered into the Propeller Health online dashboard, including the type of daily controller medication, number of puffs per administration (eg, 1 or 2 puffs), frequency of administrations (eg, once or twice per day), and approximate times per day when they expect to use the inhaler. Data from the Propeller Health sensor will be stored on the device and automatically uploaded to the study's secure dashboard via a mobile phone app or hub, as previously described. The dashboard can only be viewed by research and Propeller Health team members. Participants will not be able to access their adherence data.

The sensor contains a battery that can last up to 18 months and can hold up to 1000 pieces of data. Therefore, if the sensor and app or hub through which it communicates with the Propeller Health dashboard are not in close proximity for several days, a sync between the sensor and app or hub will effectively bring the adherence data up to date. As a result, time away from home for participants (eg, during vacations or intermittent issues with Wi-Fi connection) will not detrimentally affect the accurate collection of adherence data. Once it is time to replace or refill their inhaler prescription, the family will transfer the sensor to the participant's next daily controller inhaler. This transfer can occur without any disruption to the collection of adherence data. Before each study visit, the adherence monitoring dashboard will be checked, and the family will be asked to sync their sensor with their smartphone app or hub if a sync has not occurred in recent days.

Families will be asked to have their child use only the inhaler with the device attached for the duration of the study and that this device will track particular aspects of medication use. Reactive effects, if they occur, should be equally distributed across groups. The outcome of mean daily adherence will be calculated as the total number of puffs actuated divided by the total number of puffs prescribed and multiplied by 100. Episodes of 10 or more actuations in less than a minute will be classified as *dumps* (ie, participant's intentional attempt to appear more adherent) or device error; such data will be excluded from the analyses [38].

Feasibility and Acceptability Assessment

To assess the feasibility and acceptability of this pilot RCT, qualitative data will be collected by reviewing study records, through interviews with service providers involved in the study and via exit interviews with a subgroup of participants and parents. Interviews will be conducted with providers involved in the study at the beginning and toward the end of the course of the pilot RCT, either face-to-face or by telephone. Finally,

semistructured interviews will be conducted with a subgroup of participants and parents following completion of their involvement in the study. Exit interviews will be conducted either face-to-face or by telephone, depending on the availability and preferences of the interviewees.

The interviews will be conducted by a member of the research team who is not involved with the day-to-day running of the

study to facilitate openness among the families and providers to share their study experiences and feedback. Table 4 summarizes the feasibility- and acceptability-related variables that will be examined in this study, the data collection method that will be used to gather information related to each variable, and the schedule for data collection.

Table 4. Feasibility and acceptability outcomes and data collection plan.

Variable	Data collection method	Schedule
Feasibility: Is a definitive trial possible? Is it possible to integrate PAAP^a within routine care?		
Provider engagement (eg, facilitating and participating in study meetings)	Study records and provider interviews	Ongoing and 3-month intervals
Recruitment and retention rates	Study records and interviews with providers and families	Ongoing and 3-month intervals
Fit of study activities within clinic workflow	Provider interviews	3-month intervals
Integrity of data collection (eg, missing data)	Study records	Ongoing
Family views of study activities (eg, schedule, time involved, and types of measures)	Interviews with families	Exit interview
Adequacy of participant payments	Interviews with families	Exit interview
Acceptability: Does a PAAP meet the needs of physicians and families?		
Perceptions of value added to consultations and asthma management	Interviews with providers and families	Providers: 3-month intervals; Families: 1-month phone interview and exit interview
Adequacy of PAAP (eg, accessibility, clarity, usability, tailoring, liking, and influence)	Interviews with providers and families	Providers: 3-month intervals; Families: exit interview
Impact of group assignment on retention	Interviews with providers and families	Providers: 3-month intervals; Families: exit interview

^aPAAP: pictorial asthma action plan.

Statistical Analyses

Power Analysis

The aims of the primary quantitative analyses in this pilot RCT are to assess initial evidence for the efficacy of PAAPs in comparison with WAAPs for improving pediatric asthma management and outcomes and to produce robust effect size estimates ahead of a future definitive RCT. A power analysis was run for the primary outcome of the ACT using PASS software version 13 (NCSS, 2019) [39]. Effects were estimated based on a previous study [40], using WAAP compared with verbal instruction. Power in this study was calculated for effect sizes between 0.50 and 1 SD unit increase in the effect size of the outcome in the treatment group. The group by time interaction effect ($\sigma=2.21$, effect size σ_m/σ ranged from 0.226 to 0.452) was tested in this power calculation, with alpha set to .05. In this study, equivalence tests of means (using 2 one-sided tests on data from a parallel-group design with sample sizes of 25 in the WAAP group and 25 in the PAAP group) will result in 82% power at a 5.0% significance level when the true difference between the means is 0.0, the SD is 3.5, and the equivalence limits are -3.0 and 3.0 . Therefore, results that fall within an SD unit difference would indicate that PAAP is *as good as* guideline-recommended care (WAAP) with sufficient power.

On the basis of our previous research of similar duration, we anticipate a <20% attrition rate. Thus, we will recruit up to 60 participants from the specialist asthma and pulmonology clinics within WVU Medicine, with sufficient power to test for equivalence even with attrition and not accounting for missing data. In the event of a lower-than-anticipated attrition rate or data missing completely at random, a sample size of 50 (25 per group) will maintain high power for detecting equivalence.

Quantitative Data

Preliminary evidence of between-group differences will be examined in relation to the following outcome variables: AAP knowledge, AAP satisfaction, ACT scores, mean adherence to daily controller medication, and pulmonary function using spirometry. The hypothesis tests of interest will involve the fixed effects of the time-by-group interaction for all study outcomes, with covariates included provided they are significant and improve model fit. Specifically, to account for the correlation among the repeated measurements on each participant, general linear mixed models will be the main tools of analysis for the primary outcomes. These models are designed to model correlations among observations on subjects (over time and within groups) and are valid in the presence of missing at random (MAR) data [41]. Various random effects and covariance estimates will be compared using the Akaike Information Criterion to determine the best fitting model.

Random effects, considering the individual level (rather than just population) parameters, will be included and may also be examined in the event of assessing best treatment practices. Accurate model parameter estimation will be ensured by the use of the residual maximum likelihood (REML) approach to estimation (appropriate for use with MAR missing data), and the Kenward-Roger approximation of the degrees of freedom will allow for accurate inference.

Given our power to estimate effect sizes for a subsequent definitive RCT, we will demonstrate the overall stability of the effect of the treatment response utilizing the F test for equivalence of the effect of psi-squared, a standardized measure of difference between groups/time point means and an overall (across groups and time points) mean. This will be assessed utilizing output from the best-fitting general linear mixed model and by testing whether this psi-squared effect size measure falls in the critical region, following the method outlined by Wang and Amrhein [42].

SPSS version 24 will be used for data management and basic analyses; SAS version 9.4 (primarily PROC MIXED) will be used for all advanced statistical analyses. Every attempt will be made to minimize attrition and missing data; however, we recognize that some degree of missing data is inevitable. The REML method involved in mixed modeling is generally appropriate for use under the MAR assumption. Moreover, we will carry out models under missing not at random assumptions to assess the sensitivity of our conclusions to the missing data (eg, via selection models or pattern-mixture models, as needed or appropriate).

Qualitative Data

Thematic analysis will be used to organize and analyze the qualitative data gathered from providers, participants, and parents, including AAP satisfaction survey and exit interview data [43]. The aim of thematic analysis is to facilitate the identification of patterns of meaning across a qualitative dataset. Thematic analysis can be used to address a wide range of research questions and is widely used, increasingly as part of the processes of development, pilot testing, and evaluation of behavioral trials [43,44]. Data from interviews with providers and exit interviews with participants and parents will be transcribed verbatim and entered into *Atlas.ti* software for analysis. Data from the AAP satisfaction survey (1- and 6-month follow-up) will be transcribed and entered into a Microsoft Excel database for analysis.

In this study, a theoretical thematic analysis will be conducted with the aim of addressing the research questions related to the feasibility and acceptability of the TAAC intervention and study procedures, as opposed to approaching the data with a more exploratory aim. Analysis will progress through the phases recommended by Braun and Clarke [43], including cycles of repeated reading of transcripts, assigning descriptive codes to the data, categorizing codes under representative themes, defining and editing themes, and presenting the report of findings. All data from provider and exit interviews will be coded by one member of the research team (LH). A research assistant will independently code 20% of the provider and exit interview data, and agreement between coders will be assessed

and discussed. Data from the AAP satisfaction structured interviews will be analyzed by a research assistant, once a coding framework is agreed upon between 2 coders (LH and research assistant).

Results

Recruitment and data collection began in May 2017 and were completed in October 2018. Results are expected by March 2019.

Discussion

According to the literature, many barriers exist to asthma self-management among young people, including inadequate asthma education and knowledge [13]. Although WAAPs are an evidence-based intervention [3] designed to address these concerns, many people with asthma are not receiving or utilizing WAAPs [45] despite national guideline directives [3]. Barriers to effective asthma self-management may be addressed by the introduction of more accessible and personalized PAAPs. This study aims to assess the feasibility and acceptability of the TAAC intervention and study procedures, for example, the usability of the PAAP software and appeal of the PAAPs generated by the software. We also aim to assess whether literacy and health literacy among children and adolescents and health literacy in caregivers are associated with asthma knowledge and health outcomes. We hypothesize that relative to WAAPs, PAAPs will produce significantly greater improvements in asthma care knowledge of children and adolescents and their caregivers, their satisfaction with education regarding the child's asthma care and subsequent self-efficacy for managing symptoms accordingly, asthma health outcomes (ie, asthma symptom control and pulmonary function), and adherence to the prescribed medical regimen. It is also hypothesized that these improvements will occur as a function of PAAPs having preferred features, such as simplified and reduced text, lower literacy demand, appealing appearance, and accessible format and content.

Strengths and Limitations

Notable strengths of this protocol include the mixed-methods approach to data collection and analysis; integration of technology in the intervention; use of objective outcomes measures; identification of BCTs; and the approach of adapting the standard WAAP, an existing guideline-based tool. The findings of this study will inform the design of the next phase of this research, which will be a definitive RCT. Potential limitations of the protocol are mainly a function of the pilot nature of the study, including data collection from a small number of sites, implementation of the intervention by a small number of physicians, and reliance on Wi-Fi in a rural location in the United States. Nevertheless, this study will produce valuable pilot data for a future large-scale definitive trial that will aim to recruit a large sample from multiple sites and have substantial potential for national application.

Future Research

The planned feasibility and pilot trial, as part of a larger program of research, builds on a growing body of innovative AAP

literature [19-23]. In particular, patient education materials using a largely pictorial format may also be applicable to people with other complex conditions, such as type 1 diabetes and cystic fibrosis. Our future research will include the development of pictorial tools for diverse populations, including people with a

first language other than English. We will draw on implementation science frameworks to design and conduct this research with a view to the adoption of the use of PAAPs in routine practice.

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Conflicts of Interest

None declared.

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Abbreviations

AAP: asthma action plan
ACT: Asthma Control Test
ANQ: Asthma Numeracy Questionnaire
BCT: behavior change techniques
EMR: electronic medical record
FEF 25-75: forced expiratory flow between 25% and 75% of the forced vital capacity
FEV1: forced expiratory volume in 1 second
FVC: Forced Vital Capacity
HHS: Health and Human Services
HRSA: Health Resources and Services Administration
MAR: missing at random
PAAP: pictorial asthma action plan
RCT: randomized controlled trial
REML: residual maximum likelihood
S-TOFHLA: Short Test of Functional Health Literacy in Adults
TAAC: Take Action for Asthma Control
WAAP: written asthma action plan
WIAT-III: Wechsler Individual Achievement Test-III
WVU: West Virginia University

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Protocol

“Smartphone Medication Adherence Saves Kidneys” for Kidney Transplantation Recipients: Protocol for a Randomized Controlled Trial

John McGillicuddy¹, MD; Jessica Chandler², PhD; Luke Sox², BSc; Martina Mueller², PhD; Lynne Nemeth², PhD; Prabhakar Baliga¹, MD; Frank Treiber², PhD

¹College of Medicine, Medical University of South Carolina, Charleston, SC, United States

²College of Nursing, Medical University of South Carolina, Charleston, SC, United States

Corresponding Author:

Jessica Chandler, PhD

College of Nursing

Medical University of South Carolina

99 Jonathan Lucas Street

Charleston, SC,

United States

Phone: 1 843 792 1928

Email: chandlje@musc.edu

Abstract

Background: Kidney transplant recipients' poor medication adherence and poor control of comorbidities, particularly hypertension, are risk factors for graft rejection, graft loss, and death. Few randomized controlled trials (RCTs) have been successful in improving sustained medication adherence and blood pressure control among kidney transplantation recipients. We provide rationale for an RCT evaluating a mobile health medical self-management system for kidney transplantation recipients called Smartphone Medication Adherence Saves Kidneys (SMASK).

Objective: Our objective is to determine whether SMASK is efficacious in improving medication adherence and sustaining blood pressure control among kidney transplantation recipients with uncontrolled hypertension and poor medication adherence compared to an enhanced standard care.

Methods: This two-arm, 6-month, phase II single-site efficacy RCT will involve 80 kidney transplantation recipients. Participants will be randomly assigned to the SMASK intervention arm or control arm. SMASK includes multilevel components: automated reminders from an electronic medication tray; tailored text messages and motivational feedback, guided by the self-determination theory; and automated summary reports for providers. Evaluations will be conducted preintervention, at 3 and 6 months, and posttrial at 12 months. Specific aims are to test the hypotheses that compared to standard care, the SMASK cohort will demonstrate significantly improved changes at 3, 6, and 12 months in the primary outcome variables medication adherence (proportion with electronic monitor-derived score >0.90) and blood pressure control (proportion meeting and sustaining adherence to the Kidney Disease Improving Global Outcomes [KDIGO] guidelines for blood pressure control); the secondary outcome variables provider adherence to KDIGO guidelines, measured by timing of medication changes and changes in self-determination theory constructs; and the exploratory outcome variables estimated glomerular filtration rate, variability in calcineurin inhibitor trough levels, and proportion of patients meeting and sustaining the 24-hour ambulatory blood pressure below 130/80 mm Hg. After the 6-month evaluation, interviews with a random sample of SMASK subjects (n=20) and health care providers (n=3-5) will assess user reactions including acceptability, usability, and aids/barriers to sustainability. Data from the RCT and interviews will be triangulated to further refine and optimize SMASK and prepare for a multisite effectiveness RCT.

Results: The SMASK project received funding from National Institute of Diabetes and Digestive and Kidney Diseases in June 2016, obtained institutional review board approval in April 2016, and began data collection in July 2016. As of July 2018, we completed enrollment with a total of 80 participants.

Conclusions: This study will provide data regarding the efficacy of SMASK to improve medication adherence and blood pressure control in a cohort of hypertensive kidney transplant recipients. An efficacious SMASK intervention will pave the way for a larger, multicenter, effectiveness RCT powered sufficiently to evaluate clinical events in a real-world setting and with the potential to demonstrate improved outcomes at lower cost than standard care.

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KEYWORDS

mHealth; kidney transplant; medication adherence; digital health

Introduction

End-stage renal disease (ESRD) affects more than 700,000 people living in the United States; of these, approximately 95,000 are currently awaiting kidney transplantation [1,2]. Kidney transplantation is the treatment of choice for eligible patients with ESRD, as it offers superior quality of life, improved life expectancy, and better psychosocial functioning, all at a lower cost than maintenance hemodialysis [3-6].

Advances in the medical and surgical care of transplant recipients have not resulted in optimal long-term graft survival. The current 5-year graft survival rate is only 78% [2], and the average graft half-life is only ~9 years [7]. Poor medication adherence and poor control of comorbid medical conditions, particularly hypertension, are major drivers of suboptimal kidney transplantation outcomes [8-13]. Nonadherence to prescribed medical regimens has been identified as a primary risk factor for graft rejection, graft loss, and death [14-18]. Even small degrees of nonadherence to immunosuppressant medications confer a significantly increased risk of graft rejection or graft loss [16,18]. In a meta-analysis published in 2007, approximately 35% of American kidney transplantation recipients demonstrated nonadherence to medications posttransplantation [19], with other more recent studies reporting values of 20%-40% [20-22].

Although medication adherence is critical for optimal kidney transplantation outcomes, until relatively recently, there was a paucity of research examining interventions directed at improving adherence. Our formative research has shown that kidney transplantation recipients have a high rate of smart mobile phone ownership, are comfortable being monitored using mobile health (mHealth) technology, and have an overall positive attitude toward mHealth [23,24]. We previously conducted a small, 3-month, two-arm randomized controlled trial with 20 kidney transplant recipients that involved a patient-centered, behavioral theory-guided mHealth intervention (Smartphone Medication Adherence Saves Kidneys [SMASK]). SMASK included tailored motivational/social reinforcement short message service (SMS) messages, an electronic medication tray with cellular connectivity and reminder alerts, and Bluetooth-enabled blood pressure (BP) self-monitoring, designed to improve both medication adherence and BP control [25]. The recruitment process included confirmation of poor medication adherence using an electronic medication tray (<80% over 1-month monitoring) and documented uncontrolled hypertension prior to and following the 1-month screening process. The SMASK group demonstrated significantly greater improvements in electronically calculated medication adherence (average of 0.92 vs 0.56, $P<.50$) and guideline-based systolic BP (SBP) control (90% vs 10%, $P<.50$) across the 3-month trial compared to the standard care (SC) control group. A recent

12-month posthoc follow-up of the subjects' clinic SBPs demonstrated persistence of the SBP difference between the groups (132 mm Hg vs 154 mm Hg), suggesting that the improvement in medication adherence was sustained in the intervention group [26].

Investigation on this topic has dramatically increased. A 2017 review of medication adherence intervention trials performed in solid organ transplant recipients identified 21 randomized controlled trials (RCTs), with 15 involving kidney transplant recipients. Two of the studies identified were our 3-month RCT [25] and the subsequent 12-month post trial follow-up study [27]. Intervention approaches in kidney transplant recipient studies varied widely and included cognitive behavioral therapy aimed at improving medication adherence [28,29]; psychoeducation [30]; intensified pharmaceutical care [31]; financial assistance programs [32]; electronic monitoring and reminders [33-35]; and our mHealth system that provides reminders, tracks medication taking, and delivers tailored motivational/social reinforcement messages based on the level of adherence.

Although approximately half of these RCTs involving kidney transplant recipients demonstrated a significant improvement in medication adherence, and the methodologies and measures of adherence varied widely. Most either did not examine drug blood levels or could not demonstrate an improvement in the examined levels related to medication(s) taken. None of the five RCTs in kidney transplant recipients that examined transplant outcomes (ie, estimated glomerular filtration rate [eGFR], graft rejection, graft survival, and serum creatinine) demonstrated significant improvement. None of these RCTs lasted >12 months, and the incidence rates of rejection and other relevant parameters were too infrequent to allow comparisons. Importantly, although poorly controlled hypertension is highly prevalent (70%-93%) [8,10,11] and a leading contributor to posttransplant reductions in kidney function, changes in associated physiological function (eg, BP) were not measured in any RCT except ours [26].

The authors concluded that research on medication adherence programs in the transplant population is misguided in that it often does not include patients verified as having poor medication adherence, lacks the use of programs that are engaging and foster sustained regimen adherence, and does not evaluate clinically relevant transplant-specific outcomes. Our work has addressed several of these issues including identification and recruitment of kidney transplant recipients with verified poor medication adherence using multiple indices. We chose to employ a two-part screening process including BP measurement and one-time medication adherence via medication possession ratio screening followed by a 1-month screening to determine medication nonadherence via a Bluetooth-enabled electronic pill box with audio and visual alerts disabled. In a

pilot study, we found that 70% of otherwise eligible kidney transplant recipients were medication nonadherent [25], and thus far, we have identified a higher (~82%) proportion of such recipients in this RCT. Although medication nonadherence is on a continuum, it has been well demonstrated that even small degrees of medication nonadherence have negative effects on kidney transplant recipient outcomes [16-18]. We have employed a patient-centered, theory-guided, iterative design process to develop a medical regimen self-management program aimed at fostering self-efficacy and autonomous motivation to help ensure regimen adherence is sustained. In light of the expense and length of follow-up necessary to demonstrate significant clinical outcome improvements (eg, reduced acute rejection, graft loss, and death), we have adopted a strategy to investigate surrogate markers that are shown to be strongly predictive of worsened long-term outcomes (ie, BP and percent coefficient of variation [%cv]) [36-44]. A recent review of the literature on hypertension management in kidney transplant recipients concluded that posttransplant hypertension is prevalent (70%-90%), multifactorial, and rarely controlled (~33%) [8]. Specifically, among kidney transplant recipients at our transplant center, we found the prevalence of hypertension to be 95%, with only 34% having met the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for hypertension control at a mean follow-up of 7.3 (SD 4.5) years after transplant [45]. Uncontrolled hypertension remains a significant problem in kidney transplant recipients; thus, efficacious intervention programs are warranted.

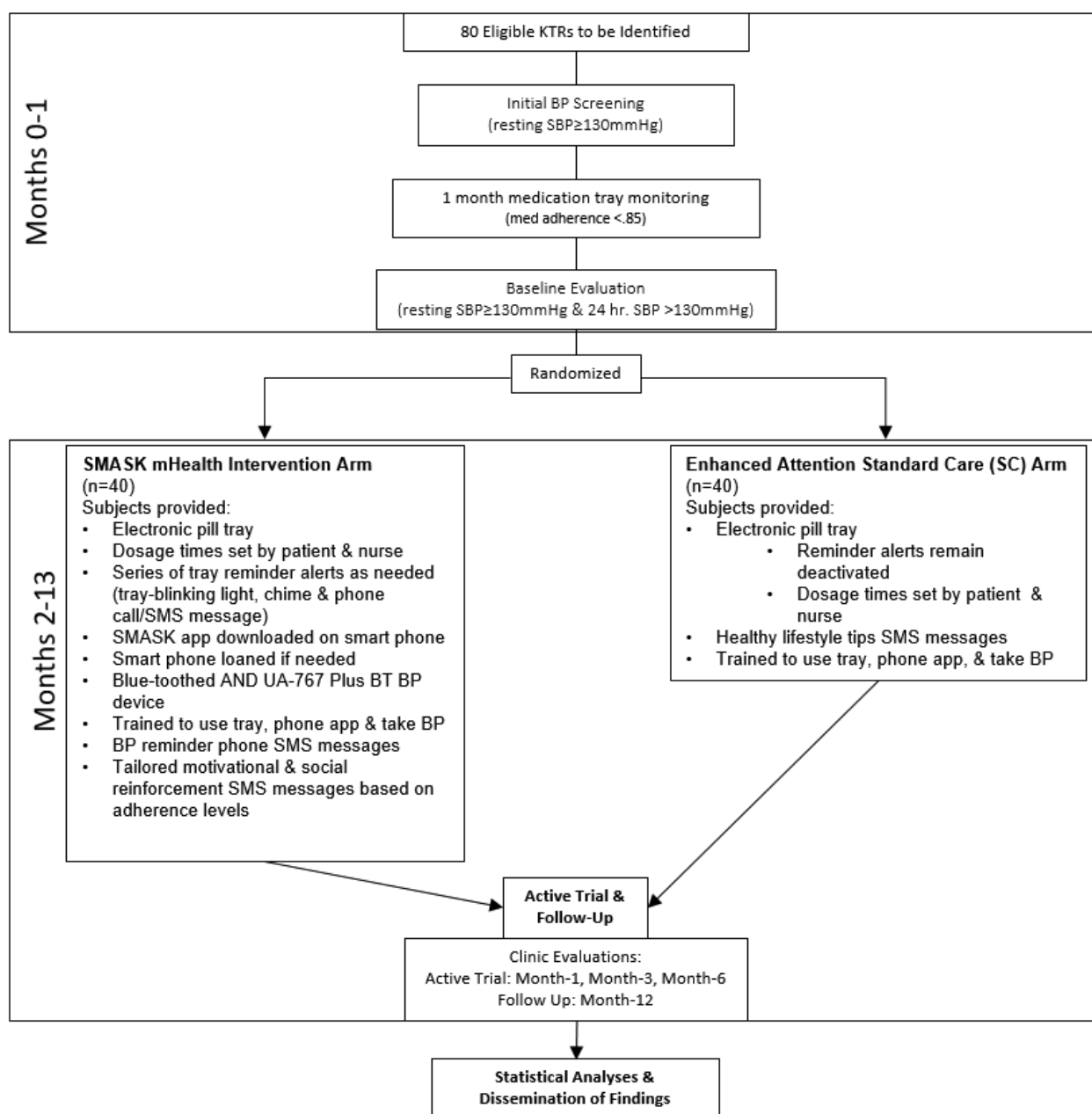
This paper describes a 6-month efficacy RCT with a 6-month posttrial follow-up, utilizing a further refined SMASK mHealth system in kidney transplant recipients verified to be medication nonadherent with poorly controlled hypertension. The aims of this study are twofold: (1) to assess the efficacy of our mHealth system for monitoring and enhancing medication adherence and BP control during the 6-month active trial and the 6-month post-trial follow-up period and (2) to evaluate provider adherence to BP management guidelines and changes in participants' levels of self-efficacy and autonomous motivation to sustain engagement in the medical regimen over time. Exploratory outcome variables will include changes in eGFR and variability of calcineurin inhibitor (CNI) trough levels (%cv).

Methods

Trial Design

This is a two-arm, phase II efficacy RCT involving 80 kidney transplant recipients with poor medication adherence and uncontrolled hypertension, with subjects as the unit of randomization (ClinicalTrials.gov: NCT02827695). Each of the subjects was recruited and randomly assigned to the intervention or control arm by a statistician (who is not involved in subject recruitment or data collection) using a computer-generated random sequence. A flow chart of the study design is presented in [Figure 1](#).

Figure 1. SMASK clinical trial flowchart. SMASK: Smartphone Medication Adherence Saves Kidneys; SBP: systolic blood pressure; BP: blood pressure; SMS: short message service; KTR: kidney transplant recipient.



Study Setting

This study is conducted at the Medical University of South Carolina (MUSC) in the Kidney Transplant Clinic. MUSC is a tertiary referral academic center in Charleston, SC, and the only transplant center in the state.

Study Participants

The participants are adult kidney transplant recipients with uncontrolled hypertension who have met the inclusion/exclusion criteria. Potentially eligible study patients were identified through weekly data extractions from the appointment database.

The inclusion criteria for participants were age > 18 years (male or female), first- or second-time recipient of a functioning solitary kidney transplantation performed 6 weeks to 60 months earlier, legally competent, assent provided by the transplant

physician so that the patient is able to participate, patient prescribed ≥ 3 medications for immunosuppression and hypertension, electronic pill tray-based medication adherence score < 0.85 across a 1-month screening period, uncontrolled systolic hypertension (SBP ≥ 130 mm Hg) at the screening visit and baseline evaluation (following 1-month medication monitoring period), and 24-hour ambulatory SBP ≥ 130 mm Hg following the medication monitoring period.

The exclusion criteria were severe cognitive impairment/dementia; inability to self-administer medications, self-measure BP, or use a mobile phone; poor cellular coverage at home; inability to speak, hear, or understand English; history of psychiatric illness or substance abuse; planned pregnancy; and vulnerable populations such as pregnant or nursing women, prisoners, and institutionalized individuals.

Prototype of the Mobile Health Smartphone Medication Adherence Saves Kidneys System

The SMASK mHealth system characterized in [Figure 2](#) consists of a wireless global system for mobile communication electronic medication tray (Vaica, Tel Aviv, Israel), a wireless validated Bluetooth low energy-enabled BP monitor (UA-767 Plus BT device [46]), and a smartphone (Android running Lollipop or newer operating system or iPhone 4 or newer). The medication tray plugs into an ordinary 110 V outlet, has 28 compartments (up to 4 doses per day for 7 days), time stamps compartment use, and is capable of providing reminder signals. At the prescribed dosing day and time, a blinking blue light is activated. If, after 30 minutes, the compartment lid has not been opened and closed, a loud intermittent chime automatically activates for 30 minutes. If, at the end of those 30 minutes, the compartment lid still has not been opened, an automated reminder phone call or SMS is delivered to the subject's mobile phone. Microelectronic circuitry in each compartment on the tray date and time stamps the opening of the compartment lid. These signals are relayed via an internal modem to the Viaca server for processing. Data will then be sent directly to a HIPAA (Health Insurance Portability and Accountability Act of 1996)-compliant relational database housed at MUSC. Personalized motivational and positive reinforcement SMS messages will be automatically delivered initially based on the previous day's calculated medication adherence. After 2 consecutive weeks of a calculated adherence score of 1.0, message delivery will be tapered from daily to several times per week on a 3-day average variable interval schedule. The schedule will revert to daily delivery when and if a subject's calculated weekly adherence score is <0.9. The library of motivational/social reinforcement SMS messages was developed by enhancing the library of messages used in the earlier mHealth medication adherence studies [25,26]. This step was guided by underlying tenants of competency (akin to self-efficacy) and autonomous motivation from the self-determination theory [47,48], tailored to the subject based on their responses to a

questionnaire designed to identify underlying motivating themes for consistently engaging in the medical regimen.

Participants will be sent SMS messages every 3 days as a reminder to measure their BP with the Bluetooth-enabled A&D UA-767 Plus BP monitor (A&D Medical, San Jose, CA). They will be instructed to measure their BP in the morning and evening every third day by using our resting BP protocol (described under Clinic Resting Blood Pressure). They will also receive a tailored positive reinforcement SMS message the day after successful completion of their BP measurements. An app will be installed on their smartphone, which will securely receive and transmit the BP data to the MUSC-housed server. The app will also provide text instructions throughout the BP protocol and a video clip module demonstrating use of the app and the BP monitor.

A weekly SMASK dashboard summary report, tailored to the treating physician's preferences, will be delivered via email ([Figure 3](#)). The report will summarize each subject's medication adherence and adherence to the BP self-monitoring schedule for the prior 2 weeks. Color coding will be used to indicate where the subject lies relative to the desired goals (ie, SBP <130 mm Hg and adherence score >0.90). In addition, a breakdown of the BP readings obtained over the 2 weeks will be provided with systolic and diastolic pressures. The treating physician will make adjustments to the medical regimen, as indicated and guided by the KDIGO guidelines [49]. The physician will notify the study coordinator of the changes via email. Any medication changes made by the treating physician will be mirrored in the programming of the medication tray after the study coordinator confirms with the patient that the changes have been enacted. The research manager and staff will be contacted via email, and the SMASK participants will be contacted via their preferred mode (SMS, email, or phone) when they fail to measure BP or when the measured BP is outside of the threshold ranges established by the treating physician, or they will be contacted via an SMS text when the SimpleMed+ tray identifies lack of medication adherence.

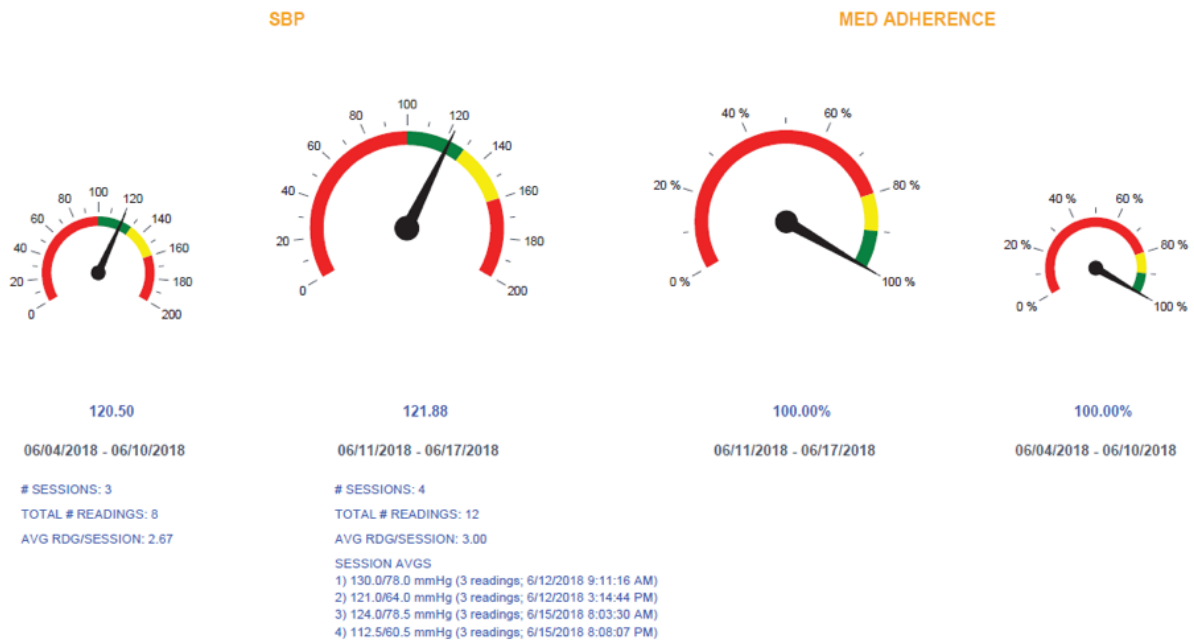
Figure 2. “Smartphone Medication Adherence Saves Kidneys” schematic.



Figure 3. Example of a “Smartphone Medication Adherence Saves Kidneys” participant’s weekly summary report to the provider. AVG RDG: average reading, SBP: systolic blood pressure; BP: blood pressure; MRN: medical record number.

Subject: 700.###

Experimental MRN: #####



BP Meds:
Amlodipine 10 mg daily
Carvedilol 6.25 mg BID

Calculation of Adherence Score

A detailed description of the medication adherence score calculation by Russell et al is available elsewhere [50]. We will employ a modification of the algorithm to allow for dosing schedules other than the twice daily schedule. Our subjects will be instructed that to be considered fully adherent, their medications have to be taken within a 3-hour window of the prescribed dosing time. A dose taken within the 3-hour window will be assigned a full score for that dosing time, a dose taken outside the 3-hour window but within a 6-hour window will be assigned a half score for that dosing time, and a missed dose will be assigned a score of 0. Each subject will be assigned a score from 0.0 to 1.0 for each day. The scores for each subject will be averaged over each week.

Identification of Medication Nonadherent Patients with Uncontrolled Hypertension

Patients who meet the initial eligibility criteria, including a resting BP evaluation (SBP \geq 130 mm Hg), and provide informed consent will be enrolled in a 30-day screening period using the SimpleMed+ with its reminder functions disabled. Subjects will be given a demonstration of how to properly use the medication tray and will be required to demonstrate successful use of the tray before completion of the visit. They will receive written and oral instructions explaining that to be considered fully adherent, they must take their medications within 90 minutes of the prescribed dosing time. After confirming successful connection with the server, the tray will be programmed by the study manager to accurately reflect the subjects' medication dosing schedule. At the conclusion of the 1-month screening period, our modification [25] of the adherence equation by Russell et al will be used to calculate a medication adherence score for each subject. Only subjects with a cumulative adherence score $<$ 0.85 across the 1-month screening period will be eligible for randomization to either the mHealth intervention group or the attention control SC group.

Attention Control Standard Care Group

The enhanced attention control SC group will receive SC at the MUSC Kidney Transplant clinic. SC includes clinic visits as deemed appropriate, education on all matters related to posttransplantation medical care, and 24-hour phone availability of transplant coordinators. Participants randomized to the SC group will continue to use their SimpleMed+ medication tray, with its reminder functions still disabled, for an additional 6 months. To control for attention exposure, the subjects in the SC group will receive SMS messages on health-related topics

excluding medication adherence. These messages include healthy lifestyle tips related to physical activity, dietary intake, nonexposure to first- or second-hand smoke, and limited alcohol intake. The SMS messages will be delivered every 3 days to approximate the schedule of the mHealth intervention group. SMS messages will include links to video or PDF content that require 3-5 minutes to review.

Mobile Health Intervention

The participants randomized to the intervention arm will receive the SMASK mHealth system, described in detail above, for the 6-month active trial. Subjects will be provided and instructed on use of the previously validated A&D BP device, and the SMASK app will be installed on their smartphone. The escalating reminder functions of the SimpleMed+ will be enabled. The SMASK subjects will again receive written and oral instructions on adherence criteria (ie, all medications are to be taken within a 180-min window centered on the dosing time; BP is to be measured every 3 days).

SMASK subjects will complete a questionnaire on beliefs, values, and life goals with the responses used in a tree-structured algorithm to generate tailored motivational and positive reinforcement messages that are delivered to promote self-efficacy for medication adherence and autonomous regulation for sustained behavior change.

A technical support phone number will be provided in several forms (paper copy, refrigerator magnet, and SMASK app) for assistance. At the conclusion of the study, subjects will return the SimpleMed+, A&D BP monitor, and smartphone (if one was borrowed) and complete a brief questionnaire assessing their opinions of the mHealth system.

Active Trial Evaluations and Follow-Up Phase

All subjects will be followed up for an additional 6 months following the 6-month active trial. Patients will continue to attend the clinic at a frequency determined by the provider. At 1, 3, 6, and 12 months after randomization into the SMASK or SC group, subjects will be assessed on medication adherence using medication possession ratio checks, clinic resting BPs, and completion of a brief set of questionnaires including measures to assess self-determination theory tenants of autonomous self-regulation and self-efficacy (Table 1). Providers are assessed on adherence to BP management protocols and goals. The timeliness and appropriateness of medication changes will be evaluated according to KDIGO guidelines across both groups at the conclusion of the study.

Table 1. List of measures and evaluation time points.

Outcome variables	Measurements/instruments used	Screening	Baseline	1 month	3 months	6 months	12 months
Primary outcomes							
Medication adherence	Vaica (time-stamped)	✓	✓	✓	✓	✓	
BP ^a	Clinic resting SBP ^b	✓	✓	✓	✓	✓	✓
Secondary outcomes							
Therapeutic Inertia	Provider adherence to KDIGO ^c goals: Timely medication changes (date of medication change following medication adherence) and BP feedback (biweekly SMASK ^d reports for SMASK participants) and from clinic visits for all subjects (Figure 2)	Weekly ^e	Weekly ^e	Weekly ^e	Weekly ^e	Weekly ^e	Weekly ^e
Self Determination Theory Constructs	TSRQ ^f autonomous self-regulation [51,52] ($\alpha=0.81-0.84$; correlation with GCOS ^g : $r=0.38$, $P<.001$; correlation with HCCQ ^h : $r=0.38$, $P<.001$), weight loss attendance ($r=0.34$, $P<.001$), body mass index ($r=-0.11$, $P<.05$), 18-month test-retest autonomous ($r=0.47$), controlled items ($r_s=0.34$) [53], correlation with medication adherence ($r=0.58$, $P<.001$) [54]	✓			✓	✓	✓
Exploratory outcomes							
eGFR ⁱ	GFR ^j estimation equations [55,56]	✓	✓	✓	✓	✓	✓
Ambulatory BP	24-h ambulatory BP with SpaceLabs 90207		✓			✓	✓
Methodological parameters							
	Recruitment and retention rates: patient/provider satisfaction and usefulness scale (TSUQ ^k) [57] (satisfaction: $\alpha=0.96$; usefulness: $\alpha=0.92$; 1-week test-retest $r=0.98$ [58])					✓	
	Fidelity checklists: patient level (eg, connection/reloads of Vaica, BP uploads via phone, and opening of messages/education information) and provider level (eg, opening of patient summary reports and phone alerts)						
Ancillary medication adherence measures	Medication possession rate	✓	✓	✓	✓	✓	✓
Potential moderators/mediators							
Demographics	Age, education level, income, type of health care insurance	✓		✓	✓	✓	✓
Anthropometrics	Height, weight, girth	✓	✓	✓	✓	✓	✓
Health literacy	Health Literacy Scale [59-62], correlated with short test of functional health literacy in adults. Three questions compared to those in the Short Test of Functional Health Literacy in Adults to detect inadequate health literacy: areas under the receiver operating characteristic curve were 0.76, 0.80, and 0.87. When correlated with Short Form-36 ($r=0.86-0.87$), it differentiates between healthy status and various types of illnesses (eg, migraine vs healthy using components: physical and mental quality of life; all $P<.001$)	✓					
Adverse events							

Outcome variables	Measurements/instruments used	Screening	Baseline	1 month	3 months	6 months	12 months
Medication Side Effects Scale [63,64]	✓	✓	✓	✓	✓	✓	
Hypertension/immunosuppression knowledge [59,65] ($\alpha=0.70$, high-low correlation: $P<.01$)	✓						
Short Form-8 ($\alpha=0.87$)	✓	✓	✓	✓	✓	✓	
Perceived Stress Scale ($\alpha=0.84-0.86$; 2-day test-retest $r=0.85$) [64]	✓	✓	✓	✓	✓	✓	

^aBP: blood pressure.

^bSBP: systolic blood pressure.

^cKDIGO: Kidney Disease Improving Global Outcomes.

^dSMASK: Smartphone Medication Adherence Saves Kidneys.

^eWeekly SMASK reports and from clinic visits for all subjects.

^fTSRQ: Treatment Self-Regulation Questionnaire.

^gGCOS: General Causality Orientations Scale.

^hHCCQ: Health Care Communication Questionnaire.

ⁱeGFR: estimated glomerular filtration rate.

^jGFR: glomerular filtration rate.

^kTSUQ: Telemedicine Satisfaction and Usefulness Questionnaire.

Clinic Resting Blood Pressure

BP evaluations will be conducted at enrollment; randomization; and 1, 3, 6, and 12 months. Patients will be seated upright with right arm resting on a table at heart level and a proper cuff size will be fitted. A Dinamap Pro-Care 200 BP device (GE Healthcare, Buckinghamshire, United Kingdom) will be used to take the clinic BP measurements. The Dinamap has been validated following standard auscultatory methods from the British Hypertension Society and the Association for Advancement of Medical Instrumentation [66]. The Dinamap, as well as all other BP devices used in the trial, are calibrated according to the manufacturers' specifications. A reading will be taken immediately, after 5 minutes of rest, and following a 2-minute interval. The average of the last two readings will be used in the analyses. Subjects in the SMASK group will use the same protocol (ie, a series of 3 BP readings with 5 and 2 minutes in between the first and second readings and between the second and third readings, respectively) at home for BP self-monitoring. This functionality will be embedded within the SMASK app and automatically guide the participants through the protocol with audio guides, timer count downs, and chimes when each waiting period is complete.

Outcome Measures

Primary Outcome Measures

These include proportion of participants achieving success in meeting and sustaining adherence to the KDIGO guidelines for SBP control (resting SBP <130 mm Hg) and proportion of participants meeting and sustaining monthly medication adherence scores >0.90.

Secondary Outcome Measures

These include provider adherence to KDIGO guidelines, as measured by the appropriateness and timeliness of BP medication changes, and subjects' self-report of changes in self-determination theory tenants (ie, self-efficacy and autonomous motivation).

Exploratory Outcome Measures

These will include changes in estimated glomerular filtration rate (eGFR) and variability of CNI trough levels (%cv). CNIs have a well-described high inter- and inpatient variability as well as a narrow therapeutic index. For these reasons, among others, therapeutic drug monitoring of CNI is the standard of care in solid organ transplantation and guides all CNI titrations [67,68]. Changes in the 24-hour ambulatory BP will also be examined.

Participant Timeline

A timeline for participant recruitment, intervention, and follow-up assessments is shown in Figure 1.

Proposed Sample Size

To evaluate SMASK treatment efficacy, 80 patients will be recruited and randomly assigned to either SMASK or SC. The primary outcomes of aim 1 include the proportion of patients with >0.90 medication adherence scores (based on the date/time stamped scores from the electronic trays) and proportion of patients meeting and sustaining adherence the KDIGO guidelines for clinic-based SBP control (<130 mm Hg). In intent-to-treat (ITT) analysis, with 40 patients per group, a two-sided Chi-square test ($\alpha=0.05$) will have >90% power to detect a difference of 35% in proportions of those who are

medication adherent (or meeting and sustaining adherence to the KDIGO BP guidelines) in the SMASK group compared to those in the SC group at the 3-month time point. A difference of 35% in medication adherence between the groups would be considered clinically relevant and warrant changes in clinical practice. Conservative estimates for medication adherence and expected BP control proportions will be used for power calculations. This approach was taken with a small pilot study, and CIs on effect sizes were quite large. Medication adherence observed in the SMASK 3-month feasibility study was 89% (versus 0% in control group; N=19). For the clinic resting BP control, we observed that 90% versus 10% of the participants controlled BP in the SMASK and control groups, respectively. Overall attrition was 10% in the intervention group [69].

Recruitment

Eligible patients were identified from hospital medical records by a research assistant. A research coordinator approached potential subjects in the kidney transplant clinic and obtained voluntary informed consent from patients who were interested in participating. After obtaining informed consent, the clinic resting BP protocol was conducted (see Clinic Resting Blood Pressure) and if SBP \geq 130 mm Hg, the subject completed a set of questionnaires (Table 1) and was instructed to wear a SpaceLabs 90207 ambulatory BP monitor (SpaceLabs, Inc, Issaquah, WA) for 24 hours. The subject then began the 1-month screening period, as described above. The study site performs approximately 20 kidney transplants per month. We provide a smartphone and an internet data plan for the SMASK subjects who do not own a smartphone compatible with the SMASK app.

Allocation and Concealment

Subject randomization will be stratified by race and gender and will be conducted by a statistician using a computer-generated random sequence of numbers. Participants who consent to the study and are eligible for randomization at the conclusion of the 1-month medication intake screening period are allocated to either the intervention (SMASK) or SC arm using the computer-generated randomization sequence. Each random sequence is kept concealed in an envelope that is opened by the research coordinator at the time of randomization.

Blinding

The research assistants responsible for assessing primary and secondary outcomes will remain blinded to the patients' group assignment throughout the study. The physician responsible for making clinical management decisions for those in the SMASK intervention arm will remain blinded to which patients are enrolled in the trial as enhanced attention SC subjects, as they are merely providing SC. However, the participants will not be blinded to their group assignment, as we provide a BP monitor and smartphone as needed to those in the intervention group.

Data Collection and Management

Instruments for data collection are listed in Table 1. Data captured electronically will be transmitted using secure encrypted algorithms and housed on site in a secure HIPAA-compliant relational database.

Statistical Analyses

Primary Outcome Measures

The ITT analysis set will be determined in accordance with the International Conference on Harmonization E9 Guideline "Statistical Principles for Clinical Trials" [70] and will include all randomized subjects. For all subjects included in the ITT analysis set, all available data points will be included in the model. We chose a mixed-effects model approach because this method is a standard method in RCTs and can handle missing data and account for correlated data such as repeated measurements within patients or patients clustered within providers [71-73].

We propose a two-level analysis strategy: Our primary analysis will include the simple mixed-effects model containing the fixed time and intervention group, time, and time-by-intervention as primary independent variables (fixed effects) and MD as a random effect to account for clustering. The main analysis will compare the two intervention groups (SMASK vs SC) at the primary time point outcome at 3 months. We will estimate medication adherence score changes and changes in resting and 24-hour BP for each subject over the trial (preintervention and 1, 3, 6, and 12 months) and the within-subject longitudinal trajectories (eg, slopes) and summarize the mean longitudinal trajectory within each group. Intraclass correlations and variance estimates will be obtained for the efficacy outcomes and covariance structure of the longitudinal scores to determine the sample size (and hence adequate power) for a future effectiveness RCT.

In secondary/exploratory analysis for aim 1 outcomes, the potential influence of *a priori* specified covariates on these models will be explored, including self-determination theory tenants, demographic and clinical characteristics, and comorbidities. In an additional exploratory analysis, effect modifications of covariates will be examined through inclusion of covariate-by-group interaction terms in the multivariable models.

Secondary Outcome Measures

Secondary outcome measures of changes in self-determination theory tenants (self-efficacy and autonomous self-regulation) and provider adherence to KDIGO guidelines (timing of medication changes) will be investigated using mixed effects models with these outcomes as separate dependent variables, group (SMASK vs SC) as primary independent variable, and the primary outcomes (medication adherence and clinic SBP) and clinical and demographic characteristics as adjustment variables.

Exploratory Outcomes Measures

In exploratory analyses, change in eGFR, variability of calcineurin trough levels, and 24-hour ambulatory BP will be compared between the two groups using pooled *t* tests (or nonparametric tests, as appropriate). If the end-of study outcomes for eGFR and 24-hour BP are missing, they will be imputed using multiple imputation methods. Further, frequency distributions of adverse events and serious adverse events will

be determined, and proportions for the SMASK versus SC groups will be compared using Chi-square analyses.

Qualitative Studies

After the conclusion of the 6-month active trial evaluation, each member of the SMASK group will be approached to participate in a key informant interview of “lived experiences” during the trial. Topic areas with probes will cover expectations, experiences, adherence, motivation, and advice from family and friends. The SMASK lead physician, the transplant nurse coordinator, and other involved staff will be invited to participate in individual interviews to assess the SMASK program from the providers’ point of view. Topics of assessment will include attitudes, barriers and facilitators for use, fidelity, and impact on therapeutic inertia. We will use the constant comparative method of qualitative analysis to code the interviews’ transcript data using NVivo 10.0. Transcripts will be independently reviewed and coded by two reviewers. Once no new themes emerge, thematic saturation will have been reached. We will compare/contrast themes from participants and providers. We will synthesize and integrate the multiple quantitative and qualitative data sources using a triangulation approach. These collective findings will guide further refinements in the SMASK system prior to our efforts to acquire external funding to enable a multisite effectiveness RCT.

Results

The SMASK project received funding from NIDDK in June 2016, obtained institutional review board approval in April 2016, and began data collection in July 2016. As of July 2018, we have completed enrollment with a total sample size of 80 participants. Currently, we are analyzing baseline data and upon completion of analysis of the final participant in the 6-month active trial, we will begin analyzing preliminary data to be submitted for peer-review publication.

Approval for important protocol modifications will be sought from the institutional review board. Written informed consent was obtained from all patients before enrollment by a trained research coordinator. There are no anticipated risks associated with participation in the study. Patients are free to withdraw at any time. Data will be kept confidential and anonymized for analyses.

Discussion

Despite evidence that medication nonadherence is a major contributor to suboptimal outcomes in kidney transplantation, little progress has been made toward improving medication adherence. To date, research aimed at improving medication adherence in this patient population has been hampered by the use of convenience samples, indirect measures of medication adherence, and ineffective strategies. We aim to address some of these shortcomings in this trial. mHealth technology offers an opportunity to unobtrusively monitor patients, to react in real time to indicators of patient nonadherence, and to tailor the intervention to foster likelihood of sustained adherence to the

regimen. Our previous research suggests that the use of an mHealth intervention in this patient population is promising.

This study is novel in both in its design and implementation. To our knowledge, this is the first RCT involving kidney transplant recipients that aimed to evaluate the efficacy of an mHealth medical regimen self-management system (SMASK), which was developed using an iterative design process guided by synergistic tenants from behavioral and technology application theories and direct guidance from kidney transplant recipients, transplant physicians, and associated health care team members. Importantly, the SMASK program utilizes timely regimen reminder tactics with immediate feedback of the results to the patient and real-time relay of patients’ regimen engagement to a HIPPA-compliant server. This allows for the use of automated, patient-tailored, motivational, and social reinforcement messages framed upon their degree of adherence. Importantly, the health care provider is intimately involved via weekly tailored emailed subject summary reports that allow more timely medical management decisions aimed at improved medication adherence, earlier BP control, and avoidance of unnecessary escalation of care. Collectively, these strategies are directed at enhancing patients’ self-efficacy to perform the medical regimen behaviors and improving the levels of autonomous, self-directed motivation to sustain these behaviors across time with the ultimate aim of improving long-term graft survival.

There are several limitations to this study that need to be addressed. First, although the study recruits from a single transplant center, limiting its generalizability, the center is the sole transplant provider for the state of South Carolina and has a catchment population of over 4.6 million persons that encompass a wide range of ethnic, educational, and socioeconomic backgrounds. Second, while it cannot be assumed that the subjects’ willingness to use the SMASK system can be divorced entirely from the appeal of the financial compensation, we targeted the compensation at a level that would only cover the inconvenience and cost of otherwise unnecessary travel and time spent waiting. Finally, while the current study duration of only 12 months is long enough to demonstrate improvements in medication adherence and BP control, it will not be long enough to demonstrate significant improvements in graft function or graft survival. However, these outcomes will be the focus of subsequent longitudinal studies, and participants in this study will be asked to continue providing relevant data to assess longer-term outcomes.

In conclusion, this study will provide important and novel data regarding the efficacy of the mHealth SMASK system to improve medication adherence and BP control in a medication-nonadherent cohort of uncontrolled hypertensive kidney transplant recipients. An efficacious SMASK intervention would lead to a larger, multicenter, effectiveness RCT powered to evaluate clinical events in a real-world setting and with the potential to demonstrate improved outcomes at lower cost than the standard of care.

Acknowledgments

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Authors' Contributions

JM, FT, LN, MM, and PB conceived the study. JM, JC, LS, and FT drafted the manuscript. JM, FT, LN, MM, and JC critically reviewed the manuscript. All authors read and approved the final submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1

National Institutes of Health (NIH) peer-review reports.

[[PDF File \(Adobe PDF File\), 127KB - resprot_v8i6e13351_app1.pdf](#)]

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Abbreviations

- CNI:** calcineurin inhibitor
 - cv:** coefficient of variation
 - eGFR:** estimated glomerular filtration rate
 - ESRD:** end-stage renal disease
 - HIPAA:** Health Insurance Portability and Accountability Act
 - ITT:** intent to treat
 - KDIGO:** Kidney Disease Improving Global Outcomes
 - mHealth:** mobile health
 - MUSC:** Medical University of South Carolina
 - NIDDK:** National Institute of Diabetes and Digestive and Kidney Diseases
 - SBP:** systolic blood pressure
 - SC:** standard care
 - SMASK:** Smartphone Medication Adherence Saves Kidneys
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Original Paper

iCanCope With Pain: Cultural Adaptation and Usability Testing of a Self-Management App for Adolescents With Persistent Pain in Norway

Erik Grasaas¹, MSc; Liv Fegran¹, PhD; Sølvi Helseth², PhD; Jennifer Stinson^{3,4,5}, PhD; Santiago Martinez¹, PhD; Chitra Laloo^{3,5}, PhD; Kristin Haraldstad¹, PhD

¹Department of Health and Nursing Science, Faculty of Health and Sport Sciences, University of Agder, Kristiansand, Norway

²Department of Nursing and Health Promotion, Faculty of Health Sciences, Oslo Metropolitan University, Oslo, Norway

³Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, ON, Canada

⁴Lawrence S Bloomberg Faculty of Nursing, University of Toronto, Toronto, ON, Canada

⁵Institute for Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada

Corresponding Author:

Erik Grasaas, MSc

Department of Health and Nursing Science

Faculty of Health and Sport Sciences

University of Agder

Universitetsveien 25

Kristiansand, 4630

Norway

Phone: 47 97524422

Email: erik.grasaas@uia.no

Abstract

Background: Persistent or chronic pain is a common health problem among adolescents. Thus, it is important that they receive evidence-based strategies for symptom management. *iCanCope with Pain* is a mobile phone app designed to help adolescents cope with chronic pain. The app comprises 5 evidence- and theory-based features: (I) symptom trackers for pain, sleep, mood, physical function, and energy; (II) goal setting to improve pain and function; (III) a coping toolbox of pain self-management strategies; (IV) social support; and (V) age-appropriate pain education. The *iCanCope with Pain* app is based on theory, identified health care needs, and current best practices for pain self-management.

Objective: The objectives of this study were to describe the translation and cultural adaptation of the app into the Norwegian context and evaluate the app's usability using a phased approach.

Methods: Phase 1 included translation and cultural adaptation of the app into the Norwegian context. This process used an expert panel of researchers and target group representatives who were responsible for the linguistic quality assurance and assessment. In phases 2 and 3 the app's usability was tested. For phase 2, the assessments of usability and user experiences included observation, the think aloud method, audiovisual recordings, questionnaires, and individual interviews in a laboratory setting. For phase 3, the assessment of usability and user experience over a 2-week home-based test included questionnaires and individual end-user interviews. Overall, app usability was determined based on ease of use, efficiency, and user satisfaction. Qualitative data were analyzed using deductive content analysis. Descriptive statistics were calculated for quantitative data.

Results: End users did not report any misunderstandings or discrepancies with the words or phrasing of the translated and culturally adapted app. Participants in both the laboratory- and home-based usability tests found the app self-explanatory and reported that all 5 of its features were easy to use. All tasks were completed within the allocated time frame (ie, efficiency), with few errors. Overall System Usability Scale scores were high, with average scores of 82 and 89 out of 100 from laboratory- and field-based tests, respectively. Participants liked the idea of a social support function (feature IV), although qualitative and internet server data revealed that this feature was rarely used.

Conclusions: This study described the cultural and linguistic adaptation and usability testing of the Norwegian version of the *iCanCope with Pain* app. High user satisfaction, ease of use, efficiency, and only minor errors cumulatively indicated that no

changes to the app were needed, with the exception of facilitating user interaction within the social support feature. The app will be used in an upcoming randomized controlled trial with a larger sample.

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KEYWORDS

health; self-management; adolescent; chronic pain; translating; mobile app

Introduction

Background

The prevalence of persistent or chronic pain in nonclinical adolescent populations is increasing and has become recognized as a growing health problem [1-3]. Chronic pain is commonly defined as pain lasting more than 3 months [4]. Previous studies have revealed high prevalence rates (approximately 15% to 35% [5-7]) of chronic pain among adolescents, which increases with age and can negatively impact all aspects of their lives. The consequences include reduced health-related quality of life and physical activity and higher risk for psychosocial problems such as stress, anxiety, and depression [8-11]. Thus, interventions focused on coping and symptom management strategies are needed to prevent adolescents' pain conditions from continuing into their young adulthoods [12,13].

An increasing number of self-management interventions have been developed and are associated with reduced chronic pain among both children and adolescents [14]. Self-management interventions often comprise behavioral therapies and types of cognitive behavioral therapy (CBT), which may include coping skills training, imagery techniques, biofeedback, relaxation, and other symptom management strategies [15]. CBT is effective among chronic pain patients and is thus the preferred intervention for adolescents with different health disorders [16,17]. In their systematic review of the literature in this area, Fisher et al showed that self-management interventions are accessible through computer-based programs or mobile phone apps, and that such interventions may reduce chronic pain intensity among children and adolescents [15].

Adolescents are comfortable using computerized technologies and have reported that internet-delivered self-management interventions are their preferred methods for gaining information about chronic pain and pain coping skills [18,19]. However, many of the available Web-based interventions and apps have not undergone scientific evaluation. For instance, Lalloo et al [20] found a total of 279 apps that focused on pain self-management; only 8% of these had included health care professionals during their development and only 1 had undergone scientific evaluation. Thus, it is important to emphasize that adolescents should receive evidence-based content, including strategies to manage chronic pain conditions, from apps.

The iCanCope With Pain App

The *iCanCope with Pain* app is an evidence- and theory-based pain self-management app [21] that was developed by Dr

Stinson and Lalloo, in collaboration with the Centre for Global eHealth Innovation at University Health Network in Toronto, Canada. The app's content was developed by an interdisciplinary team of pediatric chronic pain experts and is based on empirically identified health care needs and current best practices for pain self-management [21]. The app is currently part of an ongoing randomized controlled trial and is thus not publicly available.

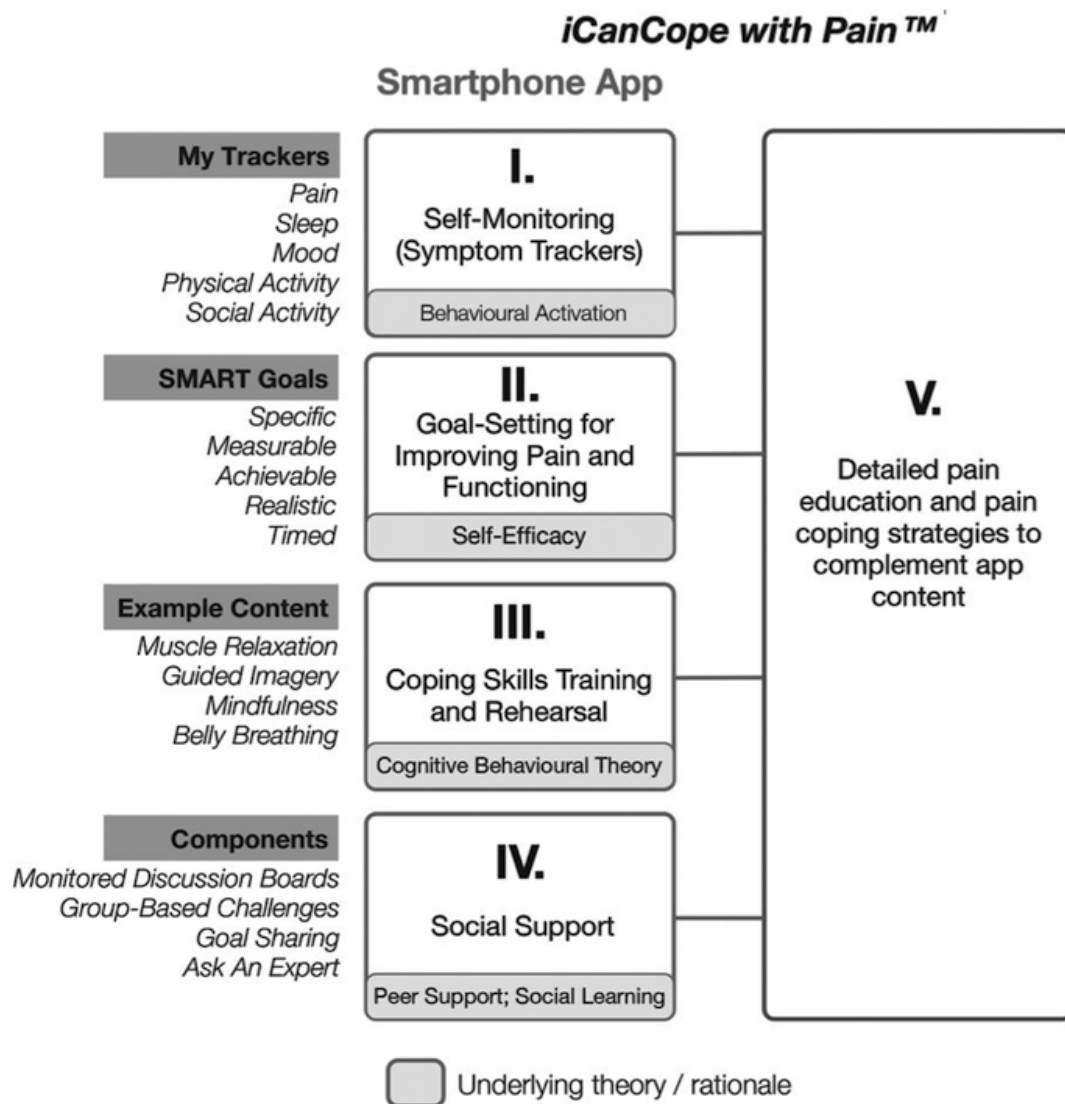
Theoretical Framework

The *iCanCope with Pain* app comprises 5 evidence- and theory-based features: (I) symptom trackers for pain, sleep, mood, physical function, and social function; (II) goal setting to improve pain and function; (III) a coping toolbox of pain self-management strategies; (IV) social support; and (V) age-appropriate pain education. Features I to IV were based on psychological theories and psychotherapies; component V is a pain education library (Figure 1).

Component I is based on behavioral activation therapy, which was originally developed to treat mood disorders and is efficacious for reinforcing engagement with, and motivation for, meaningful activity [22,23]. Allowing adolescents to track and self-monitor their daily symptoms in real time helps them to better recognize their pain patterns and set goals to improve their symptoms. It may also help them identify and be aware of their pain triggers; by tracking symptoms over time, adolescents can also monitor fluctuations in their pain [21,24]. My trackers are integrated as a daily check-in functionality in the app, wherein the adolescents can rate their level of pain intensity, pain interference, mood, physical activity, sleep quality, and energy.

Component II is based on social cognitive theory, originally called social learning theory developed by Albert Bandura, which has influenced our understanding of human behavior [25]. The theory suggests that adolescents' performance or behavior is influenced by their beliefs (cognition) and support by their peers, parents, and teachers. Bandura argues that self-efficacy is the most suitable approach to affecting cognition [26]. Self-efficacy refers to "how well one can execute courses of action required to deal with prospective situations" [27]. Thus, component II was designed to enhance self-efficacy and thereby improve pain and functioning [19]. The development of the app's goals feature was consistent with the SMART framework—specific, measurable, achievable, realistic, and timed [28,29]. Thorough formulation and evaluation of a goal is necessary for success; thus, this method provides a useful standardized tool for users to write and express their own goals in the app.

Figure 1. Conceptual framework showing the theories underlying the Norwegian iCanCope with Pain app for adolescents with persistent pain. Published as the original Canadian illustration. Source: Stinson et al. Used with permission by the original publishers [21].



Component III is based on CBT, with a focus on the interrelations among thoughts, feelings, and behaviors [30]. Consistent with this, adolescents can focus on developing personal coping strategies to solve current problems and change unhelpful cognitive patterns (eg, thoughts, beliefs, and attitudes), behaviors, and emotion regulation [30]. Thus, the aim of component III is personalized self-management instruction in terms of coping skills training and rehearsal, to promote positive changes in mood, behavior, and ultimately pain itself [21]. This component provides several coping strategies to manage pain, including muscle relaxation, guided imagery, mindfulness, and abdominal breathing. In other words, the CBT component of the app aims to provide pain management strategies that help adolescents during everyday life, despite their pain [31].

Component IV, social support, includes both quantitative (eg, number of friends) and subjective (eg, network appraisal) dimensions [32], both of which affect mental health, physical health, and mortality risk, and thus influence health throughout the lifespan [33]. Social support theory and peer support are strongly related to self-efficacy (component II) and healthy activities promotion [34]. Although numerous self-efficacy

promotion methods exist, Ashford et al's review [35] showed that vicarious experience (ie, social modeling) and feedback from peers (ie, peer support) are most effective. In the social support feature in the app, the adolescents receive *questions of the day* in monitored discussion boards. Finally, component V is a pain education library, which is integrated together with the coping skills training (component III) in the app.

The primary objectives of this paper are to describe the translation and cultural adaptation of the app into the Norwegian context and to evaluate its usability using a phased approach. The phased approach assessed the translated and culturally adapted app's usability and users' experiences with its ease of use, efficiency, satisfaction, and sociability. An additional objective was to identify the users' needs and technical issues, to refine the app for use in a planned prospective randomized controlled trial with a larger adolescent sample.

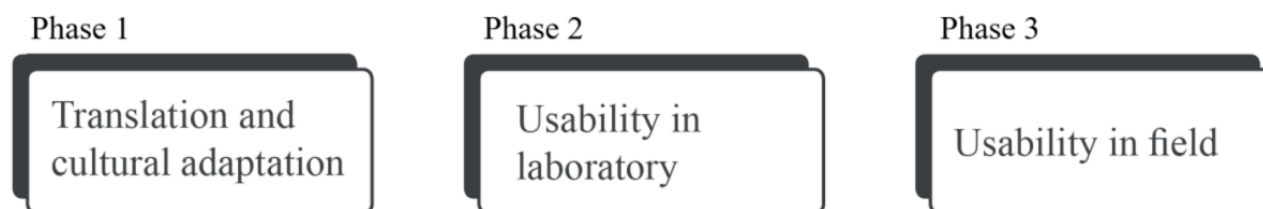
Methods

Design

During phase 1, the *iCanCope with Pain* app was translated and culturally adapted into the Norwegian language and cultural

context. This required a multistep approach, including input by an interdisciplinary group to ensure thorough translation and adaptation. During phases 2 and 3, the app's usability was evaluated. Phase 2 was conducted in a laboratory setting and phase 3 in participants' homes during a 2-week period. [Figure 2](#) illustrates the overall protocol.

Figure 2. Norwegian *iCanCope with Pain* app translation and usability testing.



Participants

Participants were recruited from a high school in Southern Norway. During phase 1, 2 representatives from the target group (both aged 17 years) participated to ensure that the app translation and cultural adaptation were appropriate for their age group. During phase 2, 6 adolescents (aged 17 to 18 years) were recruited for a laboratory-based usability test. During phase 3, 5 adolescents (aged 16 to 18 years) were recruited for a 2-week home-based test to evaluate user experiences with the app over time and to identify additional user needs. Both usability tests were gender-balanced and included users of both Android and iOS operating systems to best represent the target group for an upcoming clinical trial. The inclusion and exclusion criteria for the phase 3 end-user group were also consistent with those planned for the upcoming clinical trial. We included 16- to 19-year-old adolescents with persistent pain (weekly pain lasting 3 or more months based on subjective reporting) who were able to read and understand Norwegian and owned a mobile phone. Adolescents with cognitive disability or diseases were excluded because of their inability to correctly understand the *iCanCope with Pain* app, goal setting, or library readings. Adolescents with painful health conditions from a pathological or medical origin (eg, hematology/oncology patients) were excluded as the program was not specifically designed for these patient groups.

Phase 1: Translation and Cultural Adaptation

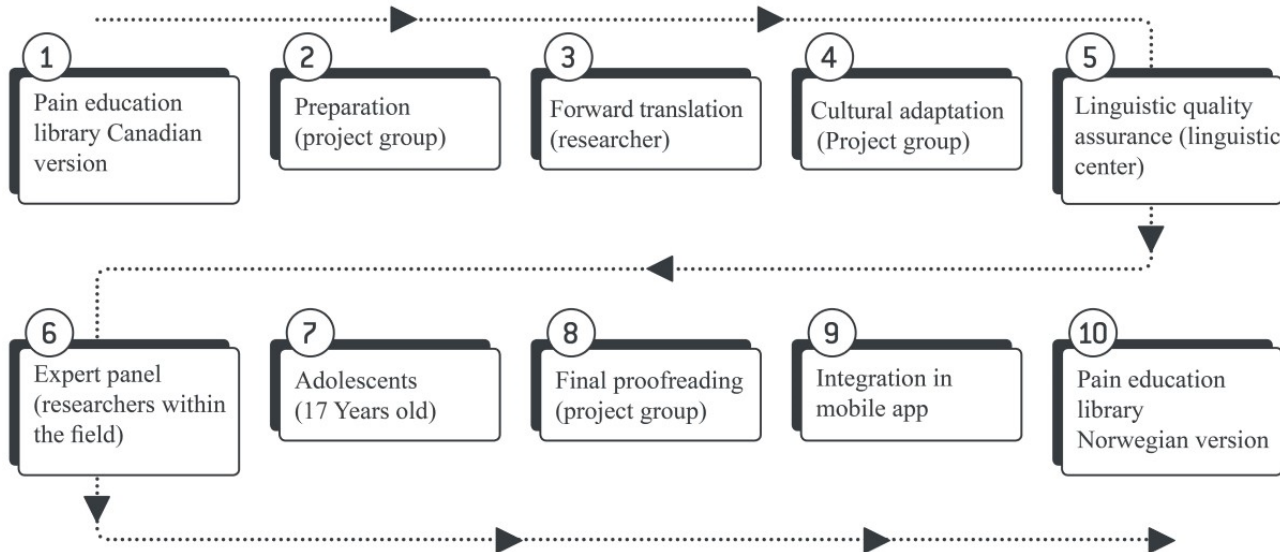
A 2-stage approach was used for language and cultural adaptation of the original Canadian *iCanCope with Pain* app

[21] to the Norwegian context, based on the principles of good practice for translation and cultural adaptation explained by Wild et al [36]. The first stage addressed the age-appropriate pain education library and the second stage addressed the software interface text of all features.

Pain Education Library

The first stage was a 10-step process to ensure quality translation and adaptation of the age-appropriate pain education library to a Norwegian context, as illustrated in [Figure 3](#). The first steps (1 to 4) were conducted by the project group and first author; these steps comprised preparation and forward-translation to Norwegian, followed by cultural adaptation, in which typical Canadian names, sports, and sayings were replaced with Norwegian versions (eg, dragon boat racing is not well-known in Norway). Quality assurance (step 5) was carried out by native Norwegian and English speakers at the linguistic service center at the University of Agder (UiA). In this step, the original Canadian English version was compared with the translated Norwegian version to assess linguistic equivalency and correct spelling. In addition, an expert panel of researchers within the field of pain ensured (step 6) that the 2 versions were conceptually equivalent. Furthermore, 2 adolescents assessed the pain education library (step 7) to ensure that its content was clear and easy to understand by their age group. A final proofreading (step 8) was conducted before formatting (step 9) each article in the pain education library as HTML to be added (step 10) to the Norwegian *iCanCope with Pain* app.

Figure 3. The 10 steps of translation and cultural adaptation of the iCanCope with Pain app’s pain education library.

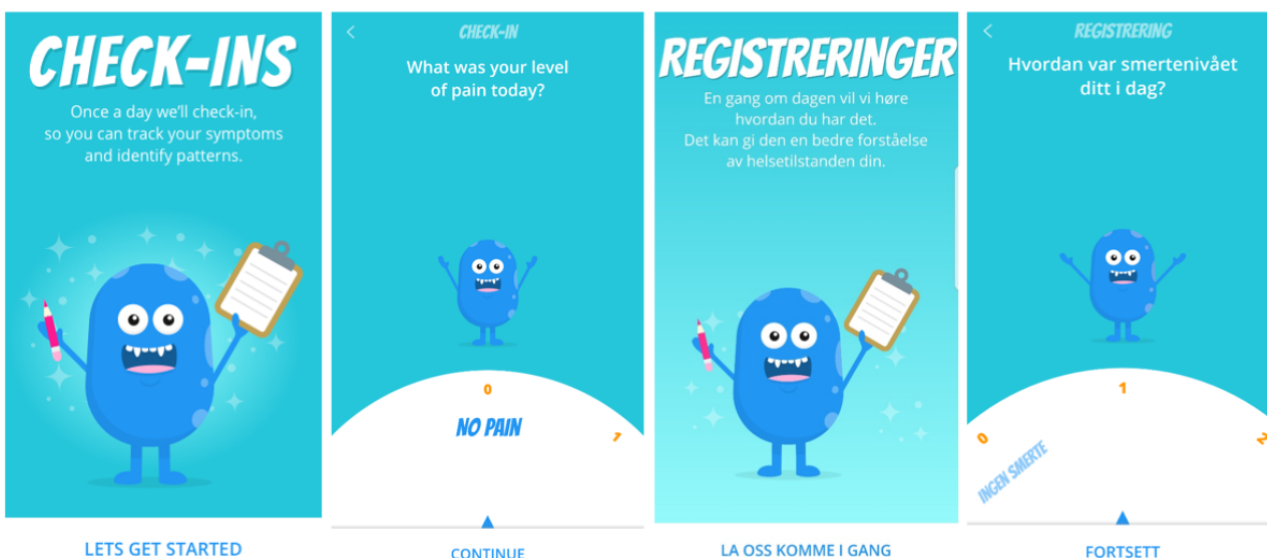


Software Interface Text

The second stage also followed the principles set forth by Wild et al to ensure credibility and understanding [36] and included another 10 steps: (step 1) preparation; (step 2) forward translation; (step 3) reconciliation; (step 4) back translation; (step 5) back translation review; (step 6) harmonization; (step 7) cognitive debriefing; (step 8) review of cognitive debriefing results and finalization; (step 9) proofreading; and (step 10) final report. The software interface text was prepared and translated into Norwegian by the authors (steps 1 and 2, respectively), then merged into a common version (step 3), and translated and validated back into English by personnel at the linguistic service center (steps 4 and 5, respectively). A

comparison of multiple language versions was not possible as the *iCanCope with Pain* app was only available in the Canadian English language of the original version (step 6). A cognitive debriefing was conducted with the end users after the usability field test (phase 3) to check its understandability and cultural relevance (step 7). Review of the cognitive debriefing, proofreading, and final report were assessed by the project group (steps 8, 9, and 10, respectively). The Norwegian software interface text was then integrated into the *iCanCope with Pain* app by the Centre for Global eHealth Innovation (Canada), with adjustments to user interface size and layout to accommodate different word lengths for various screen sizes and forms. See [Figure 4](#) for example comparisons of the Norwegian and Canadian software interfaces.

Figure 4. Screenshots of the Norwegian and Canadian user interface versions of the iCanCope with Pain app. Published with permission from the Centre for Global eHealth Innovation (Canada).



Phase 2: Usability Test in Laboratory Setting

Before the laboratory usability test, 2 pretests were used to assess the protocol, logistics, and technology, and to determine the amount of time the tests would take, the number of

participants needed, the number of tasks, and the level of app complexity. The 10 resulting predefined tasks had a stipulated time frame of approximately 1 min per task.

The task tests were carried out at the UiA laboratory facilities over 2 days with 6 adolescent participants. The laboratory facilities house control and test rooms are separated with a 1-way mirror (facility details have been previously reported by Gerdes et al) [37]. Each participant participated individually and spent approximately 60 min on research team-administered tests. Each test was conducted according to the pretested protocol, in order of: (1) 10 predefined tasks; (2) System Usability Scale (SUS) questionnaire [38]; and (3) interview. We have followed the definition by the International Organization for Standardization (ISO) by evaluating the usability in terms of the ease of use (effectiveness), efficiency, and satisfaction. The official ISO 9241-11 definition of usability is: “the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use” [39].

Ten Predefined Tasks

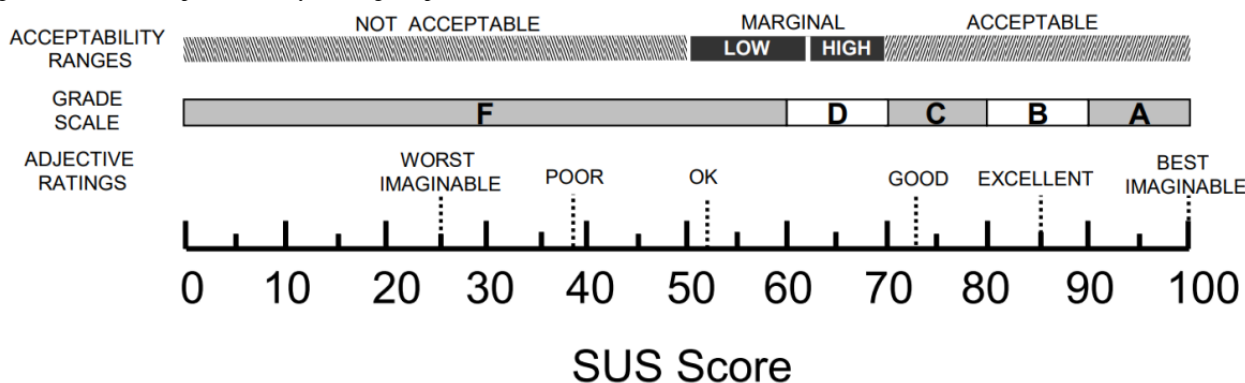
Each participant completed 10 predefined tasks corresponding to the 5 app components (Figure 1): (1) conduct a daily check-in; (2) create a goal; (3) coping skill training; (4) change goal; (5) library search; (6) create a post in the social support group; (7) complete a goal; (8) change user profile; (9) change pain area and symptoms; and (10) view history of daily check-in. The tasks were presented to each participant on a sheet of paper.

Participants could ask for help at any time, in which case help was interpreted as a moderator intervention, tabulated, and annotated. Participants also performed the think aloud (TA) method [40] while solving tasks. In the TA, participants verbalize what they are thinking as they perform a task. This method is frequently used to gain insight into users’ thoughts during a usability test [40]. Observations and audio and visual recordings were collected using a set of cameras and microphones that recorded the user interface, running commentary, and physical interactions with the app. A minimum of 2 researchers were present during each test. The ease of use and technical errors were evaluated based on the number of completed tasks and total errors. A completed task was defined as a task successfully achieved by the participant [41]. An error was defined as an incorrect selection, gesture, or landing on a screen triggered by a participant. The app efficiency was evaluated based on the time needed to achieve the tasks, expressed as the mean task completion time [41].

System Usability Scale Questionnaire

The SUS questionnaire was used to evaluate user satisfaction and comprised 10 open-ended polarity-balanced questions with a 5-point Likert scale for responses. The average scores were categorized based on the adjective ratings [42], as shown in Figure 5.

Figure 5. Adjective ratings, acceptability ranges, and school grading scales, in relation to the average System Usability Scale (SUS) score. Source: Bangor et al. Used with permission by the original publishers [42].



Interview

Finally, individual posttest semistructured interviews were conducted to assess user experiences with the app. The interview guide included 14 open-ended questions based on the 5 app components (Figure 1) and 3 additional categories for potential improvements, usage considerations, and coping. These predefined categories were considered ideal for ensuring a systematic assessment of the app and thus created a basis for the structured categorization matrix.

Phase 3: Field Usability Test

A total of 5 adolescents with persistent pain tested the Norwegian *iCanCope with Pain* app continuously over a period of 2 weeks to assess user experience over time and to identify any need for further assistance while using the app. The participants answered an electronic survey that was equivalent to the baseline questionnaires (which will also be included in the upcoming clinical trial) to ensure that they fulfilled the

inclusion criteria (eg, the Lübeck Pain questionnaire [7] for assuring the presence of pain and pain experience for 3 or more months). A detailed description of each questionnaire is available at ClinicalTrials.gov using ID NCT03551977. Each participant received an email with their username and password and an accompanying brief written introduction to the app’s features. Participants were also given a researcher’s phone number and email address, in case they needed technical assistance at any time during their 2-week participation. Participants were asked to download the app from the App Store or Google Play for their iOS- or Android-based mobile phone, respectively, after which they were to start the app and log in. User experience was assessed at the end of the 2 weeks using the SUS questionnaire and individual semistructured interviews.

Data Analysis

The data collected (eg, internet server data, observation, audiovisual recordings, and interviews) corresponded to the 5 app components. Quantitative laboratory usability test (eg, task

completion, time, errors) measures were evaluated based on users' interactions with the app and to assess the app's ease of use and efficiency. In both usability tests, quantitative data from the SUS questionnaire (10 questions, each scored from 0 to 4 points) were transformed by multiplying by 2.5 to convert scores to a 0 to 100 range and were categorized adjectivally [42]. Descriptive statistics were analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp). Both usability tests followed the same semistructured interview guide, comprising 14 open-ended questions. The 5 predefined theory-based app components (ie, self-monitoring, goal setting, coping skills training, social support, and pain education library) were the basis for developing a structured categorization matrix using deductive content analysis [43]. The collected data were coded according to 8 predefined categories, including the 5 components, potential improvements, usage considerations, and coping. Interview responses were transcribed verbatim using NVivo for Windows (QSR International Pty Ltd, version 12, 2018).

Ethics

The study was approved by the Norwegian Regional Committee for Medical Research Ethics South-East-B (REK reference 2017/350). Participants were informed verbally and in writing that their participation was voluntary, that they could withdraw at any time without a reason (in which case their data would be deleted and destroyed), and that confidentiality and anonymity of their data were ensured at all times. Participants signed informed consent forms before participating.

Results

Phase 1: Translation and Cultural Adaptation

The participants did not report having any misunderstanding about or finding discrepancies with the words or phrasing (eg, meaning or activities) of the translated and culturally adapted pain education library, in either usability test. In addition, participant interviews and debriefings in the field usability test (phase 3) were conducted to ensure credibility and understanding

of the software interface text. Overall, the participants found the software interface text, which comprised single words and short sentences, easy to understand and interpret, and found the phrasing suitable for their age group.

Phase 2: Laboratory Usability Test

Participants successfully downloaded the Norwegian version of the *iCanCope with Pain* app and logged in using their mobile phones. After logging in, participants created a mock user profile. They reported finding it easy to perform a daily check-in and liked the idea of monitoring pain patterns, which could contribute to a better understanding of their pain experience. The continuous presence of the avatar figure that changed both face and body expressions according to a numeric scale during registration and feedback made the app easy to use and self-explanatory. However, there were also comments that the profile's avatar *looked a bit childish*. These participants found it motivating to set goals and read articles in the library section based on those goals. All participants reported that they would recommend the app to others and appreciated the range of pain coping strategies. One participant said:

Hmm, actually it seems like it [the app] has control. So, there is a lot of information. I did not understand at first how an app may help with pain when I first heard about it, but I get it now when I see what it is, yes.

Participants in the laboratory usability test did not make any suggestions regarding how the app could be improved; thus, no adjustments were made before the home-based usability test.

User Satisfaction

User satisfaction scores (0 to 100) in the laboratory usability test are shown in Table 1. The average score was 82 out of 100, categorized as *good* and just below *excellent* [42]. The color-based visualization scheme is a modified version of that recommended by Smaradottir et al [44], wherein green represents a positive response, yellow a neutral response, and red a negative response.

Table 1. System Usability Scale questionnaire scores from the laboratory usability test.

Questions	P1 ^a	P2	P3	P4	P5	P6	Mean (SD)
I think that I would like to use this app frequently	3 ^b	3 ^b	3 ^b	3 ^b	4 ^c	4 ^c	3.3 (0.5)
I found this app unnecessarily complex	2 ^c	2 ^c	2 ^c	1 ^c	2 ^c	1 ^c	1.6 (0.5)
I thought this app was easy to use	5 ^c	4 ^c	4 ^c	4 ^c	4 ^c	5 ^c	4.3 (0.5)
I think I would need assistance to be able to use this app	1 ^c	3 ^b	1 ^c	1 ^c	2 ^c	4 ^d	2 (1.3)
I found the various functions in this app to be well integrated	5 ^c	5 ^c	4 ^c	4 ^c	3 ^b	5 ^c	4.3 (0.8)
I thought there was too much inconsistency in this app	2 ^c	2 ^c	2 ^c	1 ^c	1 ^c	1 ^c	1.5 (0.5)
I imagine that most people would learn to use this app very quickly	4 ^c	5 ^c	3 ^b	5 ^c	5 ^c	4 ^c	4.3 (0.8)
I found this app very cumbersome/awkward to use	1 ^c	2 ^c	2 ^c	1 ^c	1 ^c	1 ^c	1.3 (0.5)
I felt very confident using this app	5 ^c	4 ^c	3 ^b	5 ^c	5 ^c	4 ^c	4.3 (0.8)
I needed to learn a lot before I could get going with this app	1 ^c	3 ^b	1 ^c	1 ^c	2 ^c	1 ^c	1.5 (0.8)
Scores	87.5	72.5	75	90	82.5	85	— ^e
Average	82	—	—	—	—	—	—

^aPx: participant x.

^bNeutral response: neither agree nor disagree.

^cPositive response: agree or strongly agree for positive questions; disagree or strongly disagree for negative questions.

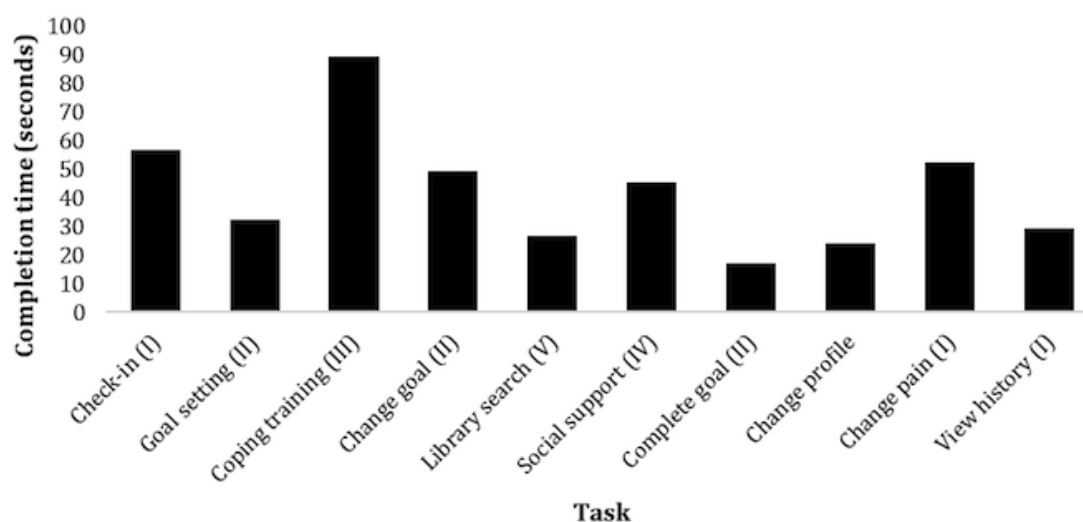
^dNegative response: agree or strongly agree for negative questions; disagree or strongly disagree for positive questions.

^eNot applicable.

Ease of Use and Efficiency

Each participant completed all 10 predefined tasks. As participants progressed through the tasks, some unwanted screen landings or touches were registered as errors. The predefined tasks were completed within the stipulated time frame. Task 3 was expected to be more time consuming as it required the

participants to first find a specific article about coping, read the article quietly to themselves, and then read the preferred information bullet points aloud. Efficiency scores are presented in Figure 6 as the mean time in seconds for the completion of each of the 10 predefined tasks related to the 5 app components (I to V).

Figure 6. Mean completion time in seconds (0 to 100) for each laboratory usability test task (N=6).

Phase 3: Field Usability Test

The daily check-in (ie, self-registration) feature is intended to give users insight into, and an overview of, how they are coping with pain. In total, 4 of the 5 participants used the daily check-in almost every day, primarily after school, with an average of

10.5 check-ins during the 14 testing days. One participant commented, “It [check-in functionality] was a reason for using the app every day” and that “I will miss doing it.” However, 1 participant only used the daily check-in twice and explained in the interview that this was because the app became a reminder

of the pain; even positive feedback from the avatar figure *Copey* after a daily check-in was interpreted as negative by this participant, as it was either *too positive* or *just a reminder that I struggled*. Participants created an average of 2.2 goals during the test period. Most goals were related to physical activities, such as participation in soccer practice or burning 200 kcal by running. They also created goals regarding sleep and energy. The participants reported that they appreciated the ability to set goals, said it was a motivating feature, and found it easier to achieve goals when they were written down. The library provided age-appropriate information and pain coping strategies; the participants found this easy to use and interesting, as it offered articles and exercises. One participant reported, “There was a lot of variation in the articles, and I even read about things

that I had not related to with my type of pain...” Another participant mentioned that he/she liked using the app in private settings, as he/she did not want to go to a psychologist. Participants favored articles related to CBT, distraction techniques, and help with developing a treatment plan. None of the participants asked for additional help or experienced any technical issues during the test period; thus, no technical issues, help, or user training needs were identified.

User Satisfaction

The average user satisfaction score (0 to 100) for the field usability test is shown in Table 2. Participants’ average score was 89, categorized as *excellent* and below *best imaginable* [42].

Table 2. System Usability Scale questionnaire scores from the field usability test.

Questions	P1 ^a	P2	P3	P4	P5	Mean (SD)
I think that I would like to use this app frequently	4 ^b	2 ^c	5 ^b	3 ^d	4 ^b	3.6 (1.1)
I found this app unnecessarily complex	1 ^b	2 ^b	1 ^b	1 ^b	2 ^b	1.4 (0.5)
I thought this app was easy to use	5 ^b	5 ^b	5 ^b	5 ^b	5 ^b	5 (0)
I think that I would need assistance to be able to use this app	1 ^b	1 ^b	1 ^b	1 ^b	1 ^b	1 (0)
I found the various functions in this app were well integrated	5 ^b	4 ^b	5 ^b	5 ^b	5 ^b	4.8 (0.4)
I thought there was too much inconsistency in this app	2 ^b	3 ^d	1 ^b	1 ^b	2 ^b	1.8 (0.8)
I would imagine that most people would learn to use this app very quickly	5 ^b	5 ^b	5 ^b	5 ^b	5 ^b	5 (0)
I found this app very cumbersome/awkward to use	1 ^b	1 ^b	1 ^b	1 ^b	1 ^b	1 (0)
I felt very confident using this app	3 ^d	2 ^c	5 ^b	4 ^b	5 ^b	3.8 (1.3)
I needed to learn a lot of things before I could get going with this app	1 ^b	2 ^b	1 ^b	2 ^b	1 ^b	1.4 (0.5)
Scores	90	72.5	100	90	92.5	— ^e
Average	89	—	—	—	—	—

^aPx: participant x.

^bPositive response: agree or strongly agree for positive questions; disagree or strongly disagree for negative questions.

^cNegative response: agree or strongly agree for negative questions; disagree or strongly disagree for positive questions.

^dNeutral response: neither agree nor disagree.

^eNot applicable.

Sociability

Sociability refers to the app’s ability to facilitate user interactions with peers [45]. All participants reported that, in theory, this was a promising idea that would allow them to share their experiences and motivate each other within a social support group. However, only one of the participants made posts to this functionality. This participant explained how this feature could have been improved, including switching to a single chat option with a health care professional (ie, physical therapist), options to create groups with other adolescents who experience similar types of pain, and that questions in the community function should focus on pain coping strategies. No changes were made to refine the app for the upcoming clinical trial on this basis, except to facilitate interaction with peers in the community function.

Discussion

Principal Findings

Here, we have described the process of translation and cultural adaptation of the *iCanCope with Pain* app into a Norwegian context, and outcomes of 2 usability tests. Our adolescent study participants did not report having any misunderstanding of or finding discrepancies within the words or phrasing of the translated and culturally adapted app. The laboratory usability tests showed that all 10 predefined tasks were completed within the allocated time frame (ie, were efficient) and were reported to be easy to use. Furthermore, both usability tests showed that the app was self-explanatory, with high satisfaction scores. One home-based usability test participant reported that the app became a reminder of their pain. The community functionality

(social support) in the app was rarely used. No technical issues, help, or user training needs were identified.

A 2-stage multistep approach was considered necessary to culturally adapt the app content. The thorough approach used herein may explain why participants found the Norwegian *iCanCope with Pain* app text suitable for their age group, with no discrepancies in phrasing or words. Although several translation and cultural adaptation techniques have been previously described, with different strengths and weaknesses, a transparent and thoroughly described procedure is essential [46]. Nevertheless, 8 steps have been recommended as a minimum when conducting a stepwise translation and adapting instruments intended for a clinical context [47]. In addition, the concept of functional equivalence in cross-cultural research involving adolescents [48] is particularly important; for example, adolescents might engage in different behaviors and understand meanings differently across diverse cultures. Nevertheless, no misunderstandings regarding activities or meanings were reported in this study.

The original Canadian *iCanCope with Pain* app underwent rigorous development and testing through a user-centered design for adolescents with chronic pain, based on their unique health care needs [21]. Furthermore, the *iCanCope with Pain* app is currently under evaluation for use by those with other health conditions, such as arthritis and sickle cells disease [49]. Such preparatory work should be highlighted as it may explain why we failed to identify any technical issues or the need for any additional user assistance or training in either of our usability tests. In addition, this may explain why we found high user satisfaction in both usability tests, with the highest scores among the participants who interacted with the app over time in their natural home environments. These participants reported that they were able to relate specifically to the different app components and thus provided the most valuable feedback from an end-user perspective [50,51].

Despite the participants' reports that they liked the idea of an app component that would allow them to seek social or peer support, this functionality was rarely used. Nevertheless, research has shown the advantages of peer support delivered via apps, which may provide effective interventions and alleviate stress within other health care systems [52]. Forgeron et al concluded their systematic review by noting that adolescents with chronic pain have peer relationship deficiencies [53]; however, we expect that the rare use of social support in this study was more likely because of our low number of participants. Regardless, social (or peer) support plays a protective role for adolescents with chronic pain and is important for their social development [54].

The app was designed for a generic target group of adolescents with persistent pain originating from different etiologies. Our participants reported appreciating that they were able to access the app from home after school and learn from psychological strategies in the app, which were the most popular articles. Given the free time of adolescents may be limited, measures such as high efficiency (tasks completed within the allocated time frame) and ease of use might be of great importance, by not taking much of the adolescents' free time. Accessibility of

the internet, with options for what, when, and where to read, and creating their own goals could be beneficial for adolescents who might be in a stressful stage of life with school and everyday activities, and for those who may find traditional psychological therapies delivered by adults more difficult [55]. One participant in our study mentioned that he/she did not want to go to a psychologist, possibly reflecting adolescents' perceived stigma with psychotherapy that has been previously reported [21,55,56]. Mobile phones may have several advantages compared with traditional face-to-face treatments, including their 24/7 availability, pocket size, interactive nature, and flexible programming [57]. However, 1 participant in our study also stated that the app served as a pain reminder and thus was a nonpreferred coping approach. Consistent with this comment, technology and apps for coping may not be suitable methods for empowering all adolescents who experience persistent pain [21].

Limitations

Several study limitations must be considered. TA was used during tasks to confirm when participants started and ended each of the predefined tasks, providing valuable insight into users' thoughts and actions [40]. However, not all participants found it natural to verbalize the task as they were performing it, which may have influenced task efficiency because of higher cognitive loads. This may call into question the reliability and validity of these data [58]. Another limitation is that we used convenience sampling of the adolescents, who conducted the translation and cultural adaptation procedure (phase 1) and who served as participants in the laboratory usability test (phase 2). Furthermore, only 2 adolescents were included in phase 1. These adolescents might have related their use of the app in a more hypothetical manner. Ideally, all participants should have been end users, who are known to provide the most valuable feedback [40]. However, recruiting end users was only possible in the final study phase (phase 3) as the first 2 phases were conducted before recruitment for the randomized controlled trial. Participants suggested several potentially valuable improvements that were not feasible. For example, including health care support would make the app a class 2 medical device, and creating groups based on different pain areas was limited by funding and did not correspond with the upcoming trial design. Finally, the app was originally developed and user-tested by groups with a relatively larger age range [21,49] than was used in this study, suggesting that our assessments may not generalize to a larger population. However, our sample was recruited specifically to match the criteria for the upcoming trial, to which they likely generalize.

Conclusions

This study presented the process of language and cultural adaptation and 2 usability tests for the Norwegian version of the *iCanCope with Pain* app. High user satisfaction, ease of use, efficiency, and only minor errors cumulatively indicated that no changes to the app were needed, with the exception of facilitating user interaction with peers within the social support feature. Despite this, iterative usability testing was fundamental to ensuring that the app is cross-culturally valid and easy to use,

before it is used in an upcoming randomized controlled trial with a larger sample.

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Authors' Contributions

KH, LF, SH, and JS developed the project protocol and contributed to the study design. SM and EG were responsible for usability tests. EG, CL, KH, LF, and SH were responsible for the translation and cultural adaptation and data analysis. All authors contributed to the manuscript preparation and approved its final version.

Conflicts of Interest

None declared.

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Abbreviations

- CBT:** cognitive behavioral therapy
- ISO:** International Organization for Standardization
- SUS:** System Usability Scale
- TA:** think aloud
- UiA:** University of Agder

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Protocol

Feasibility and Clinical Relevance of a Mobile Intervention Using TrackPAD to Support Supervised Exercise Therapy in Patients With Peripheral Arterial Disease: Study Protocol for a Randomized Controlled Pilot Trial

Katrin Paldán^{1,2}, MSc, DPhil; Jan Simanovski¹; Greta Ullrich³; Martin Steinmetz³, MD, Dr Med; Christos Rammos³, PD, MD, Dr Med; Rolf Alexander János³, PD, MD, Dr Med; Susanne Moebus¹, Prof Dr, PhD; Tienush Rassaf³, MD, Prof Dr; Julia Lortz³, MD, Dr Med

¹Centre for Urban Epidemiology, Institute for Medical Informatics, Biometry und Epidemiology, University of Duisburg-Essen, Essen, Germany

²Centre of Competence Personal Analytics at the University of Duisburg-Essen, Department of Engineering Sciences, University of Duisburg-Essen, Duisburg, Germany

³Department of Cardiology and Vascular Medicine, West-German Heart and Vascular Center Essen, University of Duisburg-Essen, Essen, Germany

Corresponding Author:

Julia Lortz, MD, Dr Med

Department of Cardiology and Vascular Medicine

West-German Heart and Vascular Center Essen

University of Duisburg-Essen

Hufelandstrass 55

Essen, 45147

Germany

Phone: 49 201723 ext 84995

Email: julia.lortz@uk-essen.de

Abstract

Background: Peripheral arterial disease (PAD) is a common and severe disease with a highly increased cardiovascular morbidity and mortality. Through the circulatory disorder and the linked undersupply of oxygen carriers in the lower limbs, the ongoing decrease of the pain-free walking distance occurs with a significant reduction in patients' quality of life. Studies including activity monitoring for patients with PAD are rare and digital support to increase activity via mobile health technologies is mainly targeted at patients with cardiovascular disease in general. The special requirement of patients with PAD is the need to reach a certain pain level to improve the pain-free walking distance. Unfortunately, both poor adherence and availability of institutional resources are major problems in patient-centered care.

Objective: The objective of this trackPAD pilot study is to evaluate the feasibility of a mobile phone-based self tracking app to promote physical activity and supervised exercise therapy (SET) in particular. We also aim for a subsequent patient centered adjustment of the app prototype based on the results of the app evaluation and process evaluation.

Methods: This study was designed as a closed user group trial, with assessors blinded, and parallel group study with face-to-face components for assessment with a follow-up of 3 months. Patients with symptomatic PAD (Fontaine stage IIa or IIb) and possession of a mobile phone were eligible. Eligible participants were randomly assigned into study and control group, stratified by their distance covered in the 6-min walk test, using the software TENALEA. Participants randomized to the study group received usual care and the mobile intervention (trackPAD) for the follow-up period of 3 months, whereas participants randomized to the control group received only usual care. TrackPAD records the frequency and duration of training sessions and pain level using manual user input. Clinical outcome data were collected at the baseline and after 3 months via validated tools (6-min walk test, ankle-brachial index, and duplex ultrasound at the lower arteries) and self-reported quality of life. Usability and quality of the app was determined using the user version of the Mobile Application Rating Scale.

Results: The study enrolled 45 participants with symptomatic PAD (44% male). Of these participants, 21 (47%) were randomized to the study group and 24 (53%) were randomized to the control group. The distance walked in the 6-min walk test was comparable in both groups at baseline (study group: mean 368.1m [SD 77.6] vs control group: mean 394.6m [SD 100.6]).

Conclusions: This is the first trial to test a mobile intervention called trackPAD that was designed especially for patients with PAD. Its results will provide important insights in terms of feasibility, effectiveness, and patient preferences of an app-based mobile intervention supporting SET for the conservative treatment of PAD.

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KEYWORDS

peripheral arterial disease; telemedicine; patient participation; patient compliance; primary health care

Introduction

Background

Peripheral arterial disease (PAD) is a common atherosclerotic disease affecting the lower extremities. The prevalence of PAD is high as almost one-fifth of the population aged 65 years or above in the high-income countries is diseased and the occurrence increases further with age [1]. Right after coronary arterial disease and the cerebrovascular arterial disease, PAD is the third most common atherosclerotic disease [1,2]. However, PAD does not only limit an active lifestyle with the risk for lower limb amputation, but it is also an independent predictor of cardiovascular morbidity and mortality [3,4]. Limitations in daily life often arise from intermittent claudication (IC), which is defined as an impairment of walking because of pain, tiredness, or discomfort in the legs during walking and is relieved by rest. IC is a common and debilitating symptom of PAD and is also associated with a significant reduction in patients' quality of life [5]. The pain-free walking distance decreases with further disease progression. In addition to this symptom and a significant lower quality of life, the most dreaded complication in PAD is the loss of the affected extremity.

Supervised exercise therapy (SET) is one of the most effective options in the conservative management of PAD [6]. Through a complex mechanism that includes arteriolar dilation, changes in microcirculation and endothelial function without directly improving limb blood flow, SET was shown to improve the pain-free walking distance and also the quality of life [7-11]. However, 2 challenges in the conservative management of patients with PAD arise. First, the availability of institutional resources for SET is rare. PAD patients are undersupplied in care, compared with patients with coronary artery disease [12,13]. Second, the adherence to guideline recommendation regarding physical training is rather low [14-16].

Studies including activity monitoring for PAD patients are rare and are mainly focusing on the overall activity, neglecting the training to the pain threshold as required for SET [16-18], although SET was shown to have more beneficial effects than the simple increase in activity. This fact may be responsible for the conflicting results in past studies. Another limiting factor in previous studies was the use of (telephone) counseling, which relativizes the effect of reduced personnel deployment.

With the use of mobile health (mHealth) technologies, we see the potential for a wider accessibility without an excessive increase of personnel resources. In particular, with an increasing focus on personalized mHealth, highlighting health education and changing people's health-related behavior [19-21], mHealth

technologies have the potential to solve the current problems of missing adherence and infrastructure. Patients with PAD deserve more attention regarding their therapeutic options as their outcome and the guideline adherence of their treating physicians is still poor [22].

We developed trackPAD (Rocket Apes GmbH) as the first app-prototype for patients with PAD that should increase patients' empowerment and improve their care. TrackPAD should support patients to implement SET in everyday life. It is also thought to overcome motivational barriers leading to a higher adherence to training instructions and therefore aiming for a slower disease progression. TrackPAD might also have the potential to (partly) compensate the missing infrastructure, such as training or support groups, by sharing personal success and competing against each other.

The overall aim for the implementation of trackPAD is to close supply gaps in care and provide digital solutions for patients with PAD to overcome personal and structural barriers by reaching a wide availability and high cost-effectiveness at the same time.

We will evaluate the potential benefits of mHealth-based SET performance to reduce disease progression and test the feasibility of the developed mobile phone app. The following app evaluation will also give important insights for the patient-centered app development in this special patient collective.

Objective

The aim of this pilot study was to evaluate the clinical relevance and the feasibility of an app to support SET in patients with PAD.

Methods

Research Questions

The trackPAD pilot study aims to answer the following questions:

1. Is trackPAD suitable for recording the patient's daily/weekly walking distance and the quality of performed SET (units)?
2. Is the app suitable for the target group and for further study purposes?
3. Does the use of the app increase physical activity and performance of SET resulting in an improvement of patients' 6-min walk test distance?
4. Is the app feasible to implement in everyday practice?

To address research question 1, 2, and 4, we asked the patients after 3 months on how they evaluated the app, assessed reasons for dropout in detail, and analyzed the log file data of the app.

To address research question 3, we analyzed whether patients directed by trackPAD showed an increase in the 6-min walk test distance after 3 months. A minimal clinical increase of 20m was already shown to be beneficial in patients with IC [17,23]. The results were compared with a control group, which did not use trackPAD during the study period.

Measures

To evaluate the feasibility of the app, a questionnaire survey regarding the trackPAD evaluation will be performed at follow-up based on an already standardized instrument for app evaluation [24].

Table 1. Relevant accessible data of trackPAD participants' use in real time.

Accessible data	Subcategories
Technical information	Mobile phone operating system and version; personal trial number (anonymous)
Overall use	Number of medals won; frequency and duration of use (not exercise!)
Summary	Total length of all SET ^a units; number of steps; number of performed SET units; breaks (number+duration)
Weekly overview	Number of chosen SET units; frequency and duration of SET units and intervals; number of steps; number of performed SET units; number of performed SET units in relation to previously set weekly goal (less or more than initially aimed for); increase of performed SET units compared with previous week
Pro-SET unit	Length of SET unit and time (date and time); number of performed steps; number of intervals needed to finish SET unit
Prointerval	Evaluation of SET unit (pain, breath, overall intensity); length of the interval; number of performed steps

^aSET: supervised exercise therapy.

Outcome Variables

Primary Outcome

The primary outcome was defined as the change in pain-free walking distance and was assessed by comparing the meters covered in a 6-min walk test using a standardized protocol [25] at baseline and after the 3 months follow-up. The 6-min walk test was performed under the supervision of a trained exercise technician. Participants were instructed to cover as much distance as possible and walk up and down a 50-m hallway for up to 6 min. Participants were instructed to push a measuring wheel along for the full 6 min of the test, but were allowed to take breaks if necessary. They were also allowed to use an assistive device during both the walking tests if they so desired. The technician stood in the middle of the course and supervised the walking test, but did not encourage participants. The total distance walked in the test was read off the measuring wheel.

Secondary Outcome

Secondary outcome measures were any changes in perfusion indices, including ankle-brachial index (ABI) at rest or after treadmill test (3.0 km/h and incline of a 10% slope), according to the current European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of PAD [26].

In addition, changes in the large elastic arterial stiffness determined through pulse wave velocity were recorded. Noninvasive duplex ultrasound was performed at the lower leg

The questionnaire, slightly adapted and shortened for the study objectives, comprises 5 parts:

- Functionality
- Aesthetics
- Information
- Overall evaluation of subjective app quality
- Perceived effects regarding the implementation of structured walking training/SET

In addition, a detailed description of the log file data of the patients (Table 1) and the verbally reported reasons for not using trackPAD over 3 months will be given. To evaluate the clinical relevance of the app, we will evaluate the following outcomes variables.

arteries (Arteria tibialis posterior and anterior). Standard techniques, as determined by Doppler and duplex ultrasonography, were used to quantify tissue perfusion.

Further assessment of quality of life and subjective physical activity should capture potential benefits resulting from improvement of activity. PAD-specific quality of life was determined through the PADQOL, a validated PAD-specific quality of life questionnaire [27].

Missing Data/Data Cleaning

Multiple imputation missing data handling procedures [28] were implemented using multivariate imputation by chained equations [29], a package for the R statistical software environment (The R foundation, version 3.5.0). As a last resolve, all missing data values in the final dataset were multiple imputed according to methodology suggested by Schafer and Graham [30] and Barnes et al [31].

Study Design and Inclusion Criteria

The trackPAD pilot study was designed as a 2-armed randomized controlled trial and included patients with diagnosed and symptomatic PAD. This was a closed user group trial, with assessors blinded, and parallel group study with face-to-face components for assessment with a follow-up of 3 months. The participants were randomly assigned and stratified by their walking distance to control and study group after giving their written informed consent. The study procedure required 2 visits

at the vascular outpatient clinic of the University Clinic of Essen at baseline (November 2018 to mid-December 2018) and 1 additional at follow-up (expected during early February 2019 to mid-March 2019). The first visit at baseline included all clinical pretestings and the quality of life questionnaires. The second baseline visit included a 10-min lecture repeating instructions for SET. After the lecture, participants received the result of the randomization, their group assignment, and the study group remained for downloading the app and a short guide to the app. The third visit was the follow-up visit at the end of the study.

No further visits during the study periods were planned. Nevertheless, in case of technical issues (such as system failures and bugs), technical support was offered to the participants, which was operated by nonmedical personnel. The support was reachable by phone (hotline) or email. All emails were answered within the next 24 hours and the hotline was operated from Mondays to Fridays (for 4 hours) between 8 and 12 pm. During the entire study period, the software engineers of trackPAD were available to fix any bugs or technical events that had occurred. Therefore, we were able to deliver necessary updates to the participants. For an update (ie, not working step counter), we contacted the participants and provided a written manual and oral instructions. For further needs, we additionally offered face-to-face appointments that took place at the vascular outpatient clinic and were provided by nonmedical personnel. As we planned, the provided updates did not change the use, behavior, or any feature of trackPAD; they only fixed bugs and technical issues in the code.

The inclusion criteria included patients with diagnosed and symptomatic PAD in the lower extremities, who were aged at least 18 years. PAD diagnosis had to be based on at least one of the following criteria: (1) ABI of 0.9 or less in at least one leg [32], (2) invasive or noninvasive imaging of stenotic lower extremity artery disease, or (3) endovascular or surgical revascularization of a lower extremity artery. Symptomatic PAD in the lower extremity had to be also characterized by Fontaine stage II (IC after walking). In addition, the possession of a mobile phone was obligatory (mobile phone with iOS 11.0 or later or Android 5.0 or later, suitable for downloading trackPAD). Giving the written informed consent before any study procedure was mandatory.

The following exclusion criteria were defined: acute or critical limb ischemia, severe angina pectoris (by Canadian Cardiovascular Society score 3-4), myocardial infarction/stroke in the last 3 months, active congestive heart failure requiring the initiation or uptitration of diuretic therapy, congestive heart failure with severe symptoms (by New York Heart Association score 3-4), active arrhythmia requiring the initiation or uptitration of antiarrhythmic therapy, severe valve disease, active cancer or malignancy, severe cognitive dysfunction (defined as dementia), leg pain at rest (Fontaine stage III or IV), no German language knowledge, walking impairment because of other causes than PAD, below or above knee amputation, wheelchair bound and/or use of a walking aid. [Textbox 1](#) summarizes the inclusion and exclusion criteria.

Textbox 1. Inclusion and exclusion criteria of the trackPAD pilot study.

<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age ≥ 18 years • Diagnosis of lower extremity peripheral arterial disease (PAD) based on any of the following: <ul style="list-style-type: none"> • Ankle-brachial index ≤ 0.9 in at least one leg • Invasive or noninvasive imaging of stenotic lower extremity artery disease • Endovascular or surgical revascularization of lower extremity artery • PAD Fontaine stage IIa—mild claudication • PAD Fontaine stage IIa—moderate-severe claudication • Mobile phone with possibility to use trackPAD: <ul style="list-style-type: none"> • Android 5.0 or later • iOS 11.0 or later • Written informed consent before any study procedures, including a specified follow-up evaluation • Best medical treatment in the last 2 months in accordance with standard guidelines <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Wheelchair bound, use of walking aid, or walking impairment because of other causes than PAD • Below or above knee amputation • PAD Fontaine stage I—asymptomatic • PAD Fontaine stage III—ischemic rest pain • PAD Fontaine stage IV—ulceration or gangrene • Acute or critical limb ischemia • Severe angina pectoris according to Canadian Cardiovascular Society class (score 3-4), or myocardial infarction, or stroke in the last 3 months • Active congestive heart failure requiring the initiation or uptitration of diuretic therapy • Severe congestive heart failure according to New York Heart Association (score 3-4) • Active arrhythmia requiring the initiation or uptitration of antiarrhythmic therapy • Severe valve disease • Active cancer or malignancy • Severe cognitive dysfunction • No German language knowledge
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Recruitment and Randomization

Information regarding the pilot study and a call for participation were announced in a local newspaper (Westdeutsche Allgemeine Zeitung, local section for Essen and Duisburg) with contact information provided, including phone number and email address (trackPAD@uk-essen.de). Further potential participants were actively asked during their visits to the outpatient clinics or during their inpatient stay in the Department of Cardiology and Vascular Medicine, University Clinic of Essen. Interested patients with known PAD were asked to fill out a questionnaire exclusively developed for our study purpose. The questionnaire included questions about the patients' social background, the knowledge about SET, the personal health status, and the possession of a mobile phone. The questionnaire ended asking whether the patient was willing to participate in the trackPAD pilot study. As the questionnaire was anonymous, willing

patients were asked to register for the upcoming pilot trial at the front desk of the outpatient clinic.

After screening in terms of inclusion and exclusion criteria of suitable participants and obtaining written informed consent from each participant, they were randomized by the Center for Clinical Studies in Essen using the TENALEA software into 2 groups. The control group included participants with standard care and no further mobile intervention. The study group included participants with standard care and additional mHealth-based self-tracking of their physical activity using trackPAD. The participants were stratified by their results during the 6-min walk test (distance lesser than 362m, between 362m and 430m, and greater than 430m). After the randomization process, no participants, regardless of the reason for exclusion, were replaced.

All participants were invited to a lecture (10 min) repeating the instructions for SET and handing out a flyer summarizing SET execution. After the lecture, participants received the result of the randomization and their group assignment. The study group remained for downloading the app and a short guide to the app. Technical issues were resolved immediately after installation by nonmedical personnel. To prevent any bias, based on disappointment or lack of motivation because of allocation into the control group, the allocation to the groups were announced only after the presentation and not before this event. All participants that did not show up to the introduction were contacted and scheduled for a new appointment within the next week. The presentation was demonstrated separately to everyone not present and the flyer was also handed out to each participant.

Baseline

Study and control group received the same baseline examinations during their first visit. Clinical measurements including 6-min walk test, ABI at rest and after physical activity, and pulse wave measurement were obtained. A blood sample was also taken to record the levels of various parameters, including total cholesterol, low-density lipoprotein and high-density lipoprotein, and triglycerides. In addition, participants' demographics and past medical history were documented. The assessors of the clinical outcomes were blinded regarding participants' randomization to the study or control group. During their first medical visit, both groups received the instruction to perform SET according to the current standard guidelines that recommend 3 units weekly for 30 to 60 min [26], but patients were kept open about how often they performed SET. The guidance in terms of SET included an oral recommendation and instruction by the same treating physician for all participants. In addition, all participants received a flyer with a summary of important information for SET, including the guideline recommendation of 3 units weekly for 30 to 60 min. The first baseline visit included a structured interview. The interview was conducted by medical personnel. A questionnaire served as structured guideline, which was used for all patients at baseline and follow-up. The questionnaire included personal data, questions on quality of life and PAD-specific quality of life [27], health status, and lifestyle-related questions (physical activity and smoking).

Follow-Up

The planned study duration was 3 months and the completion of the follow-up was planned for the end of April 2019. All participants received the follow-up examinations, including a retake of all previously performed clinical examinations and completion of the questionnaire on secondary outcomes. Moreover, any changes in personal medical history or medication since baseline were recorded. Similar to at baseline, the assessors of the clinical outcomes were blinded. Quality of life and PAD-specific quality of life [27], health status, and lifestyle-related questions were asked again in a structured interview by medical personnel. To evaluate the feasibility of the app in the study group, an additional questionnaire survey regarding the trackPAD evaluation was performed at follow-up, based on an already standardized instrument for app evaluation with slight adaption for study purposes [24]. In addition, a

detailed description of the log file data of the patients (Table 1) and the verbally reported reasons for not using trackPAD over 3 months were given.

TrackPAD

For this pilot study an exclusively developed mHealth-based app (trackPAD) was used to track patients' physical activity during the study period. TrackPAD was thought to represent the first mobile intervention to support patients with PAD regarding their implementation of SET. As mobile interventions lack in general the possibility of a direct measurement of onset and extent of claudication, we assessed breaks within each SET unit that were rated by the users in terms of pain level, breathing, and overall exhaustion before resumption of the SET unit. Through the detection of number and duration of breaks within a SET unit and the subjective pain assessment over time, we were able to detect changes in SET performance.

Patients' physical activity is tracked after actively starting a SET unit using the start button within trackPAD. No assessment of the background activity is performed and patients have to start their training actively. TrackPAD records the frequency and duration of training sessions and pain level using manual user input. The time bar in the main screen (Figure 1) indicates the minutes of exercise already performed during the SET unit. Each unit can be paused or stopped. After pausing and before the resumption of the SET unit, patients have to rate their pain level, breathing, and overall exhaustion (weekly goal and self-evaluation of the training).

TrackPAD was designed to cover the following requirements of PAD patients:

1. Weekly goal and self-evaluation of the training: At the beginning of each week, the app users are asked to set their weekly goal of SET units. On the basis of the completion rate of user's SET units during the previous week, the app suggests a new weekly goal using an internal algorithm. The number of performed weekly SET units is not limited and can exceed the previously chosen weekly goal. In case of reaching or excelling the weekly goal, the app recommends to add 1 SET unit to the following weekly goal. In case of missing the weekly goal, the app recommends to reduce 1 unit the following week. As recommended by the guidelines, each unit includes 30 min of SET, but users can extend the duration of the unit. By taking a break, the units can also be split into intervals. TrackPAD records the number of intervals of a SET unit. Therefore, all breaks of running SET units because of pain or exhaustion are captured. To continue a SET unit, the user's feedback is required. This feedback contains an assessment of each interval, regarding the pain level, breathing, and overall exhaustion.
2. Claudication reminder: After starting a new SET unit, a claudication reminder pops up (Figure 2), which needs to be confirmed actively. The user is reminded to adapt the own walking pace, incline, or even take the stairs to provoke moderate claudication during the SET unit, aiming for an increase in the pain-free walking distance. A pause button is provided to pause the SET unit after reaching a certain level of claudication.

3. Personal achievements: Personal progress of each user is recorded and linked to unlock medals (Figure 3). Achievements are rewarded, for example, a markable increase in user's physical activity, activity on public holidays, or successes such as a daily physical activity of more than 15 min.
4. Leaderboard: The leaderboard contains different categories, such as the number of steps in single training session, number of completed training sessions, total minutes of physical activity, and percentage increase in physical activity, and shows the individual placement within the group (Figure 4).
5. Patient events: Information on upcoming patient events of the Department of cardiology and vascular medicine are stored and quickly accessible via the main menu.
6. PAD-frequently asked questions (FAQ): A FAQ section is included addressing frequent technical issues, important contact information, general training advises, and also instructions in case of increasing or new pain during the training.

TrackPAD contains a password-protected admin function that allows to access data of each patient in real time. These data include weekly/monthly statistics of patients' walking distance,

time to the occurrence of pain, and frequency of exercise (Table 1). After trackPAD is once successfully installed, there is no need for further maintenance to be done by the users themselves.

The trackPAD main screen (Figure 1) is kept simple and has the following 4 components:

1. The upper part of the screen summaries the personal status of the current week, including the completed SET units of the weekly goal. The progress is presented as percentage and visualized by a moving stick figure.
2. The center of the screen shows the completed time of an active SET unit. This part also summaries the completed SET units each day of the week, including duration.
3. The lower part of the screen includes a link to the earned achievements and the personal rankings within the group.
4. Through the link in the upper right corner, events for patients, FAQ, privacy statement, and imprint are directly accessible.

There was no active reminder by the study team regarding the use of the app. A contact (eg, in case of technical problems or in case of a standard clinical examination) was always made by the patients and recorded. Except for the technical support, there were no cointerventions.

Figure 1. Main view of trackPAD. Weekly progress overview (upper part) and time bar active while training (central part). The main view also offers the possibility to access personal achievements (lower left part) or the leaderboard (lower right part). FAQ: frequently asked questions; SET: supervised exercise training.



Figure 2. Claudication reminder. After starting each supervised exercise training (SET) unit a pop-up appears reminding that a certain claudication level should be reached following a short break and repetition. The pop-up needs to be actively confirmed to begin the SET.

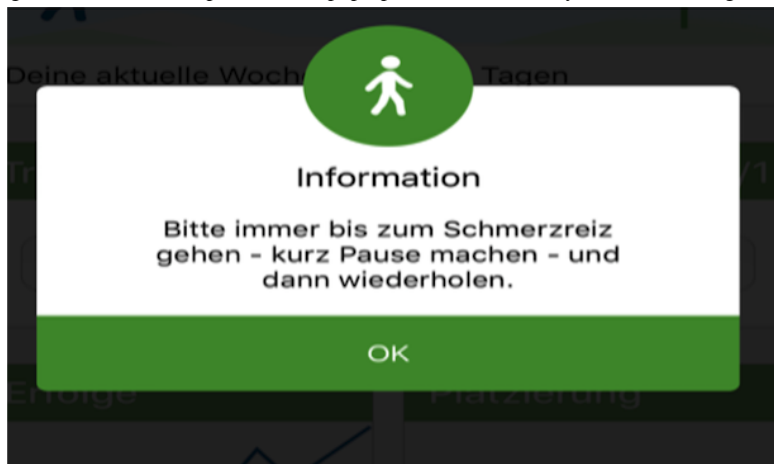


Figure 3. Personal achievements page. Reaching personal achievements unlocks medals in the medal mirror. The numbers at the right indicate the number of possible medals to unlock (eg, gold medal, silver medal, bronze medal). SET: supervised exercise training.








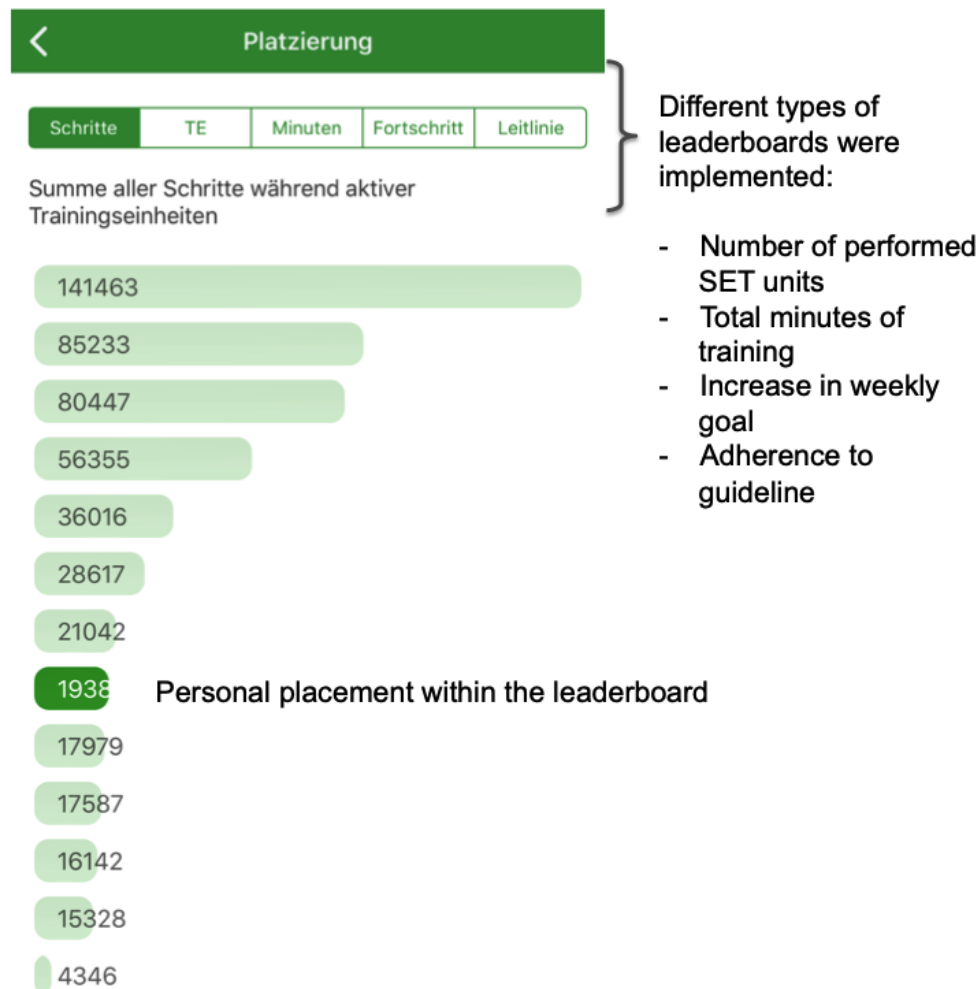
Erfolge	
 7 Tage	0/3 You trained 7 days in a row
 10 Trainingseinheiten	0/3 You finished 10 SET units
 Bergfest Du hast 6 Wochen durchgehalten 23.11.2018	1/1 Half way done of the study period
 4000 Schritte pro Tag Du hast 4000 Schritte an einem Tag geschafft 13.09.2018	3/3 4000 steps a day
 Geschafft	0/1 You finished your first training
 Mehr bewegt	0/1 You moved more
 Wochenziel gesetzt Dein erstes Wochenziel ist gesetzt 11.09.2018	1/1 You set your first weekly goal

Figure 4. Leaderboard page. Different categories of leaderboards are included. Each gives the opportunity to improve the personal placement within the group. The evaluation process at the follow-up will bring further insights about which kind of leaderboard has the most impact regarding motivational aspects. SET: supervised exercise training.



Sample Size Considerations

The primary study aim was designed (1) for the general feasibility aspect and (2) to gain information regarding preferences of PAD-patients and their individual requirements. On the basis of these results, further patient-centered adjustment for trackPAD is planned. Therefore, it was estimated that a sample size of 20 participants per study arm would be feasible in a 3-month follow-up pilot study. The achieved power was estimated to be low with 0.46 (t test; type of power analysis=post hoc; effect size $d=0.50$; alpha error probability=.05, group 1 sample size=20; group 2 sample size=20). To allow for missing data and loss to follow up, we aimed to recruit 23 to 25 participants per study arm.

Ethics Approval and Consent to Participate

This study was approved by the local ethics committee of the University of Duisburg-Essen (18-8355-BO). Written informed consent was taken from each participant, before any study procedures, and contact information was delivered to each participant. Any changes will be communicated to the ethics committee. The pilot study started in the beginning of November 2018.

Results

Recruitment and Randomization

The pilot study was funded in May 2018 by the Stiftung Universitätsmedizin and we received the IRB approval by the beginning of November 2018 (18-8355-BO). The enrollment started by December 2018 and ended in January 2019. All participants were recruited by the time of submission of the study protocol. The data analysis will start by the end of July and results to publish are expected by August 2019.

The majority of the potential participants ($n=51$) were recruited via the vascular outpatient clinic. In addition, 14 interested persons answered the announcement in the local newspaper, resulting in a total of 65 potential, eligible participants. The recruitment process took 7 weeks and was finished by November 2018. A total of 47 of the 65 recruited participants met the inclusion criteria and were enrolled to attend the initial baseline. The main reason for noninclusion of the remaining 18 potential participants was the missing of a suitable mobile phone. The summary of reasons for exclusion is listed in Table 2. To this point, no further participants dropped out.

Table 2. Dropout and exclusion reasons of recruited participants at baseline.

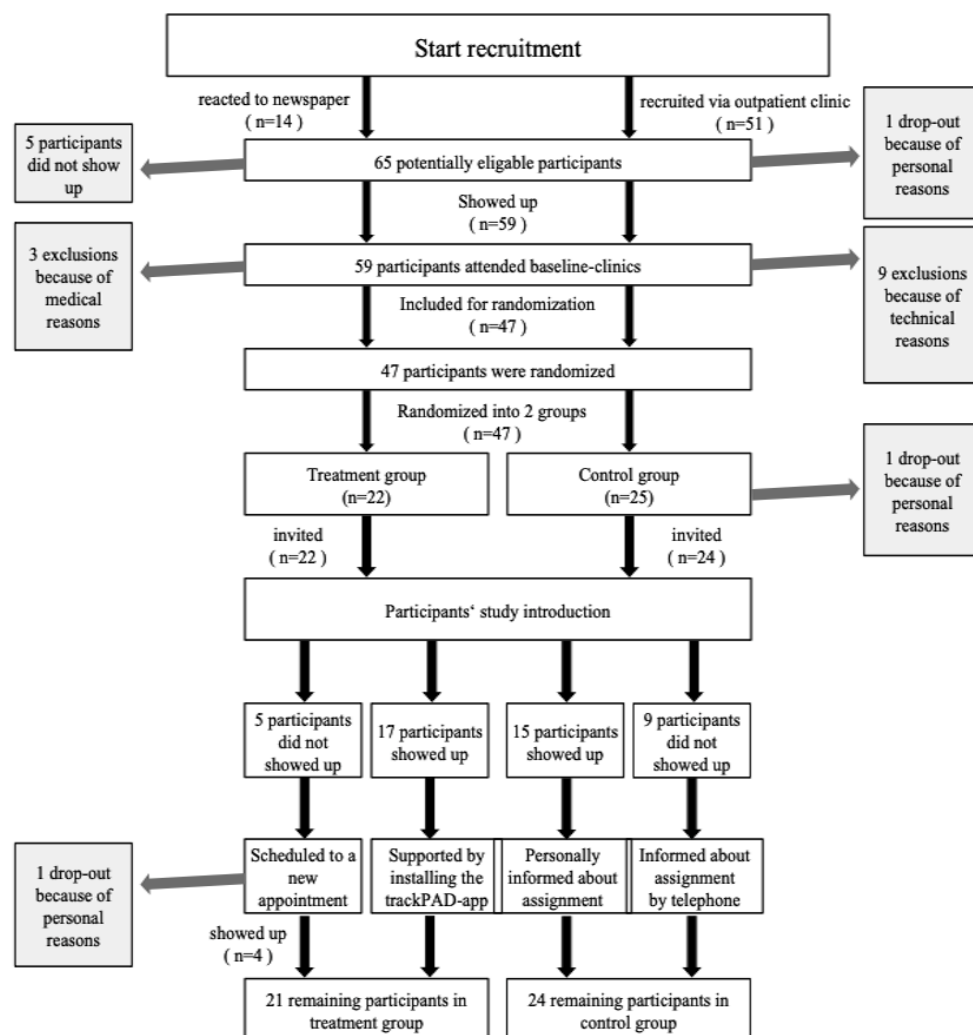
Category	Reason	Occurrences, n
Technical reasons	No suitable mobile phone	9
Individual reasons	No show up	5
	Personal reason	1
Medical reasons	No peripheral arterial disease/not matching medical inclusion criteria	1
	Matching medical exclusion criteria	2
Total dropouts and exclusions		18

All enrolled participants (n=47) were randomized, which resulted in the following assignment after randomization: 25 participants were randomized to the control group and 22 participants to the study group. One patient dropped out because of personal reasons shortly after randomization, but before announcing the result to the participant. Therefore, the control group decreased to 24 participants.

All participants (n=46) were invited to a lecture for repeating the instructions for SET and receiving the personal result of the

randomization. The study group remained after randomization for the download of trackPAD. A total of 32 of all 46 randomized participants showed up. All remaining participants (n=14) received their personal instruction including presentation, flyer, and the result of the randomization within the following 2 weeks. One dropout occurred in the study group after randomization due to technical problems. It was not replaced. Figure 5 summarizes the quantitative development of screened patients until the beginning of the trackPAD use, including dropouts and exclusions.

Figure 5. Quantitative development of screened patients until the beginning of trackPAD use. Reasons for dropouts and exclusions are shown.



Baseline

In total, 45 participants remained to take part in the pilot trial. The study group included 21 participants; the control group included 24 participants (Table 3). The mean age was 66.1 (SD 9.1) years and 44% (20/45) were male. The mean BMI was slightly elevated with 27.3 (SD 3.9) kg/m². All participants performed the 6-min walk test with a mean baseline walking distance of 390.6m (SD 89.7) that was comparable between

both groups (study group: mean 386.1m [SD 77.6] vs control group: mean 394.6m [SD 100.6]). The distance walked during the treadmill test was decreased compared with the 6-min walk test with 173.4m (SD 46.3), but also comparable between both groups (study group: mean 179.9m [SD 42.3] vs control group: mean 168.5m [SD 49.6]). It is to be noted that only 82% (37/45) of all participants were able to perform the treadmill test (study group 16/21 vs control group 21/24) because of instability or lack of balance on the treadmill.

Table 3. Summary of characteristics recorded at baseline.

Baseline characteristics	All participants (N=45)	Study group (N=21)	Control group (N=24)
Age (years), mean (SD)	66.1 (9.1)	65.3 (9.8)	66.9 (8.6)
Sex (male), n (%)	20 (44)	8 (38)	12 (50)
Body mass index (kg/m ²), mean (SD)	27.3 (3.9)	27.3 (3.6)	27.3 (4.3)
Walking distance			
6-min walk test (m), mean (SD)	390.6 (89.7)	386.1 (77.6)	394.6 (100.6)
Treadmill test (m), mean (SD)	173.4 (46.3)	179.9 (42.3)	168.5 (49.6)
Able to perform treadmill test, n (%)	37 (82)	16 (76)	21 (87)
Ankle-brachial index			
Worst extremity, mean (SD) ^b	0.8 (0.2)	0.8 (0.2)	0.7 (0.20)
Blood pressure (mm Hg), mean (SD)			
Systolic ^b	138.1 (22.5)	135.4 (26.9)	140.5 (17.9)
Diastolic ^b	77.4 (13.0)	76.9 (13.4)	77.9 (13.0)
Fontaine stage, n (%)			
Stage I	0 (0)	0 (0)	0 (0)
Stage IIa	31 (69)	14 (67)	17 (71)
Stage IIb	14 (31)	7 (33)	7 (29)
Stage III	0 (0)	0 (0)	0 (0)
Stage IV	0 (0)	0 (0)	0 (0)
Level of weekly physical activity^a			
Average number of active days, mean (SD)	2.2 (1.7)	2.2 (1.5)	2.0 (1.9)
Weekly more than 30 min active, n (%)	24 (53)	12 (57)	22 (50)
Comorbidities^a, n (%)			
Myocardial infarction	8 (18)	3 (14)	5 (21)
Heart failure	10 (22)	4 (19)	6 (25)
Hypertension	37 (82)	17 (81)	20 (83)
Stroke	30 (7)	10 (5)	2 (8)
Diabetes mellitus	13 (29)	4 (19)	9 (38)
Hypercholesterolemia	34 (76)	18 (86)	16 (67)
Smoking (including e-cigarette)			
Within past 5 years, n (%)	38 (84)	17 (81)	21 (88)

^aCharacteristics based on participants' information.

^bAll measures are before physical activity.

Most of the participants were former smokers (study group 13/21 vs control group 14/24), whereas 4 current smokers were in the study group and 7 in the control group.

Discussion

Principal Findings

As app stores are flooded with hundreds of fitness and activity apps, there is no app meeting the requirements for patients with PAD so far. The general increase in overall activity as provided by fitness apps or wearables is not equated with the execution of SET to improve the walking endurance among patients with PAD [17].

This pilot study is the first to evaluate an app prototype that was especially developed to support the implementation of SET in patients with PAD into everyday life. On the basis of the results of the evaluation process of the app prototype, a further patient-centered adjustment of trackPAD will follow. A patient-centered app development for this special patient collective is unique so far. Although some studies are recently published that deal with mHealth technologies (mainly via wearables and not as mobile phone-only solutions) and promote exercise in patients with PAD [16-18,20,33], these studies suffer from some limitations. Previous mobile interventions included apps and wearables off-the-rack, lacking tailored solution for this special patient collective and ignoring the fact of increasing SET performance rather than overall activity.

Differentiation From Previous Studies

In the following text, we describe the main differences of the current trackPAD prototype compared with commonly used fitness apps.

1. Self-tracking of performed SET units and setting of weekly goal: Each unit has a minimum length of 30 min, as recommended by the current ESC guidelines on the diagnosis and treatment of PAD [26], and offers the opportunity to compare the personal weekly progress. A disadvantage of the current version is that weekly comparisons must be viewed manually. As part of the review following the pilot study, weekly status messages should pop-up automatically to reflect patients' own progress and recommend achievable goals for the upcoming week. The reason to not include such an algorithm for the first time was the fact that PAD is a disease with high disabling potential and also affecting the functional status of capacity [34]. An automatic algorithm that is used in other common fitness apps does not seem to be feasible for this app.
2. Patient attention and empowerment: Each SET unit starts with a short reminder to reach the claudication. This note is important from our point of view as it often comes too short in the context of the activity and SET. The reminder function calls the importance of leaving the comfort zone instead of avoiding pain. Recent studies showed that patient education and empowerment through the increase of knowledge, skills, and confidence to overcome one's disease [35] is associated with the willingness for health-related behavioral changes [36,37]. To strengthen the patients'

educational background, we included information regarding patient events on different medical topics. Future app development processes should also include a larger section for evidence-based health information regarding PAD and major risk factors.

3. Gamification aspects: Gamification uses game design elements combined with principles of psychology outside the gaming context as a strategy to promote a desired behavior or sustain healthy habits of subjects over time using Web-based behavioral interventions [38,39]. In the context of mHealth technologies, these game components can be used to entertain and also educate and motivate patients. Health behavior interventions can utilize gamification to deliver highly engaging content, enhancing the degree and depth of participant interaction and increasing behavior-change learning opportunities [38-40]. In this study, we used 2 major gamification elements to reward self-performance in terms of performed SET. The achievement of predefined personal goals unlocked medals in the medal mirror and served as digital reward. In addition, the ranking in the leaderboard provided a platform for competitive interaction between the participants. Both components, digital rewards and leaderboards, are common gamification features and were previously shown to have an influence on health-related behavior [41,42].

In addition to the pure feasibility, we examined whether there is an enhanced pain-free walking distance or other improvements in our treatment group, which is referred to trackPAD. Other possible improvements are a higher patient's quality of life or a better leg perfusion resulting in reduced hospitalization, but they are limited to the 3-month follow-up period. The future vision of trackPAD is to serve as a tool for closing gaps in patient care owing to limited availability of personal and institutional resources.

Although SET is the basis of every PAD treatment, we limited the patient selection currently to Fontaine stage IIa or IIb to have a more homogeneous group in terms of walking distance and further stratification. Patients with Fontaine stage I are not limited by their walking distance and changes are hard to measure. Through the stratified randomization and dropouts, we did not receive an equal sized study and control group; however, as shown in Table 3, we currently see no reason for any potential bias caused by the distribution of this randomization. Nevertheless, the intention of this pilot study was to prove the feasibility of the upcoming main study and demonstrate potential pitfalls at an early stage. The average age of 66 years of the enrolled participants requires a highly intuitive app.

Although recent studies already investigated digital support tools on SET in patients with PAD [17,33,43], a stratification of walking distance was not performed yet. We advanced a first pilot study to access preliminary results for the inclusion into the calculation of the needed sample size.

The walking distance assessed by the 6-min walk test was chosen as primary endpoint as the increase of 20m showed a minimal clinical importance in a recent publication [23]. The

SD range assessed in the 6-min walk test in patients with PAD was 51m to 69m.

Limitations

One major limitation is surely the lack of blinding of the study participants. Motivational differences between the study and the control group might be driven by the fact that both groups were aware of the allocation to the respective group. A higher motivation to exercise because of the fact of only *having* the app or indeed *using* the app is not to differentiate. Further research is needed to address this issue. Owing to the focus on the first feasibility, this study is limited by its small sample size and its short follow-up period of only 3 months. As this paper focused on the technical development of an app especially designed for PAD-patients, it does not contain results beyond the baseline and also excludes a final app evaluation so far.

Another limitation is that although the patients were reminded via claudication reminder by starting each unit, no review of the actual activity load or walking pace until the onset of claudication was possible. Only an indirect assessment of claudication was available for the study group, including the number and duration of breaks within a SET unit and the pain assessment after each break, whereas no trend for SET performance in the control group is available. Moreover, in both study and control group, more than 50% of participants were already exercising and came from a certain exercise level assuming a simpler overcoming of motivational barriers. It is also to mention that studies including mobile interventions might serve as barriers to entry and the number of mobile phone possession in these patient groups is missing so far.

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Authors' Contributions

The conception and design of the study was performed by KP and JL and the administrative support by TR, SM and RAJ. CR, MS and RAJ supported by the provision of study materials.. The collection and assembly of data was done by KP, JS, GU, MS and JL. KP, JS, SM and TR performed the data analysis and interpretation:. All authors took part in the process of manuscript writing and gave their final approvals.

Conflicts of Interest

None declared.

Multimedia Appendix 1

CONSORT-eHealth (V 1.6.1) checklist.

[[PDF File \(Adobe PDF File\), 2MB - resprot_v8i6e13651_app1.pdf](#)]

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Abbreviations

- ABI:** ankle-brachial index
- ESC:** European Society of Cardiology
- FAQ:** frequently asked questions
- IC:** intermittent claudication
- mHealth:** mobile health
- PAD:** peripheral arterial disease
- SET:** supervised exercise therapy

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Protocol

Web-Based Self-Management Guide for Kidney Transplant Recipients (The Getting on With Your Life With a Transplanted Kidney Study): Protocol for Development and Preliminary Testing

Daniela Massierer^{1,2,3*}, BScPT, MSc, PhD; Ruth Sapir-Pichhadze^{2,4}, BMEDSC, MD, MSc, PhD, FRCPC; Vanessa Bouchard⁵, BScPT, MSc, PhD; Kaberi Dasgupta^{2,6,7,8}, MD, MSc, FRCPC; Nicolas Fernandez⁹, BA, MSc, PhD; Deborah da Costa^{2,7}, BA, MA, PhD; Sara Ahmed^{1,2}, BScPT, MSc, PhD; Marie-Chantal Fortin¹⁰, MD, PhD, FRCPC; Rosalie Langevin³, RN; Nancy Mayo^{1,2,11,12}, BScPT, MSc, PhD; Tania Janaudis-Ferreira^{1,2,3,13*}, BScPT, MSc, PhD

¹School of Physical and Occupational Therapy, McGill University, Montreal, QC, Canada

²Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, QC, Canada

³Canadian Donation and Transplantation Research Program, Edmonton, AB, Canada

⁴Division of Nephrology and Multi-Organ Transplant Program, Department of Medicine, McGill University, Montreal, QC, Canada

⁵Hôpital de Chicoutimi, Centre intégré universitaire de santé et services sociaux du Saguenay-Lac-Saint-Jean, Chicoutimi, QC, Canada

⁶Division of Endocrinology & Metabolism, McGill University Health Centre, Montreal, QC, Canada

⁷Division of Internal Medicine, McGill University Health Centre, Montreal, QC, Canada

⁸Metabolic Disorders and Complications, Research Institute of the McGill University Health Centre, Montreal, QC, Canada

⁹Department of Family Medicine and Emergency Medicine, University of Montreal, Montreal, QC, Canada

¹⁰Department of Medicine, University of Montreal, Montreal, QC, Canada

¹¹Division of Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada

¹²Division of Geriatrics, McGill University Health Centre, Montreal, QC, Canada

¹³Translational Research in Respiratory Diseases Program, Research Institute of the McGill University Health Centre, Montreal, QC, Canada

* these authors contributed equally

Corresponding Author:

Tania Janaudis-Ferreira, BScPT, MSc, PhD

School of Physical and Occupational Therapy

McGill University

Hosmer House

3654 Promenade Sir-William-Osler, Room #200

Montreal, QC,

Canada

Phone: 1 514 619 0871

Fax: 1 514 398 8193

Email: tania.janaudis-ferreira@mcgill.ca

Abstract

Background: Although it is well known that compared with dialysis, kidney transplantation improves the quality of life (QoL) of patients with end-stage renal disease, posttransplant recovery of physical health and other aspects of QoL remain well below age- and sex-matched norms. In addition, most transplant recipients are not physically active even years after the transplant and face several barriers to engaging in physical activity (PA). This is of concern as low levels of PA in transplant recipients has been associated with increased risk of mortality and poor graft function. Optimization of QoL needs a team approach involving the patients and the members of the health care team. While members of the health care team are focused on optimizing the biological responses to transplant, patients may have few or no tools at their disposal to engage in behaviors that optimize QoL. To accomplish the need of supporting these patients in the self-management of their condition and to facilitate engagement with PA, new tools tailored to this population are required.

Objective: The aim of this protocol study is to develop a Web-based, patient-centered self-management intervention to promote a healthy lifestyle, increase daily PA, and improve QoL in kidney transplant recipients.

Methods: We will use the Obesity-Related Behavioral Intervention Trials model for developing behavioral treatments for chronic diseases to guide the proposed project. We will follow a modified version of the iterative 10-step process that was used to develop educational material for people with multiple sclerosis. The development of the intervention will occur in partnership with patients and a multidisciplinary team of clinicians and researchers. A comprehensive needs assessment including data from our pilot study, literature review, and focus groups will be conducted. The focus groups will be conducted with 6 to 10 participants for each type of stakeholders: patients and professional experts to identify areas of concerns of kidney transplant recipients that are appropriate to address through self-management. The areas of concern identified through the assessment needs will be included in the website.

Results: This study has received funding from the Kidney Foundation of Canada for 2 years (2018-2020) and was recently granted ethics approval. Investigators have begun conducting the needs assessment described in step 1 of the study. The study is expected to be completed by the end of 2020.

Conclusions: This will be the first comprehensive, evidence- and experience-based self-management program for kidney transplant recipients. Once the intervention is developed, we anticipate improvements in patient experience, shared decision making, daily PA, QoL, and, in future studies, improvements in health outcomes and demonstrations of cost savings in posttransplant care.

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KEYWORDS

self-management; kidney transplantation; eHealth; quality of life; exercise; physical activity

Introduction

Benefits of Kidney Transplantation to the Individual and Society

In 2016, there were a total of 2835 solid organ transplants performed in Canada [1]. Of those, more than 61.05% (1731/2835) were kidney transplants. Kidney transplantation doubles life expectancy of the recipient compared with dialysis and, importantly, leads to considerable cost savings [1].

Shift From Transplant Outcomes and Mortality to Quality of Life

Although kidney transplantation undoubtedly prolongs life of people with end-stage renal disease (ESRD) and confers great economic benefits to the society [1], the challenges experienced by recipients do not end after the transplantation. With considerable advances in organ preservation, surgical techniques, and immunosuppressive therapy, short-term survival following solid organ transplant has greatly improved [2]. As a result of improved graft survival and reduced deaths from infection or rejection, health care professionals and researchers have started to shift their focus toward reducing morbidity from cardiovascular disease and sustaining improvements in quality of life (QoL) [3-5].

Quality of Life After Kidney Transplantation

Compared with dialysis, transplantation improves the QoL of patients with ESRD; however, physical health and other aspects of QoL among transplant recipients remain below age- and sex-matched norms [5-8]. Our group recently used a personalized measure of QoL, the Patient Generated Index (PGI) questionnaire ([Multimedia Appendix 1](#)), to evaluate 51 kidney transplant recipients (mean age 58.6, SD 11.6 years; 1 to 3+ years after transplant). We aimed to identify particular areas of QoL that are affected by having experienced a kidney transplant and found that 71% (36/51) of the kidney transplant recipients

reported at least one health concern. The top identified areas were physiological complaints (eg, urine infection and abnormal blood tests), nutrition, mobility, fatigue, pain, and mood/emotions [9].

Decreased Levels of Physical Activity

Low physical activity (PA) levels in transplant candidates and recipients are associated with important clinical outcomes including increased wait-list mortality [10,11], cardiovascular and all-cause mortality after transplant [4], and poor posttransplant outcomes [12]. Living a physically active lifestyle can help mitigate secondary chronic conditions that arise after transplant, such as high blood pressure, glucose intolerance/diabetes, osteoporosis, sarcopenia and fatigue, [13] as well as improve aerobic capacity and QoL in transplant recipients [13]. Despite numerous health benefits, most transplant recipients are not physically active even years after transplant and face several barriers to engaging in PA [14]. Our group showed, in a survey of 113 Canadian solid organ transplant recipients (65 men and 47 women) who were aged between 40 and 70 years and 1 to 5 years posttransplant, that 60% of participants were engaging in low levels of PA, and 16% had activity levels lower than what has been observed in frail individuals [14]. In addition, a large number of these individuals had never engaged in light to strenuous exercise or strengthening exercises [14].

Barriers to Being Physically Active and Poor Availability of Rehabilitation Programs

Helping people adopt a physically active lifestyle requires an understanding of the barriers to and facilitators of PA. Sullivan and colleagues [15] have described that in people with chronic health conditions, environmental obstacles (not knowing where to exercise), time constraints (believing there is not enough time to exercise), and social limitations (not having support for exercise) are important barriers that need to be addressed in tailored PA interventions. We have found that transplant

recipients report cost (of exercise facilities), side effects of medications, and lack of knowledge/guidelines on exercise after transplant as the major barriers to engaging in PA [14]. In the same study, “motivation to stay healthy” and “physician recommendation” were cited as the leading facilitators to being more physically active [14]. However, in a follow-up survey with Canadian transplant physicians [16], we found that while most of the transplant physicians reported that they counsel transplant recipients about PA, only 27% provided counseling to 100% of their patients, and 18% felt confident in doing so. Lack of time and lack of specific exercise guidelines to transplant recipients were identified as the main barriers to PA counseling. In addition, based on a Canadian survey, there are very few dedicated solid organ transplant rehabilitation programs in Canada [17]; most programs are for heart and lung transplant recipients, with only 1 program available for liver recipients and none for kidney recipients. Therefore, based on the barriers and gaps identified at the patient-health care professional—and health care system—levels, kidney transplant recipients require support in developing skills to be able to enhance their lifestyle. To accomplish the need of supporting these patients in self-managing their health burdens and to engage with PA, new easily accessible tools are required.

Self-Management—An Ideal Intervention to Improve Quality of Life in Kidney Recipients

Given the comprehensive nature of the problems experienced by kidney recipients and that every aspect of QoL can be negatively affected, a self-management intervention is the natural approach to improve QoL in these individuals [18]. Self-management is a lifelong task where the individual takes responsibility to manage the symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent in living with a chronic condition. It focuses on the development of core skills related to self-assessment, goal setting, problem solving, decision making, resource utilization, partnership between patient and health care provider, and action plans [19]. The benefit of self-management for kidney transplant recipients is that it is individualized and focuses on enhancing the ability of individuals to improve their health status, regardless of where the individual is on the journey after transplant. Although self-management has been shown to be effective in many chronic conditions, a comprehensive, evidence- and experience-based self-management program that includes support to increase levels of PA is not available for kidney transplant recipients anywhere in the world. We found only 2 papers in the literature describing the development of a self-management program for kidney transplant recipients. Schmid-Mohler and colleagues [20] developed a self-management program in Switzerland for kidney recipients who were in their first year after transplant; however, this program is only available in German, has a limited focus on the prevention of weight gain, increasing PA, and medication adherence and does not offer an electronic health app for symptom monitoring. A study from the Netherlands [21] described a self-management online support system, but this study also had a limited approach. In this study, kidney recipients were asked to use a blood pressure monitor and a

creatinine measurement device at home according to a fixed schedule. In Canada, the scenario is not different. The self-management tools that are available in Canadian Transplant Centers where kidney transplant is performed are mainly focused on medication management, side effects identification, medication interaction awareness, and infection risk (oral or email communication with collaborators in each site). Although very important, these topics do not cover other areas of concern that are important to patients such as mobility, PA, fatigue, pain, and mood/emotions. This demonstrates a gap in care after transplant in Canada and the need for new tools to assist kidney transplant recipients build the skills and attitudes required to effectively self-manage different aspects of their lives after the transplant.

The overarching goal of our study is to develop a patient-centered intervention to increase daily PA and improve QoL in kidney transplant recipients. We propose to develop *Getting on with your life with a transplanted kidney (GETONTRAK)*, a Web-based program for the promotion of PA and self-management in kidney transplant recipients. The specific aims are (1) to develop a comprehensive Web-based guide for the promotion of PA and self-management in kidney transplant recipients and (2) to examine the changes in daily step counts and QoL after delivering the GETONTRAK self-management program to kidney transplant recipients to collect preliminary data for a future pilot randomized controlled trial.

Methods

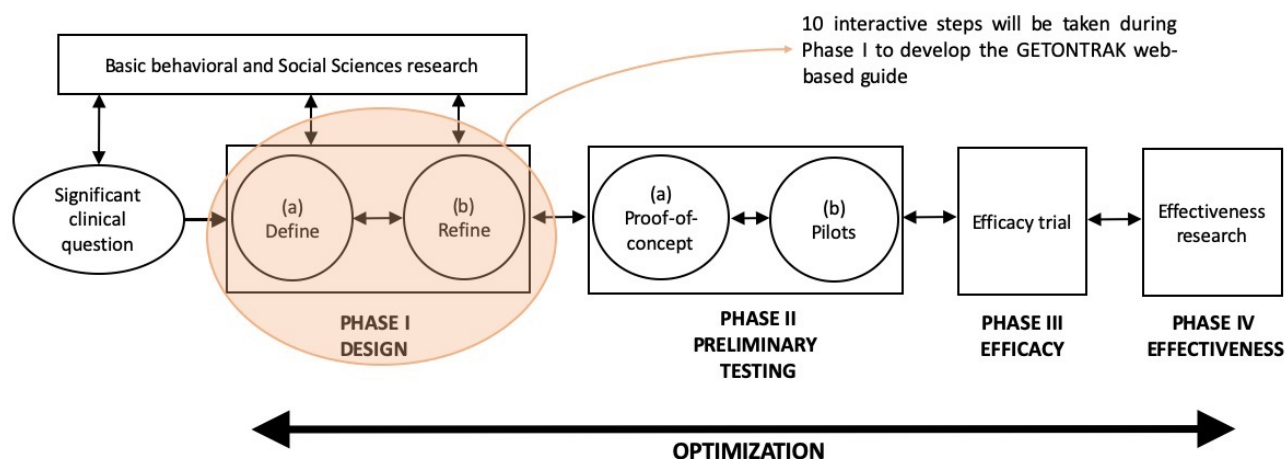
Overview

The study will take place at the Research Institute of the McGill University Health Centre (RI-MUHC) in Montreal, Canada, between December 2018 and December 2020. The study received ethics approval by the MUHC Research Ethics Board (2019-4875).

We will use the Obesity-Related Behavioral Intervention Trials (ORBIT) model for developing behavioral treatments for chronic diseases [22] to guide the proposed project and develop our Web-based guide, the GETONTRAK. The ORBIT model provides guidance on the process of treatment development using a progressive and transdisciplinary approach. Our project falls into phase I of the ORBIT model, which is the design phase of a behavioral intervention (Figure 1).

To meet the goal of phase I (design and define the intervention), we will follow a modified version of the iterative 10-step process that was used to develop educational material prepared for people with multiple sclerosis [23]. These steps will include (1) assessment of the needs of the population, (2) format development, (3) obtaining content for the topics, (4) content adaptation to fit the purpose, (5) obtaining feedback, (6) finalizing the content for the topics, (7) website screen design, (8) translation to French and peer review evaluation, (9) preliminary testing, and (10) integrating feedback to update the website.

Figure 1. The Obesity-Related Behavioral Intervention Trials model. GETONTRAK: Getting on with your life with a transplanted kidney.



The 10-Step Process

Step 1: Assessing the Needs of the Population

We will use several methods to identify the needs of kidney transplant recipients that are appropriate to address through self-management. As a starting point, we will conduct a systematic literature search of the literature on the physical and psychological impairments that kidney recipients experience after transplantation (during first year or later), affected areas of QoL, and side effects of medications. We will also use data from our pilot study that aimed to identify the particular areas of QoL that are affected by the experience of a kidney transplant. Our pilot study uncovered a large number of unmet needs (kidney recipients identified physiological issues, nutrition, mobility, pain, and mood/emotions as being the most common affected areas of their lives after the kidney transplant [9]). These data will be used to help create the topics to be addressed in the self-management guide. In addition, we will conduct focus groups with patients, clinicians, and researchers to confirm the topics identified through the review and pilot work and/or identify new ones. Our plan is to conduct between 4 and 6 focus groups for each type of stakeholders (patients and clinicians/researchers), which will last about 1.5 hours. All focus groups will be conducted at the MUHC, and informed consent for participation will be obtained at the MUHC. The focus groups will consist of 6 to 10 participants and 1 or 2 moderators. The moderators will work to create a climate of mutual respect and facilitate the discussion among the participants. Data gathering will be considered complete when (1) data saturation is reached (ie, new focus groups do not provide additional information) and (2) there is sufficient internal diversification in terms of respondent characteristics (sex, age, profession, etc). Our sampling strategy will be purposive. For example, we will select experienced professionals (at least 2 years working with kidney transplant patients) with different backgrounds (eg physicians, pharmacists, physiotherapists, occupational therapists, psychologists, nurses, and social worker), sex, age, and from different regions in Canada. We will also aim to recruit kidney transplant recipients (of both sexes, different age and ethnic background and different time after transplant) through the Patient Partnership Platform of the Canadian Donation and Transplantation Research Program (CDTRP), MUHC and Centre

Hospitalier de l'Université de Montréal (CHUM), and the Canadian Network for Rehabilitation and Exercise for Solid Organ Transplant Optimal Recovery (CAN-RESTORE) website and social media. To ensure consistency in the focus group meetings, the same facilitator will run all the focus group meetings using a meeting script ([Multimedia Appendix 2](#)). The focus group sessions will mostly be in English and will be audio-recorded, and 2 additional researchers will participate to take notes to capture nonverbal data. Participants will be excluded if they are unable or have limited ability to speak English. Due to the nature of focus groups, it is impossible to guarantee complete confidentiality as other members of the group will be aware of your identity. However, all participants are instructed to keep what is said in the focus group confidential.

Qualitative Data Analysis

Data collection and analysis will occur concurrently and iteratively. This process will be done to allow the research team to identify new areas of discussion and determine when saturation has been achieved [24]. Detailed notes and the audio recordings will be analyzed using the content and thematic analysis method described by Miles and Huberman [25]. Employing this method, the investigators will (1) establish a list of themes that will constitute the coding frame; (2) read the notes, listen to the audio recordings, and sort them according to this coding frame to create a more abstract frame of analysis; (3) add new themes or categories as they emerge from the notes; (4) organize these categories into figures, charts, or matrices; and (5) draw corresponding conclusions. A list of codes will be developed according to the research questions. To meet the quality criteria (validity and reliability) for qualitative research, we will present our results to different groups of stakeholders [24,26]. Following this comprehensive process of step 1, we will create a list of topics for inclusion in the Web-based self-management guide. These topics may be relevant to any stage after transplant (within first year of transplant or later). In addition to the topics related to the recipients' concerns after transplant, we will include generic topics relevant to self-management to enhance kidney recipients' capacity to take charge of their health (including promotion of PA). These topics will address self-management skills and attitudes of

self-assessment, goal setting, motivation, and developing an action plan.

Step 2: Develop the Format

We will work with Expression Web Solutions, a specialized company in offering digital solutions, and plan the format of the website. A preliminary website architecture is shown in [Multimedia Appendix 3](#). The website will include 5 key sections that will cover developing self-management skills as well as the specific topics chosen in step 1. The sections are described below:

Getting Started

This first section will introduce self-management and be designed to orient the new user to the goals and skills needed for self-management. Patients will identify areas of QoL (using a personalized measure of QoL, the PGI) they think are affected to identify the content of the guide that are most relevant to them. Thereafter, they will be directed to an inventory of facilitators and barriers that influences their approach to life after transplantation, form goals, and build an action plan.

Healthy Life Style for All

This section will include topics that are relevant to anyone with or without a chronic disease such as healthy eating and drinking, sleep, stress reduction, and challenging your mind and body.

Dealing With Posttransplant Challenges

This section will include content to help deal with the challenges that the life after transplant may bring to kidney transplant recipients. The topics of this section will be identified during step 1. It will contain information about the specific topic (“Did You Know?”) and the research evidence (“Research Evidence Shows”). It will also include a self-assessment tool (“How Am I Doing?”) and information on what to do (“What Can I Do?”) and how to do it (“How Can I Do it?”).

Partnering Effectively With Your Health Care Team

This section will help transplant recipients develop the necessary skills to become an active member of the health care team and will include topics such as how to get the most out of each health care meeting, managing uncertainty, understanding the vocabulary, and tests doctors use and learning how to use online resources.

Putting It All Together

This last section will show the user how to build their personal plan of action by prioritizing goals, monitoring progress, and making adjustments as needed.

Step 3: Obtain Content for the Topics

In addition to the investigative team, clinicians and researchers with expertise in kidney transplantation will be identified through our center (MUHC), the CHUM, CDTRP, and published literature. Content will be informed by published systematic reviews. When systematic reviews are not available, experts will conduct their own review to guide the content for each topic. These experts are not considered to be research participants but rather expert consultants, and they will be paid accordingly.

Step 4: Adapt the Content to Fit the Purpose

The content provided by the experts will be edited by the coprincipal investigators and other members of the investigative team and rewritten in layperson’s language, aiming at a grade 6 or 7 reading level. Medical terms will be defined. Link or references to other good electronic resources and webpages will be included into the page rather than repeating the information.

Step 5: Obtain Feedback

A minimum of 2 patient partners and 1 caregiver will be recruited from the Patient Partnership Platform of the CDTRP and the CAN-RESTORE website to provide feedback on the content of each topic. Specifically, they will provide feedback on the relevance of the content as well as on the usefulness, clarity, and applicability of the information. This feedback will be used to make changes to the content. In case of major reorganization or rewriting, a second round of patient feedback will be performed. Participants will be informed that they are participating in a study and that agreeing to provide feedback will serve as their consent to participate in the study.

Step 6: Finalize the Content for the Topics

At this stage, the coprincipal investigators and other members of the investigative team will review the feedback provided by the patient partners and caregivers and incorporate them into the content for each topic. Suggestions for images and formatting will be made in preparation for screen design.

Step 7: Screen Design

When the content of each topic is finalized, it will be sent to Expression Web Solutions for screen design. The website prototype will be reviewed by the research team and 2 patient partners for ease of reading, image choice, and placement and usability.

Step 8: Translation to French and Peer Review Evaluation

Once the website prototype is finalized, it will be translated to French. We will contact national and international experts in clinical content and self-management who will not have been involved with the development content of the website to evaluate the extent to which the GETONTRAK Web-based guide is consistent with the evidence; up to date, useful, and clear with respect to their messages and actions; and with a low risk of harm. These experts will fill out a Web-based survey to obtain structured feedback based on the Patient Education Materials Assessment Tool (PEMAT) [27]. The PEMAT uses a systematic approach to evaluate the understandability and actionability of patient education materials. Shoemaker and colleagues [27] suggested a cutoff of 70% for understandability and actionability. The reviewers will be identified through the published literature and during the focus groups with professionals (they will be asked to list names of potential reviewers). A minimum of 2 reviewers will be assigned per topic for each version of the website (English and French). Monetary compensation will be offered to enhance participation.

Step 9: Preliminary Testing

We will recruit a convenience sample of 10 kidney transplant recipients (eg, 5 French and 5 English speakers) from the outpatient clinic of the MUHC to use the GETONTRAK website as intended and provide feedback on their experience as users. GETONTRAK website will be open access to all its components. To ensure that selected participants are representative of the outpatient clinic, attention will be paid to selecting participants of different sexes, ages, levels of PA, time after transplant, and sociocultural backgrounds. We will select patients with and without computer/internet literacy. A brief explanation of the GETONTRAK online guide will be given to patients before the testing period. Informed consent for participation will be obtained at the MUHC outpatient clinic.

For baseline assessment (T0), in addition to collecting demographic data, patients will complete 3 QoL questionnaires (PGI, EuroQoL five-dimensional questionnaire, and Kidney Transplant Questionnaire) and will be asked to wear a PiezoRxD Pedometer on the waist for 7 days consecutive and at least for 12 hours per day. At this time, patients will not have seen the pedometer-based walking program offered in the GETONTRAK Web-based guide. After the initial assessment is completed, patients will meet with the research coordinator, be asked about their self-management habits, and receive instructions on how to use the website, including the pedometer-based walking program. They will be asked to use the GETONTRAK website for 2 months. After 2 months (T2), patients will complete the 3 QoL questionnaires again, and daily steps data from the last week of the 2-month period will be used for comparison with the baseline data. To monitor adherence to the pedometer-based walking program, patients will be asked to complete a diary with information on days and times they could not wear the PiezoRxD Pedometer and respective reasons. At T2, patients will be asked about the acceptability and usability of the Web-based self-management guide. We will use a mixed-methods approach comprising self-report questionnaire, semistructured telephone interview ([Multimedia Appendix 4](#)), and system usage data to assess acceptability and usability. The online survey administered at T2 will assess usability (layout, navigation, functionality, and features) and acceptability (overall usefulness, usefulness of specific topics, utility of the site for improving PA and other aspects of their life, credibility, and program length). Responses to each item will be rated on a Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). The telephone interview will inquire about the most helpful sections, barriers and reasons for nonuse, or discontinued use and solicit suggestions for additions, deletions, and improvements. The online survey and interview questions are guided by previous usability/acceptability studies [28,29] and recommendations from the Science Panel on Interactive Communications and Health [30] for website usability evaluation. Self-reported questionnaires and the interviews will be available in English and French.

Step 10: Integrate Feedback to Update the Website

At this stage, we will incorporate the feedback received, transmit the modification to the health technology partner, and a new

version of the website will be produced. The investigators intend to update the content of the website periodically.

Results

This study has received funding from the Kidney Foundation of Canada for 2 years (2018-2020) and recently been granted ethics approval. Investigators have begun to conduct the needs assessment described in step 1 of the study (January-April 2019). The study is expected to be completed by the end of 2020.

The GETONTRAK Web-based guide will improve information delivery, monitoring of symptom progression, and patient empowerment. By using our educational material, kidney recipients will develop 5 core skills: problem solving, decision making, resource utilization, forming patient/health care provider partnership, and taking action. Our knowledge tool has great potential to improve health outcomes and patient experience after transplantation as well as to reduce health care costs as patients will take charge of their health and may have fewer medical visits. However, these outcomes will be evaluated in future studies.

Discussion

Impact

The steps taken in this project will ensure that a comprehensive, evidence- and experience- based self-management program is available for kidney transplant recipients in Canada and other parts of the world.

Potential Challenges

The coinvestigators, NM and VB, who developed the process with 10 iterative steps for the development of global self-management programs [23], shared their lessons learned, which are as follows: (1) involve patient partners early on to ensure relevance of the topics, (2) have a structure and a template to plan and organize the content, (3) get a Web-design team involved early on so the format is developed along with the content, (4) there is no need to abandon medical language; rather it should be explained and simplified. (5) Recruitment is always a challenge in any clinical study, so to minimize recruitment issues and ensure consistent participation, offer an honorarium for patient partners, study participants, experts (content writers), and peer-reviewers. Finally, the 10 steps are iterative and allow for several opportunities for feedback and consequently improvements in the content and format of the website.

Once the GETONTRAK is developed and its benefits confirmed (future randomized control trial [RCT]), the authors will need to focus on the dissemination and implementation of the guide to all transplant centers and clinics in Canada and around the world to ensure that health care professionals and patients are aware of this new resource. After the self-management is developed and implemented in clinical practice, some potential challenges may appear. Some individuals may have limited access to technological resources or may show lower general engagement with health care and health-related interventions. Strategies to mitigate barriers to technological access should

be taken into consideration when offering the GETONTRAK intervention. These strategies may include offering a workbook or rented computer/tablets instead. Other barriers such as side effects of medication may interfere with the willingness of patients to participate in interventions that involve PA [14] as they may not feel well enough to become more active. Nevertheless, patients will have access to many other topics in the GETONTRAK self-management guide, which will give them the opportunity to improve their QoL regardless of their readiness to be part of a PA program.

Next Steps

When step 10 is finalized, the investigators will move to phase II of the ORBIT model (Figure 1) and conduct an RCT to pilot-test the GETONTRAK website. This RCT is not part of this protocol and will include outcomes such as adherence, patient empowerment, QoL, PA, and health care utilization. As research is always evolving, the investigators intend to update the content of the website periodically.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Patient Generated Index (PGI) questionnaire.

[PNG File, 452KB - [resprot_v8i6e13420_app1.png](#)]

Multimedia Appendix 2

Description of the script of the focus group meetings.

[PDF File (Adobe PDF File), 24KB - [resprot_v8i6e13420_app2.pdf](#)]

Multimedia Appendix 3

Preliminary website architecture.

[PNG File, 211KB - [resprot_v8i6e13420_app3.png](#)]

Multimedia Appendix 4

Semistructured telephone interview.

[PDF File (Adobe PDF File), 55KB - [resprot_v8i6e13420_app4.pdf](#)]

Multimedia Appendix 5

Peer-reviewer report from the Kidney Foundation of Canada.

[PDF File (Adobe PDF File), 192KB - [resprot_v8i6e13420_app5.pdf](#)]

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Abbreviations

CDTRP: Canadian Donation and Transplantation Research Program

CHUM: Centre Hospitalier de l'Université de Montréal

ESRD: end-stage renal disease

GETONTRAK: Getting on with your life with a transplanted kidney

MUHC: McGill University Health Centre

ORBIT: Obesity-Related Behavioral Intervention Trials

PA: physical activity

PEMAT: Patient Education Materials Assessment Tool

PGI: Patient Generated Index

QoL: quality of life

RCT: randomized controlled trial

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Protocol

Adapting the HIV Infant Tracking System to Support Prevention of Mother-to-Child Transmission of HIV in Kenya: Protocol for an Intervention Development Pilot Study in Two Hospitals

Sarah Finocchiaro-Kessler¹, PhD; May Maloba², MCH; Melinda Brown¹, MSPH; Brad Gautney³, MPH; Kathy Goggin^{4,5,6}, PhD; Catherine Wexler¹, MPH; Natabhona Mabachi¹, PhD; Beryne Odeny¹, MBChB; Silas Lagat⁷, CO; Sharon Koech⁸, BSc; Jacinda K Dariotis⁹, PhD; Thomas A Odeny^{4,8}, PhD

¹Department of Family Medicine, University of Kansas Medical Center, Kansas City, KS, United States

²Global Health Innovations, Nairobi, Kenya

³Global Health Innovations, Dallas, TX, United States

⁴School of Medicine, University of Missouri-Kansas City, Kansas City, MO, United States

⁵Health Services and Outcomes Research, Children's Mercy Kansas City, Kansas City, MO, United States

⁶School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO, United States

⁷Ministry of Health, Nandi County, Kapsabet, Kenya

⁸Center for Microbiology Research, Kenya Medical Research Institute, Nairobi, Kenya

⁹College of Education, Criminal Justice & Human Services, University of Cincinnati, Cincinnati, OH, United States

Corresponding Author:

Sarah Finocchiaro-Kessler, PhD

Department of Family Medicine

University of Kansas Medical Center

Mail Stop 4010

3901 Rainbow Boulevard

Kansas City, KS, 66160

United States

Phone: 1 913 945 7077

Email: skessler2@kumc.edu

Abstract

Background: Despite progress to expand access to HIV testing and treatment during pregnancy in Kenya, gaps still remain in prevention of mother-to-child transmission of HIV (PMTCT) services. This study addresses the need for effective and scalable interventions to support women throughout the continuum of care for PMTCT services in low-resource settings. Our research team has successfully implemented the HIV Infant Tracking System (HITSsystem), a Web-based, system-level intervention to improve early infant diagnosis (EID) outcomes.

Objective: This study will expand the scope of the HITSsystem to address PMTCT services to bridge the gap between maternal and pediatric HIV services and improve outcomes. This paper describes the intervention development protocol to adapt and pilot an HITSsystem version 2.0 to assess acceptability, feasibility, and preliminary PMTCT outcomes in Kenya.

Methods: This is a 3-year intervention development study to adapt the current HITSsystem intervention to support a range of PMTCT outcomes including appointment attendance, antiretroviral therapy (ART) adherence, hospital deliveries, and integration of maternal and pediatric HIV services in low-resource settings. The study will be conducted in 3 phases. *Phase 1* will elicit feedback from intervention users (patients and providers) to guide development and refinement of the new PMTCT components and inform optimal implementation. In *Phase 2*, we will design and develop the HITSsystem 2.0 features to support key PMTCT outcomes guided by clinical content experts and findings from Phase 1. *Phase 3* will assess complete PMTCT retention (before, during, and after delivery) using a matched randomized pilot study design in 2 hospitals over 18 months. A total of N=108 HIV-positive pregnant women (n=54 per site) will be enrolled and followed from their first PMTCT appointment until infant HIV DNA Polymerase Chain Reaction testing at the target age of 6 weeks (<7 weeks) postnatal.

Results: Funding for this study was received in August 2015, enrollment in Phase 1 began in March 2016, and completion of data collection is expected by May 2019.

Conclusions: This protocol will extend, adapt, and pilot an HITSsystem 2.0 version to improve attendance of PMTCT appointments, increase ART adherence and hospital-based deliveries, and prompt EID by 6 weeks postnatal. The HITSsystem 2.0 aims to improve the integration of maternal and pediatric HIV services.

Trial Registration: ClinicalTrials.gov NCT02726607; <https://clinicaltrials.gov/ct2/show/NCT02726607> (Archived by WebCite at <http://www.webcitation.org/78VraLrOb>)

International Registered Report Identifier (IRRID): DERR1-10.2196/13268

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KEYWORDS

HIV; eHealth; mHealth; pregnancy; retention; medication adherence; infant; diagnosis; Kenya

Introduction

Background

Despite impressive progress to expand access to HIV testing and treatment during pregnancy in Kenya [1,2], gaps still remain in achieving comprehensive prevention of mother-to-child transmission of HIV (PMTCT) services. Despite widespread access (77% to 80%) to the highly efficacious Option B+ antiretroviral therapy (ART), the current rate of perinatal transmission in Kenya is estimated at 8.3% to 11.5% [3-5]. Late and inconsistent attendance at antenatal appointments, suboptimal ART adherence during pregnancy and breastfeeding, high rates of unskilled deliveries, and high dropout throughout the PMTCT cascade are among the barriers to eliminating perinatal HIV infection in Kenya [6].

Although Kenyan national guidelines encourage 4 or more antenatal care (ANC) visits [7], an estimated 11.2% to 57.6% [8,9] attend all 4 appointments, with 95% of women attending at least 1 ANC appointment [2]. Attendance of all PMTCT appointments is crucial for monitoring treatment, progression of pregnancy, and managing risk of transmission. Poor medication adherence during pregnancy and breastfeeding compromises the efficacy of ART to prevent HIV transmission. In Kenya, approximately 15% to 20% of pregnant and postpartum women are less than 95% adherent to their ART regimen [10,11]. Since 2012, hospital deliveries are free of charge; yet, nationwide, only 61% of births are facility-based [9], with HIV positive women more likely to have a nonfacility delivery than HIV uninfected women [12]. Home deliveries among HIV positive women miss opportunities for timely infant ART prophylaxis, which can reduce the risk of perinatal transmission by up to 47% in low-resource settings [13-16]. Infants of mothers with suboptimal drug adherence are more vulnerable to perinatal HIV transmission [17,18], thus infant ART prophylaxis remains a critical safeguard.

The PMTCT cascade necessitates that women successfully navigate a series of steps including maternal HIV counseling and testing, initiation and monitoring of ART, delivery care, infant ART and cotrimoxazole prophylaxis, linkage into early infant diagnosis (EID) care for their HIV-exposed infants, and linkage to lifelong HIV care for themselves. Although HIV testing during ANC is high (93.1%) [2], rates of retention after successful linkage to PMTCT are low. In a study conducted by Ayuo et al [19], 31.9% of pregnant women enrolled in PMTCT were disengaged from care for more than 30 consecutive days

(thus missing a medication refill appointment) at least once during their pregnancy, with 22.5% of all patients disengaged during the critical phase immediately before delivery. These data reflect a setting with an active outreach program for retention and thus may underestimate attrition in facilities without outreach programs. After delivery, an additional 19.3% to 45% of infants are lost to follow-up [20,21]. At least one quarter of infants are enrolled late in EID, missing the target for EID testing by 6 weeks of age [22]. Consequently, a significant proportion of mother-infant pairs receive incomplete services [23].

Mobile phone and Web-based technologies provide viable solutions to individual and system-level challenges in the delivery of HIV services in Kenya and other African countries. Short message service (SMS) text messaging interventions have improved attendance at ANC appointments [24,25], medication adherence and viral suppression [15,16], and postpartum PMTCT retention [26]. Tailoring health messages to the individuals within the target population increases participant retention and is critical to the success of mHealth interventions [27-29]. Most mHealth interventions for EID have focused on lab-specific efficiency [30], patient-specific adherence, or retention support [31], whereas the HIV Infant Tracking System (HITSsystem) mHealth intervention was the first to link laboratory, clinical, and patient stakeholders in one integrated system [32].

This study addresses the need for effective and scalable interventions to coordinate the continuum of care for PMTCT services in low-resource settings to maximize retention and minimize infant HIV infection. Our research team has successfully implemented a Web-based mHealth intervention called the HITSsystem, which utilizes available technology (internet and texting) to improve communication and accountability between EID stakeholders to optimize outcomes for HIV-exposed infants [33,34]. The HITSsystem is unique as a *system-level* mHealth intervention combining SMS outreach to mothers of HIV-exposed infants and algorithm-based dashboard alerts to prompt provider (maternal and child health [MCH]/HIV and laboratory) action, and it demonstrated significant reductions in turnaround times for Polymerase Chain Reaction (PCR) test results (2.3 weeks faster), mother notification of results (1.3 weeks faster), younger infant age at ART initiation (7.6 weeks younger), and higher retention throughout the complete 18-month EID cascade of care (85% vs 60%; aOR 3.7 (2.5 to 5.5); $P < .001$) when compared with standard EID services [32]. This proposal responds to requests

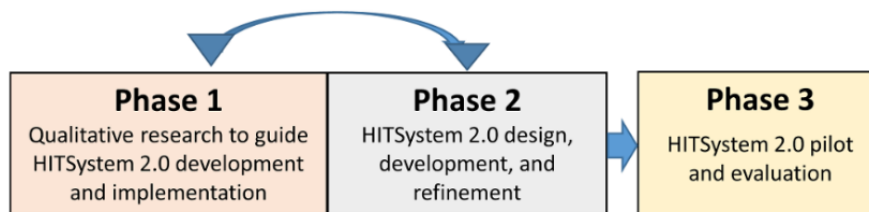
from hospital administrators and health care providers to expand the scope of the HITSsystem to include antenatal PMTCT services and to bridge the current gap between maternal and pediatric HIV services. Thus, this intervention development protocol will adapt and pilot an HITSsystem version 2.0 that prospectively tracks and supports HIV positive women through their pregnancy and delivery, linking them to EID follow-up at birth (initial HITSsystem 1.0) to facilitate linked mother-infant data and retention. We will assess the acceptability, feasibility, and preliminary impact on PMTCT retention of the HITSsystem 2.0 intervention.

Study Overview

This is a 3-year intervention development study to adapt and pilot test an extension of the current HITSsystem intervention to support a range of PMTCT outcomes including retention in ANC, ART adherence, hospital deliveries, and integration of

maternal and pediatric HIV services in low-resource settings. The study will be conducted in 3 phases (Figure 1). *Phase 1* is designed to elicit feedback from intervention users (patients and providers) to guide development of the new PMTCT components and inform optimal implementation at the intervention site. *Phase 2* involves the technical design and development of HITSsystem 2.0, a new iteration of the HITSsystem to support key PMTCT outcomes (appointment attendance, ART medication adherence, hospital-based delivery, and linkage to EID). Phase 2 development will be guided by clinical content experts and findings from Phase 1. This involves close collaboration with programmers and system users to refine the interface and customize options. *Phase 3* will pilot the HITSsystem 2.0 in 1 hospital over an 18-month period and compare targeted PMTCT outcomes with those at a matched control hospital.

Figure 1. Study phases—an iterative process of qualitative research and HIV Infant Tracking System (HITSsystem) 2.0 design, development, and refinement, which precedes the HITSsystem 2.0 pilot and evaluation.



Methods

Phase 1: Formative Research

Phase 1 seeks to understand optimal HITSsystem SMS text messaging strategies. We draw on the Information Processing Communication Theory [35-37], which identifies the conditions that encourage people to actively attend to health messages, to guide questions regarding text message content and timing. We will recruit HIV positive pregnant and postpartum women who are/were enrolled in PMTCT care at the intervention site to participate in 3 focus groups to elicit (1) strategic communication and customization of SMS text messages to motivate target behaviors while protecting confidentiality, (2) barriers to patient retention and ART adherence, and (3) strategies for mobile phone outreach and alternatives for patient follow-up. Focus groups will include n=8 women, with 2 of the 3 focus groups including HIV-positive pregnant women (second and third trimester) and the third including HIV-positive postpartum women (2 to 16 weeks), thus representing a range of gestational and postpartum periods. In addition, key informant interviews will be conducted with all staff engaged in PMTCT services (antenatal, maternity, postnatal, laboratory, pharmacy, and mentor mothers; approximately n=8) at the intervention site to strategize optimal HITSsystem 2.0 implementation, given PMTCT provider capacity and existing systems for patient flow. In addition to notetaking, with participants' consent, the focus groups and interviews will be digitally recorded. Participants will receive 500 Kenyan Shillings (approximately US \$5) in appreciation of their time. The research protocol was reviewed and approved by IRB at the Kenya Medical Research Institute in Nairobi, Kenya, and the University of Kansas Medical Center.

Informed consent was conducted with all participants before study engagement.

Analyses for Focus Group and Key Informant Interview Data

Audio files will be translated and transcribed in English, coded, and analyzed. In total, 2 study team members will independently code data for a priori (preferences for health messaging, potential barriers to retention and ART adherence, alternative strategies for patient follow-up, and provider recommendations for optimal implementation) and emergent themes. Through consensus, we will develop a codebook with typical exemplars for each theme, noting the frequency and distribution of themes within the larger topic areas. Summarized themes will directly inform HITSsystem 2.0 development in Phase 2.

Phase 2: Intervention Development

HITSsystem 1.0 is currently in use in multiple health facilities in Kenya. The primary goals of the HITSsystem 1.0 are to (1) improve EID and clinical management of HIV-exposed infants and (2) facilitate early ART initiation for HIV positive infants [33,34,38,39]. The HITSsystem is accessed on the Web using a computer or tablet, with mobile broadband modems that respond to a cellular signal. The primary components include (1) provider alerts to complete time-sensitive interventions, (2) real-time communication of PCR laboratory results to hospitals to reduce turnaround time, (3) persistent follow-up for timely ART initiation among HIV-positive infants, and (4) retention in EID care via SMS text messaging and/or patient tracing.

The HITSsystem 2.0 intervention will (1) utilize electronic prompts to notify PMTCT providers and program managers when action is required to support timely services, patient

retention and adherence, and linkage to EID once infants are born [33,34] and (2) send SMS text messages to HIV-positive pregnant women's mobile phones with the aim to motivate adherence to medication, remind women of ANC appointments and medication refills, and prompt preparation for a hospital delivery.

HIV Infant Tracking System 2.0 Intervention Specifications

Clear reporting of intervention components and implementation strategies is needed for meaningful application in practice or testing in research [40,41]. The entry point into the HITSsystem 2.0 will be the first PMTCT appointment for women previously diagnosed with HIV or newly confirmed HIV positive during antenatal HIV screening. Actions include automated prompts to PMTCT providers, prompts to central laboratory technicians who process viral load (VL) samples, and SMS texts to patients

driven by national algorithms for optimal PMTCT care (Table 1). Automated electronic prompts to providers will persist as Web-based dashboard alerts until addressed. Automated SMS texts are sent to HIV-positive pregnant women as cues to action; women can select the preferred content and frequency for one-way ART adherence text messages at the time of enrollment. This is one of the first interventions to target adherence support messages during pregnancy, thus texting options (content and frequency) will be informed by Phase 1 formative research, and actual preferences will be assessed by this pilot study. Community health care workers can reach out to patients who miss services and/or do not respond to SMS text messages or calls to encourage retention. The HITSsystem 2.0 will integrate PMTCT and EID services through 1 coordinated system-level intervention; this will permit longitudinal follow-up of mother-infant pairs to assess PMTCT outcomes.

Table 1. HITSsystem 2.0 intervention components. Expected timing, dose, and target of alerts and SMS (short message service) texts to providers and HIV positive pregnant women.

Actors	Actions	Timing	Dose ^a	Target
Hospital-based providers; providers	Algorithm-driven electronic alerts	When PMTCT ^b service late/missing (enrollment-infant EID ^c link)	Avg=8 per mom, range=0 to 14+	PMTCT quality: complete PMTCT retention (pregnancy to EID link)
Lab-based providers; lab techs	Algorithm-driven electronic alerts	When receipt of VL ^d sample or VL results delayed	Avg=1 per mom, range=0-2+	PMTCT efficiency: reduced turn-around time for key PMTCT services
HIV-positive pregnant women	Algorithm-driven electronic SMS text messages	Appointment reminders (2 days before appointment); adherence reminders (daily, weekly, biweekly, monthly); facility-based delivery reminders (4 and 2 weeks before EDD ^e)	Avg=4 per mom, range=0-8+; avg=20 per mom, range=0-245+; avg=2 per mom, range=2 to 2	PMTCT quality and PMTCT efficiency

^aDose represents anticipated study averages and ranges only, assuming one alert per alert type per pregnancy. Actual dose will depend on client-specific factors such as gestational age at enrollment, adherence to PMTCT guidelines and scheduled services, and frequency preferences for adherence reminders.

^bPMTCT: prevention of mother-to-child transmission of HIV.

^cEID: early infant diagnosis.

^dVL: viral load.

^eEDD: estimated due date.

Process for Phase 2 Development

We will employ the 4D's process to define, design, develop, and deploy the intervention [42]. The clinical algorithms and portions of the system development will be designed before completion of Phase 1, but focus group and interview findings will customize and refine critical aspects of the 4D's process, incorporating input from Kenya's current PMTCT treatment guidelines and user feedback regarding strategic messaging, patient and provider barriers, and strategic implementation. The iterative process of Phases 1 and 2 will enhance the design and development by ensuring a user-friendly, robust, interactive, and secure software system to increase engagement, retention, and quality PMTCT outcomes.

Phase 3: Trial Intervention

Trial Design

We will employ a matched, randomized pilot study design in 2 government hospitals with comparable resources, patient volume, and basic patient characteristics. One hospital will be randomized to receive the HITSsystem 2.0 intervention and the other hospital will maintain standard of care PMTCT services. An extended 18-month implementation period will allow 9 months to reach the sample size requirement of n=54 at each hospital and another 9 months to ensure complete prospective outcome data from the first PMTCT appointment in pregnancy until the infant's first HIV DNA PCR test result is determined. This follow-up period will assess complete retention throughout PMTCT services, ART adherence, and rates of infant HIV transmission. We will also collect retrospective PMTCT outcome data from each hospital for the 18 months before implementation to facilitate pre- and postcomparisons at the same facility.

Satisfaction interviews with HITSytem 2.0 users (HIV positive women and providers) will inform barriers to use that can be targeted either through future strategic refinement of the design or collaboration with key partners to address constraints beyond the scope of this intervention.

Study Sites and Setting

This study will be conducted in 2 government hospitals with similar provider-patient ratios and staffing structure, Kapsabet Hospital and Bungoma Hospital, both in western Kenya. Eligibility criteria for these hospitals include government funding; the current provision of PMTCT, EID, and ART services; at least one dedicated provider managing PMTCT services; and maintenance of individual-level patient files. Kapsabet Hospital serves a catchment area of approximately 91,000 people [43], has an average monthly EID volume of 10, and an average infant HIV transmission rate of 2.7% [44]. Bungoma Hospital serves a catchment area of approximately 92,412 people [43], has an average monthly EID volume of 18, and an average infant HIV transmission rate of 4.2% [44]. These hospitals serve less transient local populations, making them ideal pilot sites to adapt and modify the HITSytem 2.0 for the primary outcome of complete PMTCT retention.

Randomization

As a system-level intervention, it is neither feasible nor acceptable to randomize participation at the individual level. The hospital to receive the intervention will be determined by random assignment at the beginning of the study, using a random number generator program. The principal investigator and research staff will be blind to the process of assigning the sites.

Participant Eligibility

All HIV-positive pregnant women presenting for their first PMTCT appointment at the intervention and control site will be eligible for enrollment in the study. Women at the intervention site must also own or have reliable access to a mobile phone.

Procedures

Participants at both sites will receive PMTCT services guided by the Kenyan national guidelines [7]. At the time of PMTCT enrollment (first visit), all eligible women will be informed about the study by the clinical staff, and written informed consent for participation, including a review of hospital records documenting PMTCT services, will be obtained by a trained hospital staff member.

Training of Hospital and Study Staff

Key hospital personnel (PMTCT and maternity nurses and mentor mothers) will be trained by employing hands-on data entry scenarios tailored to the specific capacity in which they will utilize the HITSytem 2.0. During the first weeks of implementation, the trained research assistant (RA) will work closely to ensure thorough understanding and accurate independent use of the HITSytem 2.0 and will be available throughout the study to retrain or assist in system-related problem solving. The RA will be based in the MCH department with PMTCT providers to monitor and support fidelity to intervention implementation and timely data entry into the

HITSytem 2.0. The US-based HITSytem team will remotely review the entered data to identify any challenges or systematic errors to be addressed. This is the same training and implementation process successfully employed for the HITSytem pilot [33] and cluster randomized trial to evaluate EID outcomes [32]. Training at the control site will be limited to assessing participant eligibility, conducting informed consent, and administering the baseline survey. Nurses and mentor mothers directly involved in PMTCT service provision will conduct these research tasks. All research and clinical staff involved in the study will be trained on procedures to ensure participant confidentiality and secure data storage.

Baseline surveys will be conducted at the initial PMTCT enrollment visit at both intervention and control sites for all eligible women. In addition to the basic demographic information captured in routine care at both hospitals (age and number of children), questions will assess (1) knowledge and perceived importance of attendance at scheduled appointments; ART before, during, and after delivery; consequences of poor adherence; and infant testing, (2) motivation and self-efficacy to complete the targeted behaviors (eg, attendance, medication adherence, plan for delivery, and prompt EID enrollment) using scaled and Likert responses, (3) assessment of depression symptoms (6 questions to assess frequency of symptoms between 0 to 7 days a week) and risk for intimate partner violence (3 screening questions to facilitate counseling referral), and (4) male partner involvement. Study staff will enter completed paper surveys in Excel 2016 (version 1708).

PMTCT service utilization will be documented in the patient file and relevant PMTCT-related facility registers (intervention and control) as required by the Kenyan Ministry of Health. At the intervention hospital, a new record will be created in the HITSytem 2.0 during PMTCT enrollment and will be updated at each subsequent visit, including mobile phone number(s) and residence tracing information. Prospective clinical data from the mother-infant pair will be captured in the HITSytem 2.0 to track medication adherence, appointment attendance, delivery outcomes, and postpartum infant prophylaxis data, automating provider alerts and SMS text messages to participants as indicated. Any information that is not captured in the HITSytem at the time of the patient's visit (owing to workflow, connectivity, or other challenges) will be updated as soon as possible after the visit, referencing any relevant paper-based patient and facility records needed. All relevant data to measure the targeted PMTCT outcomes will be entered and maintained in the HITSytem 2.0.

At the control site, paper-based patient files and facility registries are the primary record-keeping source for PMTCT data. A study staff member will visit the control site quarterly to review clinical records to document and update PMTCT services received by women enrolled in the study. Multiple sources will be cross-referenced to collect standard of care data at the control hospital: (1) pregnant women/mothers' medical records, (2) hospital ANC registry book, (3) pharmacy ART registry, (4) maternity registry, and (5) HIV-exposed infant registry.

*HITS*System 2.0 user satisfaction will be assessed with semistructured interviews to solicit feedback on usefulness and acceptability of the content and frequency of the targeted SMS text messages, patient tracing efforts, and other recommendations to improve the intervention. Participants (n=35) will be purposively selected to include variation among women with complete/incomplete retention, low/high ART adherence, and facility/home deliveries. Interviews will be conducted in the language they prefer (Swahili or English) once study participation is complete. We will also conduct interviews with providers and hospital administrators to better understand the strengths and limitations of the *HITS*System 2.0 implementation, its integration with the current *HITS*System 1.0, and suggestions for improvement. Remuneration for interview participation and the analysis plan for qualitative data will be the same as described in Phase 1. Interviews will not be conducted at the control site as they did not experience the intervention.

Fidelity Assurance Procedures

Standard operating procedures were developed for each step of the study process to standardize training, enrollment, and all data collection procedures. As it is Web-based, any modification or corrections to the *HITS*System are instantly applied across all users. *HITS*System entries are routinely reviewed to ensure completeness and appropriate utilization of the comments section. Study personnel will make quarterly visits to the control site to cross-reference enrollment records with patient files and the relevant PMTCT-related facility registers and to review informed consent documents and surveys for accuracy, completeness, and secure storage.

Primary Outcome: Complete Prevention of Mother-to-Child Transmission of HIV Retention

The primary outcome is complete PMTCT retention, measured from the first PMTCT appointment until the infant's first HIV test, which is targeted at 6 weeks of age. The aggregate measure of complete retention—calculated as retention before delivery, at delivery, and after delivery—will be dichotomously coded as complete or incomplete retention. Complete retention is defined as maternal ART initiated (if not already on ART at the time of pregnancy), all scheduled PMTCT appointments attended, hospital-based delivery, and HIV DNA PCR testing by 6 weeks (<7 weeks) postnatal.

Secondary Outcomes

Duration of Prevention of Mother-to-Child Transmission of HIV Retention

We will estimate the duration (number of weeks) of PMTCT retention for each participant by subtracting the last date of documented service engagement from the date of enrollment. This will allow comparisons between total time retained in PMTCT services between groups and identify when (antenatal, delivery, or early postnatal) disengagement from PMTCT most often occurs.

Prevention of Mother-to-Child Transmission of HIV Appointment Attendance

We will measure the proportion of mothers who attended all scheduled ANC appointments, documenting late (>7 days past scheduled date) and missing (>14 days past scheduled date) attendance. The number of possible appointments will vary on gestational age at PMTCT enrollment; thus we will measure the median number of visits, the proportion who received the recommended 4 or more appointments, and the proportion enrolled by the recommended 14 weeks gestation.

Viral Load Suppression

We will document the proportion of pregnant women who had a VL sample collected during pregnancy: 6 months after ART initiation for those diagnosed during ANC or within the past 6 months for those already established on ART, in accordance with national guidelines. We will abstract data on VL from the *HITS*System 2.0 (intervention) and the patient file and laboratory records (control) to assess the proportion with VL tests taken, the turn-around time (TAT) for return of results, and the proportion with suppressed VL results (defined as <1000 viral copies/ml) during pregnancy.

Medication Adherence

As VL is still not consistently collected during pregnancy, we will rely on other indicators of adherence including self-report of missed doses in the 7 days before appointment (prescribed vs taken) and pill counts conducted by relevant providers (dispensed vs returned). Adherence data will be entered in the *HITS*System 2.0 at each appointment. We will calculate the proportion of patients who report >95% adherence to doses prescribed (7-day self-report) and pill count.

Hospital delivery will be estimated from the proportion of pregnant mothers who deliver at a health facility. Women who do not deliver at the study hospital will be contacted within 2 weeks of their estimated due date to check on their progress, document location of birth, and encourage prompt return to the facility for postpartum and postnatal care. *EID enrollment* will be measured using the proportion of HIV-exposed infants tested by 6 weeks of age (<7 weeks).

Infant and maternal mortality will be reported separately, noting all available data on date and cause of death. A future study will utilize a design with a longer follow-up period and larger sample size to adequately evaluate perinatal transmission of HIV.

Power and Sample Size

The required sample size was calculated to compare differences in proportions of complete PMTCT retention for the intervention (p1) and control (p2). We estimated complete retention by combining available retention data from Kenya for each phase: antenatal retention (68%) [19], hospital-based deliveries (61%) [36], and postnatal retention for HIV-exposed infants within 12 weeks (54.9% [21] to 80.7% [20]; average 67%). Recognizing that these estimates do not represent cumulative risk for the same individuals, we conservatively estimate complete PMTCT at the control site to be 20%. Our EID pilot data showed that retention doubled at 9 months with retention rates as high as 94.2% [33]. Using a midrange between differences achieved

from published studies and our own pilot study, we conservatively estimate complete retention of 47% for HITSsystem 2.0 participants. A sample size of 108 (54 intervention and 54 control participants) is needed to achieve 80% power to detect a significant difference in the proportion of complete PMTCT retention with chi-square tests (goodness of fit test: contingency table) with an effect size of 0.27 and a 2-tailed alpha of .05. Accounting for the proportion with mobile phone utilization, and 1.5% maternal mortality [45] and 3.7% [46] perinatal mortality, we estimate $n=70$ eligible participants. During Phase 3 enrollment, we plan to enroll $n=54$ of the $n=70$ eligible PMTCT patients per hospital. On the basis of our initial HITSsystem pilot where $<1\%$ of women declined, we anticipate high participation.

Statistical Analyses

To examine the baseline participant and facility characteristics, we will calculate descriptive statistics including proportions for categorical variables and means (SD) or median (interquartile range) for continuous variables [47]. For the primary outcome, chi-square tests will be used to compare the proportion with complete PMTCT retention between groups [48]. We will explore correlations between complete PMTCT retention and possible predictors (eg, knowledge, motivation to complete care, maternal HIV disclosure, perceived benefit of ART, maternal depression, and risk of intimate partner violence) using Phi, point-biserial, or Spearman rho statistics depending on the measurement level of each predictor [49]. Analytic models will control for significantly different preintervention covariates across conditions and hospitals, clustered observations (eg, time nested within setting), and gestational age as it impacts the eligible/recommended number of appointments or services.

For secondary analyses, Kaplan-Meier curves will illustrate differences in the duration of PMTCT retention before, during, and after delivery, accounting for the woman's eligible period of engagement (based on the timing of enrollment and accounting for premature infant or maternal mortality). We will then identify time periods when meaningful decreases in PMTCT retention occur, using Cox proportional-hazard regression for survival analyses (ie, retention), if all assumptions are met [50]. Known variables associated with HIV service retention (age, disclosure status, educational level, and number of children [22,51,52]) and those correlated ($P<.10$) will then be included in a generalized linear mixed model to identify a parsimonious list of predictors.

Using chi-square tests, we will compare the proportion of pregnant women (1) attending all scheduled PMTCT appointments (4 or more PMTCT visits and late or missed visits), (2) tested for VL (VL sample collected, results returned, and detectable VL values), (3) delivery at the hospital, (4) enrolling in EID (dried blood spot sample collected by <7 weeks), and (5) have an infant diagnosed with HIV, between intervention and control sites. The median number of PMTCT appointments, median gestational week at first PMTCT appointment, and median TAT for VL results will be calculated and compared using Mann Whitney U tests. Although medication adherence documentation at the control site (typically described as poor, fair, or good) will not permit direct

comparison, the proportion of pregnant women at the intervention site with $>95\%$ adherence will be described. Participant preferences for the content and frequency of SMS text messages for medication adherence support will also be described. P values will be adjusted (using Tukey correction) for multiple tests, where appropriate. Quantitative data will be analyzed using Statistical Application Software (SAS) version 9.4.

Results

We are actively enrolling participants and collecting data at the intervention and control sites. Only formative data have been analyzed and the HITSsystem has been adapted. There are no planned interim analyses of the primary outcome. No analyses comparing intervention versus control outcome data have been conducted at this time.

Discussion

Previous HITSsystem pilot data and studies have demonstrated significant success in improvement of EID outcomes particularly in improving the efficiency and quality of key EID outcomes [32-34,38]. Leveraging the improved linkage of health facilities, mother-infant pairs, and laboratories in the context of EID, the HITSsystem 2.0 (PMTCT) will expand the current Web-based platform to bridge the gap between maternal and pediatric HIV services. Outcomes at each step of the PMTCT cascade will be analyzed, and specific challenges will be identified.

This study will design and implement the HITSsystem 2.0 through formative qualitative research, intervention development using the 4Ds process, and a pilot implementation period as described above. It will also provide user satisfaction data by highlighting the HITSsystem 2.0's usefulness, acceptability, challenges, and recommendations to improve the intervention. The proposed HITSsystem 2.0 will integrate maternal and infant HIV services in one system-level, Web-based intervention that will provide linked, prospective data for mother-infant pairs, which has been identified as a problematic gap in the current system. The findings of this study will refine the HITSsystem 2.0 intervention, particularly tracking and utilization of challenging measures such as medication adherence and antenatal VL results to enhance system performance and implementation strategies in a larger scale efficacy trial.

Although this intervention will focus on health system improvement to enhance quality of care for women and infants in the facility setting, the study will not directly target PMTCT uptake, which would require community-based outreach. Given that intervention site data will be tracked via the HITSsystem whereas control site data will be captured via disparate paper-based registries and patient files, there may be discrepancies in data quality and documentation of services rendered between control and intervention sites; all efforts will be made to capture any available data at control sites to minimize this limitation. As the study design and implementation evolve, we anticipate that eHealth technologies in the study regions will likewise evolve and influence the

standard of PMTCT care. These external factors will be documented and accounted for in the design and analyses.

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Authors' Contributions

SFK, BG, KG, MM, and NM conceived and designed the protocol. SFK is the grant holder. SFK, MM, TO, MB, CW, SL, and SK led the study implementation. JKD developed the power calculations and analysis plan. SFK, MB, and BO drafted the manuscript with significant technical input from KG, TO, and all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report from the National Institutes of Health.

[\[PDF File \(Adobe PDF File\), 902KB - resprot_v8i6e13268_app1.pdf\]](#)

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Abbreviations

- ANC:** antenatal care
- ART:** antiretroviral therapy
- EDD:** estimated due date
- EID:** early infant diagnosis
- HITSystem:** HIV Infant Tracking System
- MCH:** maternal and child health
- PCR:** Polymerase Chain Reaction
- PMTCT:** prevention of mother-to-child transmission of HIV
- RA:** research assistant
- SMS:** short message service

TAT: turn-around time

VL: viral load

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Protocol

Using Temporal Features to Provide Data-Driven Clinical Early Warnings for Chronic Obstructive Pulmonary Disease and Asthma Care Management: Protocol for a Secondary Analysis

Gang Luo¹, DPhil; Bryan L Stone², MD, MS; Corinna Koebnick³, DPhil; Shan He⁴, DPhil; David H Au^{5,6}, MD, MS; Xiaoming Sheng⁷, DPhil; Maureen A Murtaugh⁸, DPhil, RDN; Katherine A Sward⁷, DPhil, RN; Michael Schatz^{3,9}, MD, MS; Robert S Zeiger^{3,9}, MD, DPhil; Giana H Davidson¹⁰, MD, MPH; Flory L Nkoy², MD, MS, MPH

¹Department of Biomedical Informatics and Medical Education, University of Washington, Seattle, WA, United States

²Department of Pediatrics, University of Utah, Salt Lake City, UT, United States

³Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA, United States

⁴Care Transformation, Intermountain Healthcare, Salt Lake City, UT, United States

⁵Center of Innovation for Veteran-Centered & Value-Driven Care, VA Puget Sound Health Care System, Seattle, WA, United States

⁶Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Washington, Seattle, WA, United States

⁷College of Nursing, University of Utah, Salt Lake City, UT, United States

⁸Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT, United States

⁹Department of Allergy, Kaiser Permanente Southern California, San Diego, CA, United States

¹⁰Department of Surgery, University of Washington, Seattle, WA, United States

Corresponding Author:

Gang Luo, DPhil

Department of Biomedical Informatics and Medical Education

University of Washington

UW Medicine South Lake Union, 850 Republican Street

Box 358047, Building C

Seattle, WA, 98195

United States

Phone: 1 2062214596

Email: gangluo@cs.wisc.edu

Abstract

Background: Both chronic obstructive pulmonary disease (COPD) and asthma incur heavy health care burdens. To support tailored preventive care for these 2 diseases, predictive modeling is widely used to give warnings and to identify patients for care management. However, 3 gaps exist in current modeling methods owing to rarely factoring in temporal aspects showing trends and early health change: (1) existing models seldom use temporal features and often give late warnings, making care reactive. A health risk is often found at a relatively late stage of declining health, when the risk of a poor outcome is high and resolving the issue is difficult and costly. A typical model predicts patient outcomes in the next 12 months. This often does not warn early enough. If a patient will actually be hospitalized for COPD next week, intervening now could be too late to avoid the hospitalization. If temporal features were used, this patient could potentially be identified a few weeks earlier to institute preventive therapy; (2) existing models often miss many temporal features with high predictive power and have low accuracy. This makes care management enroll many patients not needing it and overlook over half of the patients needing it the most; (3) existing models often give no information on why a patient is at high risk nor about possible interventions to mitigate risk, causing busy care managers to spend more time reviewing charts and to miss suited interventions. Typical automatic explanation methods cannot handle longitudinal attributes and fully address these issues.

Objective: To fill these gaps so that more COPD and asthma patients will receive more appropriate and timely care, we will develop comprehensible data-driven methods to provide accurate early warnings of poor outcomes and to suggest tailored interventions, making care more proactive, efficient, and effective.

Methods: By conducting a secondary data analysis and surveys, the study will: (1) use temporal features to provide accurate early warnings of poor outcomes and assess the potential impact on prediction accuracy, risk warning timeliness, and outcomes;

(2) automatically identify actionable temporal risk factors for each patient at high risk for future hospital use and assess the impact on prediction accuracy and outcomes; and (3) assess the impact of actionable information on clinicians' acceptance of early warnings and on perceived care plan quality.

Results: We are obtaining clinical and administrative datasets from 3 leading health care systems' enterprise data warehouses. We plan to start data analysis in 2020 and finish our study in 2025.

Conclusions: Techniques to be developed in this study can boost risk warning timeliness, model accuracy, and generalizability; improve patient finding for preventive care; help form tailored care plans; advance machine learning for many clinical applications; and be generalized for many other chronic diseases.

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KEYWORDS

decision support techniques; forecasting; machine learning; patient care management

Introduction

Three Major Gaps in the Current Predictive Modeling Method for Implementing Care Management

COPD and asthma are chronic respiratory diseases incurring heavy health care burdens on society, health care systems, and payers. In the United States, COPD affects over 6.5% of adults, is the third leading cause of death, and incurs 700,000 inpatient stays, 1.5 million emergency room visits, and US \$32 billion in cost annually [1]. Asthma affects 8% of adults [2] and 9.6% of children [3,4] and incurs 3630 deaths, 493,000 inpatient stays, 1.8 million emergency room visits, and US \$56 billion in cost annually [2,5]. As a service intended to prevent poor outcomes such as hospitalization, care management is widely adopted to provide tailored preventive care for COPD and asthma patients. Purchased by most large employers and offered by almost all private health plans [6-8], care management is a collaborative process to evaluate, plan, implement, coordinate, and monitor options and services to accommodate an individual's health and service needs [9]. In care management, a care manager calls a patient regularly, helps arrange for medical appointments, and schedules health and related services. Appropriate use of care management can cut hospital use (emergency room visits and inpatient stays) by up to 40% [7,10-15], lower cost by up to 15% [11-16], and enhance patient adherence, quality of life, and satisfaction by 30% to 60% [10].

Predictive models are widely used, for example, by health plans in 9 of 12 regions [17], as the best method [18] to warn of poor outcomes and to identify COPD and asthma patients for care management [6-8]. Multiple models have been built for predicting the health outcomes of individual COPD and asthma patients [19-28]. However, current modeling methods have 3 major gaps restricting their effectiveness owing to inadequate use of temporal features showing trends and early health change. A temporal feature, such as the slope of pulmonary function across the last year, is an independent variable formed by transforming longitudinal attributes.

Gap 1: Late Warning

Existing models for predicting the health outcomes of individual COPD and asthma patients seldom use temporal features [19-28] and often give late warnings, making care reactive and missing

opportunities for clinical and therapy teams to intervene early to reduce the risk of poor outcomes. A health risk is often identified at a relatively late stage of declining health, when the chance of a poor outcome is high and resolving the issue is difficult and costly. A typical model predicts patient outcomes in the next, say, 12 months. For patients with imminent poor outcomes, this does not warn early enough. If a patient will actually be hospitalized for COPD next week, intervening now could be too late to avoid hospitalization. If temporal features were used, this patient could be identified a few weeks or months earlier; when health decline is still at an early stage, resolving the issue is easier and preventing hospitalization is likely.

Gap 2: Low Prediction Accuracy

Models for predicting a patient's health outcome and cost typically have low accuracy. When projecting the health outcome of a patient, the accuracy measure of area under the receiver operating characteristic curve (AUC) is typically much lower than 0.8 [19-28]. When projecting the health care cost of a patient, the accuracy measure of R^2 is typically lower than 25% [29,30], and the mean error is as big as the mean cost [31]. These large errors in prediction results create difficulty in properly aligning care management's use with the patients needing it the most [10].

Care management can require over US \$5000 per person per year [11] and usually enrolls only 1% to 3% of patients because of resource limits [32]. For patients predicted to have the worst outcomes or the largest costs [10,33], care managers review patient charts and manually make allocation decisions.

A small percentage of patients use most of the health care resources and costs. The upper 20% of patients use 80% of the resources and costs. The upper 1% use 25% [19,32,34]. Accurately identifying patients at high risk for poor outcomes or large health care costs is critical for effective targeted application of care management resources. Yet, Weir et al [33] showed that in the upper 10% of patients who actually spent the largest health care costs, over 60% of them were not included in the upper 10% risk group identified by a predictive model. In the upper 1% of patients who actually spent the largest health care costs, around 50% and over 80% of them were not included in the identified upper 10% and 1% risk groups, respectively.

Assume the care management program could take 1% of all patients. In this case, even if the care managers could afford to examine the upper 10% risk group found by the predictive model and manually make correct decisions for enrollment, the care managers would still not find around half of the upper 1% of patients who spent the largest health care costs. For COPD and asthma, if we could identify 10% more of the upper 1% of patients who spent the largest health care costs and enroll them in care management, we could boost outcomes and spare possibly up to US \$120 million in COPD care [1] and US \$210 million in asthma care each year [19-21]. In general, owing to the large patient population, a small boost in accuracy will benefit numerous patients and have a big positive impact.

Current models for predicting the health outcomes and health care costs of individual COPD and asthma patients have low prediction accuracy for several reasons:

1. Many temporal features with high predictive power are either frequently unused in an existing model or yet to be found. Google recently applied long short-term memory (LSTM) [35], one kind of a deep neural network, to all the attributes in the electronic health record to automatically learn temporal features from longitudinal data [36]. For forecasting each of the 3 outcomes: long hospital stay, unanticipated readmissions within 30 days, and in-hospital mortality, this increased the AUC by approximately 10% [36]. Multiple other studies [37-39] showed similar results for a variety of clinical prediction tasks. This aligns with what has taken place in areas such as video classification, natural language processing, and speech recognition, where temporal features that LSTM automatically learned from data outperform those mined from data by other methods or specified by experts [40,41].
2. Although >40 risk factors for undesirable outcomes in COPD/asthma have been identified [19,20,23,28,42-48], an existing model usually uses only a few (eg, <10) [19-24,26-28]. Existing models were often constructed based on data obtained from clinical trials or old fashioned electronic health records collecting limited variables [49]. No published model adopts all of the known risk factors available in modern electronic health records collecting extensive variables [49].
3. Environmental information such as air quality and weather variables are known to impact COPD and asthma outcomes [43,50-52], but with rare exceptions [25], are infrequently used in existing models.

Gap 3: Lack of Information on Why Patients Are at High Risk for Poor Outcomes and Possible Interventions to Mitigate Risk

Before enrolling a patient, care managers need to know why the patient is at high risk for a poor outcome and about possible interventions to mitigate risk. Complex predictive models, which include most machine learning models such as LSTM, give no explanatory or prescriptive information. Frequently, a patient's records have many variables on hundreds of pages accumulated over a long period of time [53]. Unlike physicians who see patients from time to time, care managers often have not previously seen the records when needing to make enrollment

decisions. When the model offers no explanation, busy care managers often spend extra time reviewing the records to find the reasons. This is time consuming and difficult.

A care manager may use subjective, variable judgment to form a care plan, but may miss some suited interventions because of 2 factors:

1. Several reasons can make a patient at high risk for a poor outcome. Each reason is shown by a feature combination as a risk pattern. For instance, the ratio of inhaled steroid to beta agonist dispensing to the patient decreased over 12 months and the sulfur dioxide level was ≥ 3 parts per million for ≥ 5 days in the past week. Many features exist. Like any human, an ordinary care manager can deal with ≤ 9 information items simultaneously [54], making it difficult to identify all reasons from numerous possible feature combinations.
2. Huge variation in practice, often by 1.6 to 5.6 times, appears across care managers, facilities, and regions [34,55-58].

Missing suited interventions can degrade outcomes. Typical automatic explanation methods [59,60] do not handle longitudinal attributes and cannot fully address these issues.

Our Proposed Solutions

To fill the gaps for more COPD and asthma patients to receive appropriate and timely care, we will (1) use temporal features to provide accurate early warnings of poor outcomes and assess the potential impact on prediction accuracy, risk warning timeliness, and outcomes; (2) automatically identify actionable temporal risk factors for each patient at high risk for future hospital use and assess the impact on prediction accuracy and outcomes; (3) assess actionable information's impact on clinicians' acceptance of early warnings and on perceived care plan quality. Here, actionable information refers to the explanations and their linked interventions provided by our automated approach.

Innovation

This study will lead to several innovations. We will develop new, general informatics techniques. We will transform care management for COPD and asthma by directing it to the patients needing it in a more timely fashion and more precisely than current methods:

1. We will build models to predict a patient's hospital use earlier and more accurately than current models, which often give late warnings and have low accuracy.
2. We will be the first to semiautomatically extract predictive and clinically meaningful temporal features from longitudinal medical data. This process helps us address data quality issues and automatically find and drop uninformative variables. All of these boost model accuracy and generalizability and reduce the effort needed to build models usable in clinical practice. Currently, to build such models, clinicians typically need to manually identify such features, which is difficult and time consuming.
3. We will be the first to provide rule-based automatic explanations of machine learning prediction results directly on longitudinal data. Explanations are critical for care

managers to understand the results to make appropriate care management enrollment and intervention decisions. Compared with other forms of automatic explanations such as that used in Rajkomar et al [36], rule-based explanations are easier to understand and can more directly suggest actionable interventions. Most automatic explanation methods [60], including our previous one [59], for machine learning prediction results cannot handle longitudinal attributes. Also, our previous method [59] gives explanations for a limited portion of patients. We will improve our previous method, handle longitudinal attributes, and expand automatic explanations' coverage of patients.

4. We will be the first to automatically identify actionable temporal risk factors and suggest interventions based on inclusion of objective data. Currently, care managers use subjective, variable judgment to manually form care plans. Some suited interventions for patients at high risk for a poor outcome get missed. Also, care managers provide a finite input on the patient to the other clinical care team members. With automatic explanations and suggested interventions in hand, care managers can pass this tailored information to the other clinical care team members so they can act accordingly. This could transform the care management process and make it more effective via closer collaboration between care managers and the other clinical care team members.
5. Current models for predicting the health outcomes of individual COPD and asthma patients were built mostly using a small number of patients (eg, <1000) or variables (eg, <10) [19-28], making it difficult to identify many predictive features and the interactions among them. Air quality and weather variables impact COPD and asthma outcomes [43,50-52] but are rarely used in existing models. The predictive power of many known risk factors for undesirable outcomes is unused. Also, many predictive features have not yet been found. In contrast, we will use many patients and variables, enabling us to identify more predictive features and the interactions among them. The variables will include air quality, weather, and patient variables, cover many known risk factors for undesirable outcomes, and be used to find new predictive features in a data-driven way. Many features are new, capturing trends that existing models rarely touch.

To build and validate models for predicting the health outcomes of individual COPD and asthma patients, we will use data from 4 different electronic health record systems HELP, HELP2, Cerner, and Epic. This boosts model generalizability. In contrast, every existing model for predicting the health outcomes of individual COPD and asthma patients was built using data from only 1 electronic health record system [19-28].

In short, this study is significant as it will produce new techniques to advance machine learning for clinical applications and potentially transform preventive care for more patients to receive appropriate and timely care. The wide use of these techniques could boost outcomes and save resources.

Methods

Computing Environment

All experiments will be done on a secure computer cluster at the University of Washington Medicine (UWM) that is encrypted and password protected. With proper authorization, all of the UWM care manager and physician test participants and research team members can log into this computer cluster from their UWM computers. We will install Oracle database, R, Weka [61], and TensorFlow [62] to be used in the study on the computer cluster. Weka is a major open-source machine learning toolkit. It incorporates many popular machine learning algorithms including both base and ensemble algorithms, feature selection techniques, and methods for dealing with imbalanced classes [63]. TensorFlow is Google's open-source deep neural network package.

Datasets

We will employ clinical and administrative data from the enterprise data warehouses (EDWs) of 3 leading health care systems: Intermountain Healthcare (IH), Kaiser Permanente Southern California (KPSC), and UWM, as well as publicly available air quality and weather data. All of the data to be used are structured. We will use all patients' data that are needed for computing health care system features [64,65], rather than only COPD and asthma patients' data. As the largest health care system in Utah, IH has 185 clinics and 22 hospitals. The EDW of IH contains numerous variables [66]. In this study, we will start with using the following of these variables: "admission date and time; age; orders (medications, labs, exams, immunizations, imaging, and counseling), including order name, ordering provider, performing date, and result date; allergies; barriers (hearing, language, learning disability, mental status, religion, and vision); cause of death; chief complaint; death date; diagnoses; discharge date; exam result; facility seen for the patient visit; gender; health insurance; healthcare cost; height; home address; immunizations; lab test result; languages spoken; medication refills; primary care physician as listed in the electronic medical record; problem list; procedure date; procedures; provider involved in the visit; race/ethnicity; referrals; religion; visit type (inpatient, outpatient, urgent care, or emergency department); vital signs; weight" [65]. An IH data analyst will download a de-identified IH dataset, encrypt it, and transfer it to the secure computer cluster. The IH dataset has information on clinical encounters in the previous 14 years (2005 to 2018). For the previous 5 years, the IH data for adults cover over 5,786,414 clinical encounters and 878,448 adult patients (aged ≥ 18 years) per year. The IH data for children cover over 1,557,713 clinical encounters and 360,698 pediatric patients (aged <18 years) per year. COPD prevalence is approximately 4.1% in the IH adult population. Asthma prevalence is approximately 8.6% and 7.6% in the IH adult and pediatric population, respectively. The IH dataset provides the electronic record of care for approximately 60% of adults and approximately 95% of children in Utah [56,67]. IH devotes many resources to maintain data integrity and accuracy. Owing to its huge size and variable richness, the dataset provides many advantages for us to explore the proposed predictive models.

KPSC and UWM have similar strengths. KPSC is the largest integrated health care system in Southern California, providing care to approximately 16% of residents in 227 clinics and 15 hospitals [68]. A KPSC data analyst will download a de-identified KPSC dataset, encrypt it, and transfer it to the secure computer cluster. The KPSC dataset has information on clinical encounters in the previous 10 years (2009 to 2018). For the previous 5 years, the KPSC data for adults cover over 9,448,987 clinical encounters and 2,890,027 adult patients per year. The KPSC data for children cover more than 1,380,900 clinical encounters and 975,249 pediatric patients per year. COPD prevalence is approximately 4.1% in the KPSC adult population. Asthma prevalence is approximately 10.8% and 10.9% in the KPSC adult and pediatric population, respectively.

As the largest academic health care system in Washington, UWM has 12 clinics and 4 hospitals. A UWM data analyst will download a de-identified UWM dataset, encrypt it, and transfer it to the secure computer cluster. The UWM dataset has information on adult patient encounters in the previous 7 years (2012 to 2018). The UWM data cover over 1,714,196 clinical encounters and 277,289 adult patients per year. COPD prevalence among patients is approximately 4.1%. Asthma prevalence is approximately 9%.

In addition to the clinical and administrative data, we will use 11 air quality and weather variables, which were recorded over the previous 14 years (2005 to 2018) by the monitoring stations in the regions served by UWM, IH, and KPSC and are available from federal data sources [69,70]. These variables include ozone, sulfur dioxide, particulate matter up to 10 μm in size, particulate matter up to 2.5 μm in size, nitrogen dioxide, temperature, carbon monoxide, wind speed, relative humidity, precipitation, and dew point.

In the following, we sketch our techniques. Our design paper [71] describes the ideas in more detail. In this study, for each technique, we will flesh out its technical details, do computer coding, tune its parameters, and test it. The discussion below focuses on COPD. Whenever we mention COPD, the same applies to asthma.

Aim 1: Use Temporal Features to Provide Accurate Early Warnings of Poor Outcomes and Assess the Impact on Prediction Accuracy.

We will semiautomatically extract predictive and clinically meaningful temporal features from patient, air quality, and weather data, and build models to predict a patient's health outcome. Each feature involves one or more raw variables. The number of possible features is almost infinite. In addition, factors such as environmental variables beyond air quality and weather can influence patient outcomes. This study does not intend to exhaust all of the possible features and factors that can influence patient outcomes and achieve the highest possible prediction accuracy in theory. Rather, our purpose is to show that using temporal features can improve risk warning timeliness, prediction accuracy, and care management. A nontrivial boost in health outcomes can greatly benefit society. As is adequate for our target decision support application and typical with predictive modeling, our study focuses on associations.

Data Preprocessing

We will write Oracle database SQL queries and R and Java programs for data preprocessing. Our source code will be made freely available on a project website hosted by UWM. In our future publications on this study's results, we will describe all of the decisions made for data preprocessing, such as the thresholds used for determining the physiologically impossible and invalid values of an attribute. We will transform all of the datasets into the Observational Medical Outcomes Partnership (OMOP) common data model format [72] and its related standardized terminologies [73]. We will extend the data model to include patient, air quality, and weather variables that are in our datasets but not covered by the original data model. We will adopt conventional techniques such as imputation to manage missing values and to find, rectify, or drop invalid values [74,75]. To avoid using too many longitudinal attributes, we will employ grouper models such as the Diagnostic Cost Group system to merge diseases, drugs, and procedures [31,34]. We will use the method given in our paper [71] to select the most relevant laboratory tests.

We will use patient, air quality, and weather variables. The patient variables include standard variables such as diagnoses that the clinical predictive modeling literature [34,55,74] has studied and many known risk factors for undesirable COPD outcomes listed in Bahadori et al [45]. For air quality and weather variables, we will do spatial interpolation [76] to obtain their daily average values at the patient's home address from those at regional monitoring stations [77].

Chronic Obstructive Pulmonary Disease and Asthma Cases and Outcomes

As test cases, we will develop and test our approach using (1) COPD, (2) pediatric asthma, and (3) adult asthma. For COPD, we will adjust the criteria used by the Centers for Medicare and Medicaid Services and National Quality Forum [78-80] to incorporate outpatient and emergency room visit data [81] to find COPD patients. A patient is deemed to have COPD if he/she is ≥ 40 years and has one of the following:

1. 1 outpatient visit diagnosis code of COPD (International Classification of Diseases, Ninth Revision [ICD-9]: 491.21, 491.22, 491.8, 491.9, 492.8, 493.20, 493.21, 493.22, 496; International Classification of Diseases, Tenth Revision [ICD-10]: J41.8, J42, J43.*, J44.*) and ≥ 1 prescription of tiotropium within 6 months of the outpatient visit.
2. ≥ 2 outpatient or ≥ 1 emergency room visit diagnosis codes of COPD (ICD-9: 491.21, 491.22, 491.8, 491.9, 492.8, 493.20, 493.21, 493.22, 496; ICD-10: J41.8, J42, J43.*, J44.*).
3. ≥ 1 hospital primary discharge diagnosis code of COPD (ICD-9: 491.21, 491.22, 491.8, 491.9, 492.8, 493.20, 493.21, 493.22, 496; ICD-10: J41.8, J42, J43.*, J44.*).
4. ≥ 1 hospitalization with a primary discharge diagnosis code of respiratory failure (ICD-9: 518.81, 518.82, 518.84, 799.1; ICD-10: J80, J96.0*, J96.2*, J96.9*, R09.2) and a secondary discharge diagnosis code of acute exacerbation of COPD (ICD-9: 491.21, 491.22, 493.21, 493.22; ICD-10: J44.0, J44.1).

The outcome measure is whether a patient used the hospital (inpatient stay and emergency room visit) with a primary diagnosis of COPD (ICD-9: 491.21, 491.22, 491.8, 491.9, 492.8, 493.20, 493.21, 493.22, 496; ICD-10: J41.8, J42, J43.*, J44.*) in the subsequent year.

For asthma, we will use Schatz et al's [20,82,83] method to find asthma patients. A patient is deemed to "have asthma if he/she has 1) ≥ 1 diagnosis code of asthma (ICD-9 493.*; ICD-10 J45/J46.*) or 2) ≥ 2 asthma-related medication dispensing records (excluding oral steroids) in a one-year period, including β -agonists (excluding oral terbutaline), inhaled steroids, other inhaled anti-inflammatory drugs, and oral leukotriene modifiers." [84] The outcome measure is whether a patient used the hospital with a primary diagnosis of asthma (ICD-9 493.*; ICD-10 J45/J46.*) in the subsequent year.

Temporal Feature Extraction

We will use a new method to semiautomatically extract predictive and clinically meaningful temporal features from longitudinal data. These features will be used to build the final predictive model and to automatically identify actionable temporal risk factors for each patient at high risk for future hospital use. Our new method is semiautomatic, as its final step involves a human to extract features through visualization [71]. It generalizes to many clinical applications and is sketched as follows, with more details described in our design paper [71].

Our method uses LSTM [35], a type of deep neural network that models long-range dependencies and often reaches higher prediction accuracy than other algorithms [40]. A lot of work has been performed using LSTM to construct predictive models on medical data [36-39,85]. LSTM performs computations on a sequence of input vectors from the same patient, one vector after another. Every input vector is marked by a time step t . After finishing the whole sequence, LSTM gains results that are combined with static attributes such as gender [86] to predict the outcome of the patient. Every input vector contains information of one patient visit such as vital signs and diagnoses. The sequence length can differ across patients. This helps increase model accuracy, because LSTM can use as much of each patient's information as possible, without dropping information to make every patient have the same length of history. In addition, this enables us to make timely predictions on new patients without waiting until every patient acquires history of a certain length. With information from only one visit, LSTM can start making projections on the patient.

As Figure 1 shows, an LSTM network includes a sequence of units, one for each time step. In the figure, each unit is denoted by a rounded rectangle. \odot represents the element-wise multiplication. \oplus represents the element-wise sum. A unit contains an input gate i_t , a hidden state h_t , an output gate o_t , a forget gate f_t , and a memory cell c_t . The memory cell maintains long-term memory and keeps summary information from all of the previous inputs. Every element of the memory cell vector represents some learned temporal feature. As shown by Karpathy

et al [87], only approximately 10% of the memory cell vector elements could be interpreted [88]. This is because LSTM puts no limit on the number of input vector elements that can connect to every memory cell vector element. All of the input vector elements could be adopted in every element of the input and forget gates' activation vectors and connect to every memory cell vector element. Consequently, no limit is put on the number of attributes utilized in every learned temporal feature.

It is difficult to understand a feature that involves many attributes. To address this issue, we will use multi-component LSTM (MCLSTM), a new type of LSTM that can automatically drop uninformative attributes. As Figure 2 shows, an MCLSTM has several component LSTM networks, each using some rather than all of the longitudinal attributes. By limiting the number of attributes connecting to every memory cell vector element, more memory cell vector elements will depict clinically meaningful and more generalizable temporal features. As LSTM often produces more accurate models than other algorithms [36-39], the learned features tend to be predictive. As patient attributes are collected at a different frequency from air quality and weather attributes, we specify certain component networks for the former and the others for the latter. To let data tell which component network uses which attributes, we use a new exclusive group Lasso (least absolute shrinkage and selection operator) regularization method. It combines exclusive Lasso [89,90] and group Lasso [91] to reach 2 goals jointly. First, in each component network, every attribute competes with every other attribute. When one is employed, the others are less likely to be employed. Second, in each component network, all of the input vector weight matrix elements connecting to the same attribute tend to become nonzero (or zero) concurrently. Nonzero means the attribute is employed. We will use TensorFlow [62] to train MCLSTM and use our previous method [84,92] to automate hyperparameter value selection.

Kale et al [93-97] showed that in a deep neural network, we can use training instances that incur the highest activations of a neuron to find clinically meaningful features. After training the MCLSTM network, we proceed as follows to identify zero or more such features from every memory cell vector element at the final time step of the network. First, we find several training instances that incur the highest activations in the memory cell vector element. Second, in each of those training instances, we find one or more segments of the input vector sequence termed effective segments, each tending to represent a useful temporal feature. Third, we partition all spotted effective segments into multiple clusters and visualize each cluster separately to identify zero or more clinically meaningful temporal features. As shown in Wang et al [98], such a visualization could help us find and address data quality issues such as an implausible order of events, boosting model accuracy. For each identified feature, Dr Luo and a clinician in our team will jointly arrive at an exact mathematical definition of an extracted feature. Many extracted features capture trends more precisely than the raw features learned by LSTM. This also boosts model accuracy.

Figure 1. A long short-term memory network.

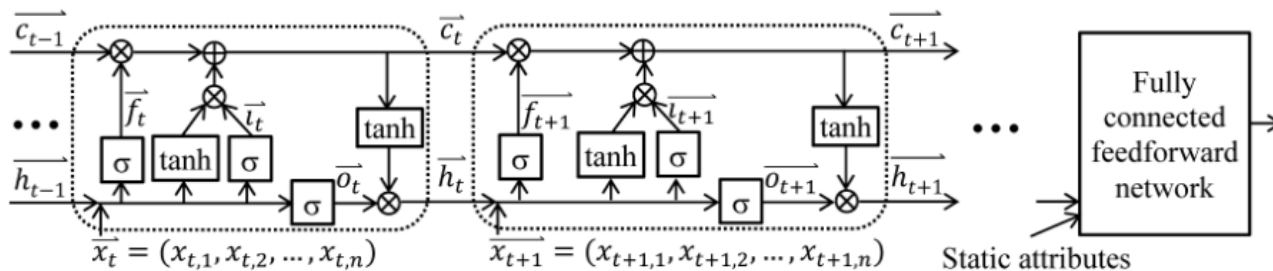
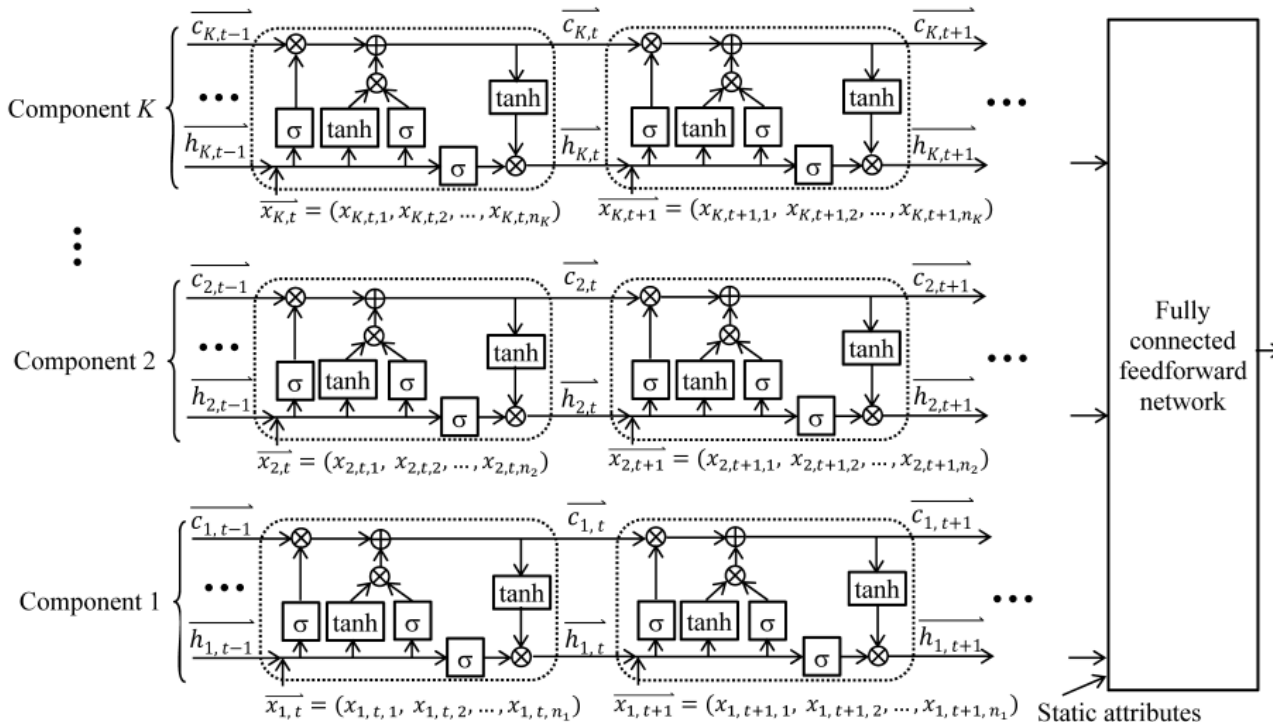


Figure 2. A multi-component long short-term memory network having K components.



Aim 1's Final Predictive Models

We will use the extracted temporal features to convert longitudinal data to tabular data, with 1 column per feature, and add static features. Health care system features such as the number of a physician's patients of a given race can boost model accuracy [64,65,99] and are included as static features. We will employ Weka [61] to construct Aim 1's final predictive models. As shown in Aim 4, these models are suitable for automatic explanation. We will use supervised algorithms and our previous method [84,92] to automatically select the algorithm, feature selection technique, imbalanced class handling method, and hyper-parameter values among all of the applicable ones. We will do manual fine-tuning if needed.

Using historical data up to the prediction time point, we will build 3 sets of models, one for each of 3 combinations: COPD at IH, KPSC, and UWM. For each of IH, KPSC, and UWM, the corresponding set of COPD models will be built for all of the COPD patients in that health care system. Unlike integrated health care systems IH and KPSC, UWM has most of its patients referred from other health care systems and has fairly incomplete data on many of its patients. To reduce incomplete data's impact on model accuracy, we will use our previous constraint-based

method [100] to find patients tending to receive most of their care at UWM and build models on and apply models to them. Previously, we showed that a good constraint for all types of UWM patients on average is that the patient lives within 5 miles of a UWM hospital and has a UWM primary care physician [100]. Yet, the optimal distance threshold could vary across various types of patients because of their different characteristics. Intuitively, a UWM COPD patient is likely to keep using and get a large portion of his/her care from UWM, even if the patient lives at some distance away from the closest UWM hospital. In comparison, a patient who visited a UWM emergency room once owing to a car accident may no longer use UWM after that visit. We will use the approach in our previous work [100] to find an optimal distance threshold for COPD patients. As noted earlier, we will develop and test our techniques on asthma as well.

Accuracy Evaluation and Justification of the Sample Size

The discussion below is for IH data. The cases with KPSC and UWM data are similar. As we need to compute outcomes for the subsequent year, we essentially possess 13 years of IH data over the past 14 years. We will train and test models in a usual way. We will do a stratified 10-fold cross-validation [61] on

the data in the first 12 years to train models and to estimate their accuracy. The data in the 13th year will be employed to gauge the performance of the best models, mirroring future use in clinical practice. We will select the best model using the standard performance metric AUC [61]. A care management program typically enrolls 1% to 3% of COPD patients [32]. Of the upper 1% of COPD patients the model projects to be at the highest risk of using the hospital, we will report the percentage of patients using the hospital in the subsequent year. For a program taking 1% of COPD patients based on the model's prediction results, this percentage reflects the degree of correct enrollment. To find the variables vital for high accuracy, we will conduct backward elimination [74] to remove features on the condition that accuracy does not drop >0.02 . We will compare the variables vital for high accuracy on IH data with those on KPSC and UWM data. Using the variables available in both the IH and KPSC/UWM datasets, we will build the best predictive model on IH data and compare the model's accuracy on IH data with that on KPSC/UWM data.

We will test the hypothesis that using our techniques can boost model accuracy. To do this, we will use a 2-sided Z test to compare the AUCs of 2 predictive models built in a way like that in Obuchowski [101]. The first predictive model will use the best machine learning algorithm and take all features essential for high accuracy. The second model will be adapted from those in the literature. For each predictive model for hospital usage reported in the literature [19-28], we will retrain it on our dataset using the attributes appearing in both the original model and our dataset. The most accurate one of the retrained models will be the second model. Our hypothesis is as follows:

1. Null hypothesis: The first model reaches the same AUC as the second.
2. Alternative hypothesis: The first model reaches a higher AUC than the second.

The categorical outcome variable of hospital usage has 2 possible values (classes). To the best of our knowledge, every predictive model for hospital usage reported in the literature reaches an AUC <0.8 [19-28]. "Using a two-sided Z-test at a significance level of 0.05 and assuming for both classes a correlation coefficient of 0.6 between the two models' prediction results, a sample size of 137 instances per class has 90% power to detect a difference of 0.1 in AUC between the two models," [65] like an increase of AUC from 0.8 to 0.9. The IH data in the 13th year include around 35,000 COPD patients, offering enough power to test our hypothesis. This conclusion remains valid if the actual correlation coefficient differs somewhat from the assumed one.

Aim 2: Assess Using Temporal Features' Impact on Risk Warning Timeliness

The discussion below is for IH data. The cases with KPSC and UWM data and with asthma are similar.

Outcome of the Number of Days of Early Warning the Model Provides for the Patient and the Estimation Approach

Consider a predictive model and a patient who used the hospital on date D in the 14th year. The outcome is the number of days of early warning the model provides for the patient. To measure the number, we find the first date D' ($D-365 \leq D' \leq D-1$) such that if we use D' as the prediction time point and input the patient's history up to D' into the model, the model predicts hospital use in the subsequent year. In this case, the model warns the first hospital use k ($0 \leq k \leq D-D'$) days in advance, with $D' + k$ being the first day between D' and D when the patient used the hospital. k is the outcome number. Otherwise, if the model still predicts no hospital use when we reach $D-1$, the model warns zero day in advance and zero is the outcome number. We expect using our techniques will raise the outcome number. We will assess the outcome on the cohort of COPD patients who ever used the hospital during the 14th year. For these patients, the average number of days of early warning given by the model shows how timely it warns.

Outcome Evaluation and Justification of the Sample Size

We will test the hypothesis that using our techniques can boost risk warning timeliness. To do this, for the patient cohort, we will use an F test to compare the number of days of early warnings provided by the 2 models mentioned in Aim 1's accuracy evaluation section, assuming a Poisson model with an offset of 365 days. Our hypothesis is as follows:

1. Null hypothesis: The number of days of early warning provided by the first model is the same as that provided by the second.
2. Alternative hypothesis: The number of days of early warning provided by the first model is larger than that provided by the second.

Assuming the number of days of early warning has an exponential distribution and employing an F test at a one-sided significance level of 0.05, a sample size of 600 patients offers 80% power to detect a minimum raise of 27.8 days of early warning by the first model, when the second model warns, on average, 180 days in advance. About 2000 COPD patients ever used IH hospitals during the 14th year, giving enough power to test our hypothesis. The conclusion remains valid if the actual situation differs somewhat from the assumed one.

For Aims 1 and 2, our goal is to reach a boost of ≥ 0.1 in accuracy and ≥ 30 days in risk warning timeliness, respectively. If we cannot reach this goal on the entire COPD patient group, we will construct distinct models for differing patient subgroups. The patient subgroups are described by characteristics such as age or co-morbidity, which are often independent variables in the original predictive models. If we still cannot reach this goal, we will do subanalyses to find the patient subgroups, for which our predictive models show good performance, and then apply our ultimate predictive models only to these patient subgroups.

Aim 3: Assess Using Temporal Features' Potential Impact on Outcomes Via Simulations

To assess the value of a predictive model for future clinical deployment, we need to appraise care management outcomes if the model is adopted and decide how to generalize the predictive model to other sites gathering differing sets of variables. Our predictive models will be constructed on IH, KPSC, and UWM data. Our simulations will guide how to employ the predictive models in other health care systems. No previous study has decided the variables most crucial for COPD and asthma model generalization. We will apply our simulation method to care management of (1) COPD patients, (2) asthmatic children, and (3) asthmatic adults.

Outcomes of the Number of Inpatient Stays and the Number of Emergency Room Visits in the Subsequent Year and the Estimation Approach

The number of inpatient stays in the subsequent year is the primary outcome. The number of emergency room visits in the subsequent year is the secondary outcome. The following discussion focuses on IH data and inpatient stays. The cases with KPSC and UWM data and/or emergency room visits can be handled similarly. From statistics reported in the literature [102,103], we will obtain the percentage of inpatient stays, p , a care management program can help avoid. Given a set of variables, we will adopt the same method used in Aim 1 to train a predictive model on the data in the first 12 years. For the data in the 13th year, we will gather prediction results, then estimate the outcome. Consider a patient who will have n_e inpatient stays in the subsequent year without enrolling in the program. If the patient gets enrolled, for each inpatient stay of the patient, we will simulate whether it will occur or not based on probability $1-p$. The gross outcome estimate will be the sum of the estimated outcomes of all patients. Adopting a similar method, we will find the minimum accuracy required for the predictive model to be valuable in clinical practice.

Sensitivity Analysis

IH, KPSC, and UWM collect many variables. Another health care system may collect fewer. To ensure generalizability, we will evaluate various variable combinations and obtain the estimated outcomes when the revised model is adopted. These estimates will pinpoint crucial variables. If a crucial variable is not available in a given health care system, these estimates can hint alternative variables having minimal adverse impact on the outcomes.

We will employ a variable grouping approach relating variables likely to co-exist, such as those linked in a laboratory test panel, according to the judgment of our clinical experts. We will create and post a table showing many possible combinations of variables by groups, encompassing the trained parameters and the simulated outcomes of the predictive model. A health care system wanting to deploy the model can employ this table to estimate the expected outcomes in the system's data environment, as well as to determine the variables to be gathered. The table has 3 columns, one for each of IH, KPSC, and UWM. Many variables collected by IH, KPSC, and UWM and used in this study are commonly available in many other

systems. Thus, all variables used in each of many rows in the table will already exist in these systems.

Outcome Evaluation and Justification of the Sample Size

The following discussion focuses on IH data. The cases with KPSC and UWM data are similar. We will employ McNemar test to compare the paired-sample outcomes reached by the 2 predictive models mentioned in Aim 1's accuracy evaluation section. We will test 2 hypotheses: using our techniques will link to a potential drop in (1) inpatient stays and (2) emergency room visits in the subsequent year. Our primary hypothesis is as follows:

1. Null hypothesis: The number of inpatient stays in the subsequent year reached by the first model is the same as that reached by the second.
2. Alternative hypothesis: The number of inpatient stays in the subsequent year reached by the first model is smaller than that reached by the second.

Among the patients truly at high risk for future hospital use, the first model will find some missed by the second and vice versa. Assuming the former cuts inpatient stays in the subsequent year by 5% and the latter increases them by 1%, at a one-sided significance level of 0.05, a sample size of 251 instances provides 80% power to verify the primary hypothesis. The IH data in the 13th year cover about 35,000 COPD patients, offering enough power to test the primary hypothesis.

Aim 4: Automatically Identify Actionable Temporal Risk Factors for Each Patient at High Risk for Future Hospital Use and Assess the Impact on Prediction Accuracy and Outcomes

Care managers currently give finite input on the patient to the other clinical care team members. Owing to bandwidth constraints, care managers can afford to examine only a finite number of patients top ranked by the predictive model—those whose projected risk for future hospital use is over a given threshold like the 95th percentile. For those patients, we will automatically explain early warnings, identify actionable temporal risk factors, and suggest tailored interventions. This helps care managers make enrollment decisions and form tailored care plans. This also enables care managers to pass actionable information on to the other members in the clinical care teams and collaborate more closely with them. To implement the new function, we will improve our previous method [59] to automatically explain a machine learning model's prediction results without incurring any accuracy loss. For nonlongitudinal tabular data, our previous method separates explanation and prediction by employing 2 models simultaneously, each for a distinct purpose. The first model gives predictions to maximize accuracy. The second employs class-based association rules mined from historical data to explain the first model's results. Our previous method cannot handle longitudinal attributes and has not yet been applied to COPD, asthma, or care management.

As mentioned in Aim 1, we will use temporal features to convert longitudinal data to tabular data, with 1 column per feature.

Then we can apply our previous automatic explanation method [59]. Each patient is represented by the same set of features and is marked as either high risk for future hospital use or not. From historical data, our method mines association rules linked to high risk. An example rule is as follows: the ratio of inhaled steroid to beta agonist dispensing to the patient decreased over 12 months AND sulfur dioxide level was ≥ 3 parts per million for ≥ 5 days in the past week high risk. The first item on the left-hand side of the rule is an actionable temporal risk factor. Two interventions for the first item are to (1) assess COPD controller medication compliance and change, prescribe, or raise the dose of the medication if needed and (2) assess the patient for COPD triggers and ensure the patient stays away from them. Our paper [71] listed several interventions for a few other temporal risk factors. By discussion and consensus, the clinical experts in our team will check the mined rules and drop those making little or no sense clinically. For every rule that remains, our clinical team will mark the actionable temporal risk factors in it and list zero or more interventions that address the reason shown by the rule.

At the time of prediction, for every patient our most accurate model projects to be at high risk for future hospital use, we will find and show all of the association rules whose left-hand side conditions the patient satisfies, and list the interventions linking to these rules as our suggestions. Each rule shows a reason why high risk is anticipated for the patient. Users of our automatic explanation function can give feedback to help us find and drop unreasonable rules [64].

Boost Automatic Explanations' Coverage of Patients, Model Accuracy, and Generalizability

For a nontrivial portion of patients, our previous automatic explanation method [59] cannot explain the prediction results of the model. Our previous method employs a conventional approach to mine association rules at a specific level of 2 parameters: minimum confidence and support. This approach is suboptimal for imbalanced data. There, the outcome variable takes the high-risk value for future hospital use much more often than the low-risk one. Adopting the same minimum support for both values is inadequate [104]. If the minimum support is too small, the rule mining process will form many overfitted rules, making it daunting for clinicians to check all of the mined rules. If the minimum support is large, we cannot identify enough rules for the high-risk value. Consequently, for many patients projected to be at high risk for future hospital use, we cannot explain the prediction results of the model.

To enlarge automatic explanations' coverage of patients, we will use a new technique. It generalizes to many clinical applications and is sketched as follows, with more details given in our design paper [71]. We will use Paul et al's [104] approach to mine association rules, by replacing support by value-specific support termed commonality. This has 2 advantages. First, the rule-mining process produces fewer overfitted rules, cutting the time clinicians need to check the mined rules. Second, we obtain more rules for the high-risk value of the outcome variable. Thus, for more patients projected to be at high risk for future hospital use, we can explain the prediction results of the model.

Using automatic explanations and the method described in our paper [64], we will find and drop uninformative features and retrain the predictive model. For the model, this can boost its accuracy, as well as make it generalize better to other health care systems beyond where it was originally built. On nonmedical data, Ribeiro et al [105] showed a similar method with a narrower scope boosted model accuracy by approximately 10%.

Performance Evaluation

We will compare the association rules obtained from IH, KPSC, and UWM data. The following discussion focuses on IH data. The cases with KPSC and UWM data are similar. We will do analyses similar to those in Aim 1 to compare using our new techniques in Aim 4 versus the current method of offering no explanation. We will compare the outcomes of the number of inpatient stays and the number of emergency room visits in the subsequent year and the accuracy reached by the 2 models: the best ones produced in Aims 1 and 4. We will test 3 hypotheses: using our new techniques in Aim 4 will link to a potential drop in (1) inpatient stays and (2) emergency room visits in the subsequent year and (3) boost prediction accuracy. Our primary hypothesis is as follows:

1. Null hypothesis: The number of inpatient stays in the subsequent year reached by the second model is the same as that reached by the first.
2. Alternative hypothesis: The number of inpatient stays in the subsequent year reached by the second model is smaller than that reached by the first.

We will employ McNemar test to compare the paired-sample outcomes reached by the 2 models.

Among the patients truly at high risk for future hospital use, the second model will find some cases missed by the first and vice versa. Assuming the former cuts inpatient stays in the subsequent year by 2.5% and the latter increases them by 0.5% and using McNemar test, at a one-sided significance level of 0.05, a sample size of 503 instances provides 80% power to verify the primary hypothesis. The IH data in the 13th year cover approximately 35,000 COPD patients, offering enough power to test the primary hypothesis.

To assess our technique's impact on model generalizability, we will compare 2 predictive models' accuracy on KPSC/UWM data. The first model is the best one produced in Aim 1 on IH data using the variables available in both the IH and KPSC/UWM datasets. The second is produced by using our technique to drop uninformative features from the first model and retrain it on IH data. We will develop and test our techniques on asthma as well.

Aim 5: Assess Actionable Information's Impact on Clinicians' Acceptance of Early Warnings and on Perceived Care Plan Quality

As an essential preparatory step for future clinical deployment, we will evaluate actionable information's impact on UWM care managers and physicians' decision making in a test setting. For physicians, we will use primary care physicians, pulmonologists, and allergists managing COPD patients. The discussion below

focuses on care managers. The case of evaluating with 10 physicians is similar.

Subject Recruitment

As an operational project at UWM, we are working on COPD outcome prediction and can access approximately 25 UWM care managers for adults. By making announcements in their email lists and personal contact, we will recruit 10 care managers. We will adopt purposeful sampling to ensure adequate variability in work experience [106]. All evaluation test participants will give consent and be up-to-date on privacy and information security policy training required by UWM. Participants will obtain pseudonyms, connecting their responses to questions to protect privacy. After completing the task, each will obtain US \$2400 as compensation for participation for approximately 40 hours of work. We will conduct 2 experiments.

Experiment 1

Procedures

From the IH data in the 13th year, we will randomly select 400 IH COPD patients who used the hospital in the subsequent year and automatically explain the prediction results of the best IH model built in Aim 4. We will use patients outside of UWM to help ensure no care manager is aware of any of those patients' outcome in the subsequent year. We will show every care manager a different subset of 40 patients and proceed in 3 steps:

- Step 1: For every patient, we will present the historical de-identified patient attributes and the prediction result to the care manager and ask him/her to record the enrollment decision and interventions, if any, that he/she plans to use on the patient. For the historical patient attributes, we will show the static attributes' values at the top, followed by the longitudinal attributes' values in reverse chronological order. No care manager will see any automatic explanation in this step.
- Step 2: For every patient, we will present the automatic explanations and their linked interventions to the care manager and survey him/her using both semistructured and open-ended questions. The automatic explanations will appear as a list of association rules. Below each rule is the list of interventions linked to the rule. The questions will include whether these explanations would change the enrollment decision for the patient, whether he/she believes they would improve care plan quality, their usefulness on a 1 to 7 scale with anchors of not at all/very useful, and their perceived trustworthiness on a 1 to 7 scale with anchors of not at all/completely. Our questionnaire will embrace a text field for writing comments.
- Step 3: We will use the standard Technology Acceptance Model (TAM) satisfaction questionnaire [107] to survey the care manager about the automatic explanations. A technology is unimportant unless people will accept and use it. Developed based on multiple well-accepted behavioral theories, TAM is the most widely adopted model of people's acceptance and usage of a technology. The TAM satisfaction questionnaire will measure the perceived usefulness and the perceived ease of use of automatic explanations. Perceived usefulness is known to link strongly

to future usage intentions and to actual function usage [108,109]. Multiple studies have demonstrated the validity and reliability of the TAM satisfaction questionnaire [110,111].

Analysis

We will adopt the inductive approach described in Patton et al [106,112] to conduct qualitative analysis. Care managers' textual comments will be put into ATLAS.ti qualitative analysis software [113]. In total, 3 people in our research team will independently highlight quotations on prediction results and automatic explanations for all records. Quotations will be examined, classified into precodes, and merged into categories via discussion and negotiated consensus in several iterations. We will find general themes via synthesis of categories. The quantitative analyses will include giving descriptive statistics for every quantitative outcome measure. We will test the hypothesis that for the patients who will use the hospital in the next year, giving actionable information will improve the perceived care plan quality. Our hypothesis is as follows:

1. Null hypothesis: For the patients who will use the hospital in the next year, the care manager does not believe that showing the automatic explanations and their linked interventions would improve care plan quality.
2. Alternative hypothesis: For the patients who will use the hospital in the next year, the care manager believes that showing the automatic explanations and their linked interventions would improve care plan quality

We will fit a random effect logistic model to account for correlation among the outcomes of the same care manager on whether the perceived care plan quality is improved.

Justification of the Sample Size

Assuming a moderate intra-class correlation of 0.1 within the same care manager on the outcome of whether the perceived care plan quality is improved, a sample size of 40 instances per care manager for 10 care managers is equivalent to totally 82 independent instances after adjusting for the clustering effect. At a 2-sided significance level of 0.05, we will have 80% power to identify a 9.7% increase in the odds of improving the perceived care plan quality with actionable information. A similar conclusion holds if the actual correlation differs somewhat from the assumed one.

If giving actionable information has no significant impact on the perceived care plan quality on the whole group of COPD patients, we will do subanalyses to find those patient subgroups on which significant impact occurs.

Experiment 2

Procedures

We will randomly partition the 10 care managers into 2 disjoint groups: the intervention group and the control group. Each group has 5 care managers. From the IH data in the 13th year, we will randomly select 200 IH COPD patients who used the hospital in the subsequent year and whose data are unused in Experiment 1 and automatically explain the prediction results of the best IH model built in Aim 4. For each group, we will show every

care manager in the group a different subset of 40 patients. With random assignment, each patient is shown to 2 care managers, one in the intervention group and the other in the control group. In the control group, for every patient, we will show the care manager the historical de-identified patient attributes and the prediction result but no automatic explanation. In the intervention group, for every patient, we will show the care manager the historical de-identified patient attributes, the prediction result, the automatic explanations, and their linked interventions. In both groups, we will ask the care managers to record their enrollment decisions.

Analysis

We will test the hypothesis that for a patient who will use the hospital in the next year, giving actionable information will increase the likelihood that a care manager decides to enroll the patient in care management. Our hypothesis is as follows:

1. Null hypothesis: For a patient who will use the hospital in the next year, the likelihood that a care manager in the intervention group decides to enroll the patient in care management is the same as that in the control group.
2. Alternative hypothesis: For a patient who will use the hospital in the next year, the likelihood that a care manager in the intervention group decides to enroll the patient in care management is higher than that in the control group.

We will fit a random effect logistic model to compare care managers' enrollment decision outcomes between the intervention group and the control group, while accounting for correlation among the enrollment decision outcomes of the same care manager and correlation between the enrollment decision outcomes of the same patient examined by 2 care managers.

Justification of the Sample Size

Assuming a moderate intra-class correlation of 0.1 within the same care manager and within the same patient examined by 2 care managers on the enrollment decision outcome, a sample size of 40 instances per care manager for 10 care managers is equivalent to totally 74 independent instances after adjusting for the clustering effect. At a 2-sided significance level of 0.05, we will have 80% power to identify a 9.7% boost in the intervention group in the odds that a care manager decides to enroll the patient in care management. A similar conclusion holds if the actual correlations differ somewhat from the assumed ones.

As mentioned right before Aim 1, the above discussion focuses on COPD. Whenever we mention COPD, the same applies to asthma and will be developed and tested on asthma also in Aims 1 to 5.

Ethics Approval

We have obtained from IH, UWM, and KPSC institutional review board approvals for this study.

Results

We are currently downloading clinical and administrative data from the EDWs of UWM, KPSC, and IH. We plan to start data analysis in 2020 and finish our study in 2025.

Discussion

Clinical Use of Our Results

Care managers collaborate with the other members in the clinical care teams. We will automatically explain early warnings and suggest possible interventions to help clinical care teams form tailored care plans on the grounds of objective data. This could facilitate clinicians to review structured data in patient charts faster and enable closer collaboration between care managers and the other members in the clinical care teams. Once our methods find patients at the largest projected risks for future hospital use and provide explanations, clinicians will check patient charts, examine factors such as social dimensions and potential for improvement [102], and make care management enrollment and intervention decisions.

As time goes by, both the feature patterns linked to high risk for future hospital use and patient status keep changing. In clinical practice, we can re-apply our techniques regularly to the latest clinical, administrative, air quality, and weather data sets to move patients into and out of care management and to find new feature patterns over time.

As in the case with LSTM, with information from only one visit, our proposed predictive models can start making projections on the patient. Yet, all else being equal, we would expect the prediction accuracy and risk warning timeliness reached by our models to improve as the length of patient history increases.

Generalizability

We will semiautomatically extract predictive and clinically meaningful temporal features from longitudinal data, solving an open computer science challenge [60]. Both our feature extraction and automatic explanation methods will help drop uninformative variables, reducing the variables used in the model. This boosts model generalizability and partly addresses the limitation that one study cannot afford to test models on all US patients. As Gupta et al [114] showed, many extracted features represent general properties of the attributes used in the features and can be valuable for other predictive modeling tasks. Using the extracted features to build a temporal feature library to aid feature reuse, we can cut down the effort required to construct models for other predictive modeling tasks.

The principles of our techniques are general, depending on no unique characteristic of a specific disease, patient cohort, or health care system. Care management is also widely used for patients with diabetes and heart diseases [34], where our techniques could be used. Our simulation will find out how to generalize a predictive model to other sites gathering differing sets of variables and those variables most crucial for generalization. We will use data from 3 health care systems IH, KPSC, and UWM to illustrate our techniques on the cases of COPD and asthma patients. These health care systems include 2 integrated systems (IH and KPSC), an academic system with most patients referred from other systems (UWM), and many heterogeneous facilities. These facilities cover 41 hospitals and 424 clinics spread over 3 large geographic areas, ranging from rural and community urban clinics staffed by a variety of

clinicians including physicians, nurses, therapists, and advanced practice practitioners with limited resources to metropolitan tertiary care hospitals staffed by subspecialists. These systems use 4 different electronic health record systems: IH uses Cerner, HELP, and HELP2; UWM uses Cerner and Epic; KPSC uses Epic. Variation in scope of services, staff composition, geographic location, cultural background, patient population, health care system type, and electronic health record system allows us to find factors generalizable to other facilities nationwide. Our models will be based on the OMOP common data model [72] and its related standardized terminologies [73], which standardize clinical and administrative variables from ≥ 10 large US health care systems [115,116]. At a minimum, our models will apply to those systems using OMOP.

After extension, our techniques can be applied to various decision support applications and diseases and advance clinical machine learning: (1) more precise models giving earlier warnings will boost decision support tools for managing limited resources, such as planning for health care resource allocation

[117] and automatically finding patients tending to be readmitted soon, triggering home visits by nurses to cut readmissions and (2) using our techniques can boost prediction accuracy and risk warning timeliness of other outcomes such as missed appointments [118], patient satisfaction [119], and adherence to treatment [120]. This will help target resources, such as reminder phone calls to cut missed appointments [118], or interventions to boost adherence to treatment [120].

We expect our more accurate predictive models giving earlier warnings to have value for clinical practice. Future studies will test our techniques on some other patient cohorts and diseases, implement our techniques at UWM, IH, and KPSC for care management for COPD and asthma, and evaluate the impacts in randomized controlled trials.

In summary, the techniques that will be developed in this study will advance machine learning for many clinical applications and help transform preventive care to be more efficient, effective, and timely. This will boost outcomes and save resources.

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Authors' Contributions

GL was mainly responsible for the paper. He conceptualized and designed the study, performed the literature review, and wrote the paper. FLN, BLS, CK, DHA, MAM, KAS, MS, RSZ, and GHD offered feedback on study design and medical issues and revised the paper. SH took part in retrieving the IH dataset and interpreting its detected peculiarities. XS took part in conceptualizing and writing the statistical analysis sections. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

- AUC:** area under the receiver operating characteristic curve
- COPD:** chronic obstructive pulmonary disease
- EDW:** enterprise data warehouse
- ICD-10:** International Classification of Diseases, Tenth Revision
- ICD-9:** International Classification of Diseases, Ninth Revision
- IH:** Intermountain Healthcare

KPSC: Kaiser Permanente Southern California
Lasso: least absolute shrinkage and selection operator
LSTM: long short-term memory
MCLSTM: multi-component LSTM
OMOP: Observational Medical Outcomes Partnership
TAM: Technology Acceptance Model
UWM: University of Washington Medicine

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Protocol

Older People With Type 2 Diabetes—Individualizing Management With a Specialized (OPTIMISE) Community Team: Protocol for a Safety and Feasibility Mixed Methods Study

Rajna Ogrin^{1,2}, BSc, BPod, PhD; Sandra Neoh³, MBBS, BMedSci, MPhil; Tracy Ayles⁴, BHS, Grad Cert; Ralph Audehm⁵, MBBS, Grad Cert; Leonid Churilov^{6,7}, BSc, PhD; Lorenna Thurgood¹, BPTH, MBA, MAS; Georgia Major^{1,8}, BSc; Jeffrey Zajac^{2,9}, MBBS, PhD; Elif I Ekinci^{2,9}, MBBS, PhD

¹Bolton Clarke Research Institute, Bolton Clarke, Bentleigh, Australia

²Austin Health Clinical School, University of Melbourne, Heidelberg, Australia

³Austin Health, Heidelberg, Australia

⁴Bolton Clarke, Forest Hill, Australia

⁵Department of General Practice, University of Melbourne, Parkville, Australia

⁶Florey Institute of Neuroscience and Mental Health, University of Melbourne, Heidelberg, Australia

⁷RMIT University, Melbourne, Australia

⁸National Ageing Research Institute, Parkville, Australia

⁹Department of Endocrinology, Austin Health, Heidelberg, Australia

Corresponding Author:

Rajna Ogrin, BSc, BPod, PhD

Bolton Clarke Research Institute

Bolton Clarke

Suite 1 01, 973 Nepean Highway

Bentleigh, 3204

Australia

Phone: 61 400253459

Email: rogrin@boltonclarke.com.au

Abstract

Background: The prevalence of diabetes is rising in older people. In 2018, over 574,000 Australians reported having diabetes. The highest prevalence (19.4%) of diabetes has been observed in people aged 85 years and older. Clinical guidelines recommend that diabetes management should be individualized; however, there is limited information regarding the current management patterns of diabetes in older people, given most clinical trials exclude participants from this age group. Available data identify that few individuals achieve optimal glycemic levels in the general population, potentially leading to adverse health outcomes and impact on quality of life. The data on glycemic profiles of older population are limited.

Objective: The aim of this study is to examine individualized diabetes management intervention for older people through home visits with a credentialed diabetes educator (CDE) and telehealth consultations with an endocrinologist located at a tertiary hospital.

Methods: This paper describes the design and methodology of a mixed methods feasibility and safety study to identify the current management of type 2 diabetes in people aged 65 years or older. We will implement and evaluate a personalized approach to management in the community of an Australian metropolitan city. This management approach will utilize flash glucose monitoring and home visits with the support of a community home nursing service CDE and telehealth consultation with an endocrinologist located at a local tertiary hospital.

Results: The study commenced in February 2017 and has recruited 43 participants, with final data collection to be completed by July 2019. Data analysis will commence after final data collection, with results expected to be published by the end of 2019.

Conclusions: This study is the first of its kind to explore individualized diabetes management for community-dwelling older people, with an aim to achieve optimal glycemic levels (glycated hemoglobin between 53 and 69 mmol/mol [7%-8.5%] depending on the fitness and frailness of the older individual). The data drawn from this study may be used to inform policy makers, service providers, clinicians, and older adults living with diabetes.

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KEYWORDS

type 2 diabetes mellitus; aged; person-centered; telehealth

Introduction

The prevalence of type 2 diabetes in older Australians is increasing. In 2015, 1 in 6 Australians aged 65 years or older reported living with diabetes [1]; the incidence of this disease peaks between the ages of 65 and 74 years [2]. Diabetes care is particularly challenging in older adults because of the longer duration of the disease and the increased likelihood of complications, comorbidities, falls, and polypharmacy [3]. In addition, there is a lack of an evidence base regarding the safety and efficacy of diabetes pharmacotherapy in this population.

International guidelines recommend that diabetes care and glycemic targets should be individualized with consideration of the patient's age, comorbidities, functional status, and living situation [4,5]. In particular, treatment of hyperglycemia should be carefully balanced with the avoidance or minimization of hypoglycemia [6]. This is often difficult in older individuals with long durations of diabetes and possible underlying secondary pancreatic failure.

Currently in Australia, health care delivery of diabetes management in older adults is conducted through primary care or hospital-based diabetes clinics. These environments are not necessarily ideal, as they do not easily allow assessments of home situations and true functional status [7]. An alternative approach is telemedicine, defined by the American Telemedicine Association as the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status. Telemedicine has been successfully used for the management of chronic diseases in this age group [8]. The current approach involves the credentialed diabetes educator (CDE) using their laptop to link into Web videoconferencing in the home of the person living with diabetes to link with the endocrinologist located in the hospital for joint initial and final review appointments. This approach has been used effectively previously, with good acceptability [9].

We hypothesize that a specialist-led telemedicine service, including flash glucose monitoring technology, is a safe and feasible method of delivering diabetes care to older Australians in Melbourne, Victoria. This study is the first of its kind to trial individualized diabetes management plans for older people through home visits with a CDE and telehealth consultations with an endocrinologist located at a tertiary hospital [10].

Methods

This protocol paper structure is per the Standard Protocol Items for Clinical Trials guidelines [11].

Study Design and Setting

This is a feasibility and safety trial, using Simon's 2-stage design [12], of a new model of health care. This study will use a mixed methods approach describing quantitative glycemic data and qualitative interviews regarding person-centered outcomes.

The study will include older individuals, aged 65 years or older, living with type 2 diabetes, and residing in the northern region of metropolitan Melbourne. The Older People with Type 2 diabetes—Individualizing Management with Specialized (OPTIMISE) team delivering care consists of the following: (1) a CDE working with a home service organization providing home visits and (2) an endocrinologist based at the tertiary teaching hospital. Joint telehealth consultations will be conducted with the endocrinologist at the hospital and the CDE with participants with diabetes in the participants' home, including the use of flash glucose monitoring data collected by participants in the preceding 2 weeks to inform clinical decision making.

Aim

The primary aim is to trial the safety and feasibility of a new model of diabetes care, aimed to optimize diabetes management and improve quality of life at home using a specialized OPTIMISE community team.

The secondary aims are as follows:

1. To describe the current diabetes management
2. To trial the effectiveness of a specialized community-based team to optimize diabetes management and improve quality of life of older people with type 2 diabetes.

Primary Research Questions

The primary research questions are as follows:

1. Among community-dwelling older adults with type 2 diabetes, is the OPTIMISE model of care safe?
2. Among community-dwelling older adults with type 2 diabetes, is the OPTIMISE model of care feasible?

The OPTIMISE model will be deemed safe if all the following conditions are met:

1. There are no deaths associated with diabetes intervention.
2. There are no serious adverse events causally related to the intervention as adjudicated by a panel of physicians within 1 week of the event.
3. The participant spends <30% of time in severe hyperglycemia (>20 mmol/L) measured by flash glucose monitoring, and
4. The participant spends <5% of time in hypoglycemia (<4 mmol/L) measured by flash glucose monitoring.

The OPTIMISE model will be deemed as feasible if the following conditions are met:

1. The approached participant agrees to proceed with the intervention at the first visit by the CDE.
2. The participant completes the 4-month intervention by supplying a flash glucose monitor data capture rate of at least 40% (defined as the number of 15-min time points with glucose values captured divided by the total number of 15-min time points for the duration the sensor was applied); 40% was chosen as the feasibility value as previous larger clinical trials involving younger participants with type 1 and 2 diabetes have accepted 50% as clinically sufficient data [13,14].
3. The participant attends at least 80% of scheduled follow-up appointments.

Secondary Research Questions

The secondary research questions were as follows:

1. What are the perceptions of older adults with type 2 diabetes regarding their experiences of telehealth consultations in delivering home-based diabetes care?
2. What are the perceptions of older adults with type 2 diabetes regarding using flash glucose monitoring technology to support diabetes management?
3. What are the perceptions of the OPTIMISE team care providers regarding their experiences with this model of care?

The outline of the participant pathway for this study is shown in [Multimedia Appendix 1](#).

Participants

There will be 2 groups of participants:

1. Older adults with type 2 diabetes.
2. Health care providers within the OPTIMISE team.

Older Adults With Type 2 Diabetes

Potential participants will be eligible for the study if they are aged 65 years or older, have been diagnosed with type 2 diabetes, can speak and understand English, and live in the community nursing organization's catchment area for home visits.

Individuals will be excluded from the study if they

- Are unable to consent
- Are unable to self-manage their diabetes or do not have a caregiver to provide support

- Are already under the care of an endocrinologist
- Have an acute condition that destabilizes their glycemic levels or are likely to require hospital readmission
- Are in residential care or palliative care

Health Care Providers in the Older People With Type 2 Diabetes Individualizing Management With Specialized Team

The endocrinologist and CDE involved in the study will also be invited to participate in the research.

Recruitment

Participants with type 2 diabetes will be recruited from several sources, which are as follows:

1. Existing home nursing clients: the CDE will screen and identify eligible participants from the Northern site of the home nursing organization.
2. Tertiary hospital: the endocrinologist will screen new referrals to the diabetes clinic.
3. Tertiary hospital: the endocrinologist will screen all recently admitted inpatients with glycated hemoglobin (HbA_{1c}) level of greater than or equal to 6.5%.
4. Referrals from other clinicians in the region: diabetes educators, geriatricians, and general practitioners who have working relationships with the research team will be invited to refer eligible participants.
5. Self-referrals from the community who meet eligibility criteria.

Once identified, the CDE will contact potential participants to inform them of the study. If interested, the first home visit will be arranged to explain the study and answer questions. If the participant agrees to proceed, a second home visit is organized to discuss the participant information and consent form and obtain informed consent.

Health care providers involved in the OPTIMISE team will be invited to participate, provided with the participant information and consent form, and given the opportunity to ask questions.

Baseline Clinical Data Assessments

Once recruited, the CDE will organize a third home visit with the participant for baseline data collection; the details are shown in [Table 1](#).

Table 1. Older people with type 2 diabetes individualizing management with specialized baseline participant and biochemistry data collection.

Baseline participant information components	Content of the baseline participant information
Demographic data	Age, gender, country of birth, language(s) spoken, education level, and socioeconomic index for areas
Descriptive data	Height, weight, blood pressure, medical history, medical diagnoses, medication names, doses and directions of use, and history of falls in the past 12 months
Mini Nutritional Assessment-Short Form [15]	Nutrition
Rowland Universal Dementia Assessment Scale [16]	Dementia or Cognitive Impairment: The Rowland Universal Dementia Assessment Scale
Charlson Comorbidity Index [17]	Prognostic comorbidity for mortality
Diabetes-specific information	Duration of diabetes, family history, current pharmacotherapy, relevant comorbidities, hypoglycemia, and hyperglycemia risk
Biochemistry data collection	Glycated hemoglobin, Liver function tests, lipid profile, fasting plasma glucose, renal function, full blood examination, and spot urinary albumin to creatinine ratio

Intervention

The intervention involves the implementation of a management plan developed after a telehealth consultation with the endocrinologist at the hospital linking with the CDE and participant with diabetes in the participant's home. The management plan is based on the clinical assessment and the profile of data collected using the flash glucose monitor in the preceding 2 weeks. The participant with diabetes is then supported by the CDE to implement the management plan, through face-to-face visits and phone calls. A final follow-up telehealth consultation with the endocrinologist at the hospital, linking with the CDE and participant with diabetes in the participant's home is undertaken. In this consultation, an ongoing plan for diabetes management is decided based on assessment outcomes, including the profile of data collected using the flash glucose monitor in the preceding 2 weeks. Specific details on each component are provided below.

Flash Glucose Monitoring

During the third home visit, the flash glucose monitoring system (Freestyle Libre, Abbott Diabetes Care Inc) will be placed on the back of the participant's upper arms by the CDE, as per the manufacturer's guidelines. The system involves a very small glucose-sensing filament (<0.4 mm thick and 5 mm long) worn under the skin and connected to a water-resistant, plastic on-body patch the size of a 1 dollar coin. The participant is shown how to scan the sensor using the supplied touchscreen reader device and asked to scan the sensor at least 4 times per day for 2 weeks and advised how to interpret the results and act on them.

Biochemistry Collection

The participant will be contacted by a research officer to organize a home visit to complete quantitative questionnaires and to arrange biochemistry collection (Table 1).

Telehealth Consultation With Participant, Credentialed Diabetes Educator, and Endocrinologist

The fourth home visit (week 2, Multimedia Appendix 1) by the CDE occurs 2 weeks after the flash glucose sensor is applied. Data from the flash sensor are downloaded and emailed to the endocrinologist for review. The CDE and participant then

teleconference with the endocrinologist, located at the tertiary hospital, using the Skype software (Microsoft Corporation, Luxembourg) installed on the CDE's laptop. An individualized care plan will be developed, which may involve the initiation or adjustment of oral medicine, injectable therapy initiation or adjustment, and diabetes education.

The management plan will be underpinned by goal-setting theory, where the process of goal setting facilitates behavior change by guiding people's effort and attention [18]. Feedback strategies will be incorporated into the goal-setting practices to enhance goal attainment [19].

Treatment care plans are based on current best practice guidelines [3,20]. Education will be individually tailored to meet the needs of the participant [3,20]. The endocrinologist will inform the participant's general practitioner of the care plan and recommendations via a letter.

Care Plan Implementation and Monitoring

The CDE will implement the care plan with participants and will facilitate referrals to local community services where required. The CDE will contact the participants monthly for the occurrence of adverse events and will report this accordingly. Additional telehealth consultations with or without repeat flash glucose monitoring with the endocrinologist will be scheduled only if changes to management plans are required. Participants may discontinue the intervention at any time.

Follow-Up Assessments

At week 18, the CDE will visit the participant to apply the flash glucose monitor sensor, collect weight and blood pressure data, apply the flash glucose monitor sensor, and provide a repeat pathology slip. At week 20, the CDE will return to the participant's home, download the flash glucose data, and email this to the endocrinologist, just before a repeat telehealth consultation, using Skype.

At this consultation, the participant, endocrinologist, and CDE will determine if further diabetes support is required. Either ongoing diabetes care will be handed back to the general practitioner via a letter or a referral will be made to the diabetes clinic at the tertiary hospital if ongoing specialist endocrine support is required.

After the final telehealth consultation, the research officer will arrange a final home visit for quantitative data collection and a semistructured qualitative interview. The interview will be audio-taped and transcribed verbatim. The interview will start with an open question asking the participants to describe their experiences of the care they received from the team. Prompts will be used, if needed, to ensure inclusion of the following pivotal information: their perceptions of being seen by the CDE in their home; the experience of seeing the specialist over the computer, including the performance of telehealth such as connectivity; their experiences of using the flash glucose monitor; what they thought could have been improved, and what worked well in the care delivery; how confident they were in managing their diabetes; if they sought outside help for their diabetes management; and whether they would recommend this program to others with diabetes.

A pathology slip for a follow-up final HbA_{1c} is emailed to the participant to be performed at week 32.

At the end of the trial, the CDE and endocrinologist will be invited to participate in a face-to-face interview, which will be audio-taped and transcribed, to ascertain their experiences of providing care to participants. The interview will start with an open question asking them to describe their experiences of the care they provided as part of the team. Prompts will be used, if needed, to ensure inclusion of the following pivotal information: their satisfaction with their role in the team; their experiences of working with the endocrinologist or CDE; their experiences of using the flash glucose monitor; the experience of using telehealth, including the performance of telehealth such as connectivity; whether they encountered safety concerns during the study; what are their thoughts about the impact of this program on the participants with diabetes; what they thought could have been improved and what worked well in the care delivery; and if the program were to be run as business as usual at their organization, whether they would want to be a part of the team.

The intervention will be deemed as both feasible and safe, worthy of further investigation in a subsequent randomized comparative trial, if it proceeds to the second phase of Simon's 2-stage design [12] and more than 31 out of 43 participants do not experience feasibility or safety issues.

To evaluate the impact of the program on participants, secondary outcome measures will be collected, including: biochemical markers, person-centered measures, and service data (shown in [Multimedia Appendix 2](#) [21-25]).

Data Management

The research officer will manage the study data and enter data into a statistical database, supervised by the project leads. No names will be used on any data collection forms, and all data will be deidentified when entered into the database. Electronic databases will be kept on secure, password-protected drives on a secure network, and hard copy data will be stored in a locked cupboard in a secure area. Data entry will be undertaken by research officers involved in the study, with random 10% of data checked for accuracy. Range checks for data values will be undertaken to ensure any errors are identified.

Sample Size

Simon's 2-stage design is used where a group of participants is enrolled in the first stage, and depending on the successful outcome of this group, a second group of participants is then enrolled [12]. In the first stage, 11 participants will be recruited. If 7 or more participants do not experience feasibility or safety issues, the study will proceed to phase 2, where 32 additional participants are recruited for a total of 43. The study design yields a type 1 error rate of 0.05 and power of 0.8 when the true proportion of patients without a negative composite feasibility/safety outcome is 0.8.

Statistical Methods/Analysis

Baseline clinical, social, demographic, and biochemical data will be presented as counts (proportions), means (SDs), or medians (interquartile ranges), depending on the nature of the underlying distribution. The proportions of patients with specific outcomes will be reported with corresponding 95% CIs.

If more than 31 out of 43 participants do not experience feasibility or safety issues, the intervention will be deemed worthy of further investigation in a subsequent randomized comparative trial.

Statistical analysis will be undertaken by STATA (ICv 14) software (StataCorp, College Station, TX).

Interviews with participants will be analyzed thematically using a constant comparative approach [26]. Transcripts will be read by researchers, emergent themes discussed, and interpretations compared.

Safety Considerations and Dissemination

The project has ethical oversight from the organizational human research ethics committee (HREC): home nursing organization HREC (HREC, project number 183) and from the tertiary hospital HREC (project HREC/16/Austin/496). In the case of major adverse events, both HRECs will be informed on the same day by the project manager. Confidentiality and security of participant data will involve deidentification and the use of codes generated using a random number generator. The principal investigators will conduct auditing of the dataset at the end of data entry, following data analysis to ensure compliance with the protocol. Access to data will only be given to researchers involved in the trial. Investigators will publish results of findings in peer-reviewed journals and present the findings at conferences associated with diabetes management and health services research. There are no publication restrictions.

Results

The project was funded in November 2016 and approved by the respective organizations (as noted above) in February 2017. Data collection commenced in July 2017, with anticipated data collection to cease in July 2019; 43 participants have consented to participate, with data analysis to commence after final data collection is complete. We anticipate results to be published by the end of 2019.

Discussion

This study is the first of its kind to trial the safety and feasibility of a new model of diabetes care, aiming to optimize diabetes management and improve quality of life in the home using a specialized community team involving CDE home visits and telehealth consultations with an endocrinologist.

The increasing prevalence of type 2 diabetes, particularly in older adults, highlights the importance of identifying knowledge gaps and potential risks in the management and care of older people living with this disease. This study is unique in trialing person-centered home-based diabetes care, which adheres to current guidelines and recommendations [3]. We will describe the current management and interventions implemented in this cohort, as well as the key issues and perceptions of the older community members receiving the care. The perceptions of the providers on delivering this care will also be explored.

The strength of this project is its ability to comprehensively assess the feasibility and safety of this multifaceted home-based model of care. This study also uses new technology such as telehealth and flash glucose monitoring and will add to the growing evidence base for use of technology in supporting diabetes self-management in older adults.

Potential limitations of this study include its small sample size and lack of participants from non-English-speaking backgrounds. Furthermore, the study may be prone to ascertainment bias because of convenience sampling from a geographic location limited to 1 community nursing organization and 1 tertiary hospital.

We anticipate that the data generated by this project will be used to inform service providers, clinicians, and older adults living with diabetes of the care currently provided, how guidelines for optimal treatment translate into practice, and to inform future research of the effectiveness of this kind of multimodal intervention.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Flowchart of participant pathway.

[PNG File, 21KB - [resprot_v8i6e13986_app1.png](#)]

Multimedia Appendix 2

Study outcome measures and data collection.

[PNG File, 9KB - [resprot_v8i6e13986_app2.png](#)]

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Abbreviations

CDE: credentialed diabetes educator

HREC: human research ethics committee

OPTIMISE: Older People with Type 2 diabetes—Individualizing Management wIth SpecializEd

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Original Paper

Web-Based Eligibility Quizzes to Verify Opioid Use and County Residence Among Rural Young Adults: Eligibility Screening Results from a Feasibility Study

April M Ballard^{1,2}, MPH; Hannah LF Cooper³, SCD; April M Young^{1,4}, MPH, PhD

¹Department of Epidemiology, University of Kentucky, Lexington, KY, United States

²Department of Environmental Health, Emory University Rollins School of Public Health, Atlanta, GA, United States

³Department of Behavioral Sciences and Health Education, Emory University Rollins School of Public Health, Atlanta, GA, United States

⁴Center on Drug and Alcohol Research, University of Kentucky, Lexington, KY, United States

Corresponding Author:

April M Young, MPH, PhD

Center on Drug and Alcohol Research

University of Kentucky

845 Angliana Avenue

Lexington, KY, 40508

United States

Phone: 1 859 218 2090

Email: april.young@uky.edu

Abstract

Background: Web-based methods can be used to collect data from hidden populations, including people who use drugs (PWUD). These methods might be especially advantageous among PWUD in rural areas, where transportation barriers are prevalent, stigma may heighten concerns about confidentiality, and internet access is improving. However, Web-based research with PWUD can be challenging, especially in verifying eligibility. Administering *quizzes* to verify residential and substance use eligibility could prove valuable in online research among PWUD, yet the utility of this approach is currently unknown.

Objective: This study describes the implementation of online eligibility quizzes about the local community to verify residence in the target study area along with drug dose, appearance, and price to verify opioid misuse.

Methods: To be eligible, individuals had to live in 1 of 5 eastern Kentucky counties, report using opioids to get high in the past 30 days, and be 18 to 35 years old. Participants recruited from August 2017 to July 2018 were asked questions about their opioid use followed by a quiz about drug dose, appearance, and price to verify substance use eligibility. Residential eligibility was verified with 5-question quizzes assessing knowledge of the county where they reported living. Questions tested knowledge about towns, festivals, and landmarks; local school mascots and colors; and presence of certain retail stores, restaurants, and facilities (eg, jails). A subsample that reported using opioids in the past 24 hours was randomly selected to complete urine drug testing (UDT). Nonparametric tests were performed to explore differences across demographic subgroups.

Results: Of the 410 entries assessed for eligibility, 39.3% (161/410) were ineligible as they reported no substance use, being outside the age range, or living outside the study area. Of the remaining 249 who met the eligibility criteria based on age, residency, and opioid misuse, 94.0% (234/249) *passed* the eligibility quizzes. Among those who passed the heroin quiz, 99.4% (167/168) recognized the image of powdered heroin, 94.6% (159/168) answered the cap size (ie, the purchase unit) question correctly, and 97.0% (163/168) answered the street price question correctly. Among those who passed the drug quiz for prescription opioids, 95% (36/38) answered the dose question correctly, and 82% (31/38) selected the correct image. In a random sample of participants who completed UDT within 3 days of their online screening, 74% (25/34) tested positive for an opioid.

Conclusions: This study demonstrated the utility of using online eligibility screening quizzes to verify opioid misuse and residence. Participants accurately recognized heroin and prescription opioid doses, prices, and images and correctly answered questions about features of their county. Online quizzes to screen and enroll PWUD hold promise for future research as an alternative to more time- and resource-intensive approaches that could offset the advantages of Web-based methods.

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KEYWORDS

Web-based methods; eligibility determination; rural health; substance-related disorders; opioid use; surveys and questionnaires; internet; confidentiality; sampling methods; recruitment

Introduction

Background

Studies have shown that Web-based methods can successfully be used to collect data from hidden populations, including men who have sex with men (MSM), people with sexually transmitted infections, and people who use drugs (PWUD) [1-9]. Web-based data collection can decrease barriers to study participation by allowing individuals to complete surveys from any location and by providing participants with a heightened sense of anonymity [10-14]. These methods may be particularly pertinent for research among PWUD because of concerns around legality and stigma of the behaviors they are reporting. Furthermore, the importance of innovations in substance use research is heightened by the increase in substance use and related harms such as overdose mortality in several countries including the United States, Australia, and Europe [15,16].

Rural areas such as central Appalachia have a longstanding and continued problem with prescription opioid misuse and drug-related harms [17]. A steady increase in substance use has occurred over the past 2 decades, with abuse rates exceeding national averages [17]. Methodological innovations in research among rural US populations have, therefore, become increasingly important because of the disproportionate burden of opioid use and related harms (ie, hepatitis C and overdose) affecting rural young adults [17-23]. Furthermore, with 78% of rural adult Americans reporting use of the internet [24], the methodological advantages of Web-based data collection and recruitment might be especially advantageous for research among hard-to-reach populations in rural settings, where transportation barriers are prevalent and fear of breaches to confidentiality may be heightened because of stigma [25,26]. However, no studies to our knowledge have developed and piloted Web-based methods for data collection among rural PWUD, though a number of studies have used Web-based methods to recruit and collect data from PWUD [1,3,9,27-31] in urban settings.

Regardless of rurality, verifying eligibility criteria for studies related to recent substance use with PWUD and residence in a targeted geographic area can be challenging. Web-based methods can further compound these challenges. Substance use self-report can be employed for eligibility screening; however, validation studies using biologic techniques have shown a range of accuracy and under-reporting, with frequency and magnitude depending on drug class and socioecological factors [32,33]. Many in-person studies of PWUD use urine drug testing (UDT), saliva testing, or visual inspection for injection stigmata to verify eligibility [34-42]. These methods, of course, are not possible during online screenings, and using UDT or in-person/virtual consultation to confirm eligibility in Web-based studies would be time- and resource-intensive and could offset the advantages of online research.

Similarly, methods to recruit participants from specific geographic areas and verify residence in those areas can be difficult to implement. Even if study advertisements are targeted (ie, via local outreach and posting local flyers), once a survey link is revealed online and/or the link is shared with peers, people who live outside the target area can access the link. Many online survey platforms have the capacity to record geolocation based on user internet protocol (IP) address and allow researchers to restrict access to online surveys based on geolocation [43-45]. However, geolocation linked to IP address can be inaccurate because when a device is connected to a virtual private network or network address translation, only an external IP address is displayed, causing all devices to have identical IP addresses and geolocation. In addition, smartphones can display multiple different IP addresses within minutes because of network proxies within the carrier's network, resulting in inaccurate geolocation based on IP addresses [46-48]. Recent research among MSM in Kentucky revealed that a substantial proportion of entries with ineligible geolocations based on IP addresses belonged to verified eligible participants [49].

An alternative to in-person UDT and/or visual inspection of participants to verify substance use and IP address geolocation to verify residential location is assessing knowledge about drug use and the target study area. Previous studies have used trained interviewers to assess prospective participants' knowledge about the preparation of drugs for injection, administration of injections, and the size and color of needles and syringes, in addition to visual inspection for injection stigmata [42,50]. Other studies that include PWUD through noninjection routes have used interviewer-administered questionnaires to assess knowledge of street terminology, major formula doses (eg, milligram), and pill images [41,51]. To our knowledge, research that verifies residential eligibility through the assessment of knowledge about the target study area has not been conducted. However, assessing knowledge of local community features such as the names of nearby cities and towns, local businesses, and physical landmarks, in addition to in-person or targeted recruitment strategies (ie, direct marketing, respondent-driven sampling, and venue-based sampling) could be useful in enrollment of participants from a specified geographic area. Thus, substance use and local community *quizzes* could prove valuable in Web-based survey research among PWUD and in research targeting specific geographic areas.

Objectives

The aim of this study was to explore the utility of using an online survey to screen and enroll young adult PWUD from rural Kentucky into an online survey about substance misuse and related risk behaviors. This study describes the implementation of an online eligibility screening quiz about the local community to verify residence in the target study area along with drug dose, appearance, and price to verify substance use.

Methods

Overview

Young adults who use opioids were recruited from August 2017 to July 2018 from 5 counties in rural Appalachian Kentucky to participate in an online survey, programmed in SurveyGizmo [42]. The survey contained questions about participants' substance use, sexual and drug-related risk behaviors, and risk environments. Eligibility criteria included being 18 to 35 years old, living in the 5-county study area, and using opioids to get high in the past 30 days. Opioids included prescription pain pills, heroin, buprenorphine, methadone, and synthetic opioids. The study was funded to focus on individuals aged 18 to 35 years because of the disproportionate burden of opioid use and related harms (ie, hepatitis C and overdose) impacting young adults in rural settings [21-24,28,52].

Participants were recruited using both targeted and Web-based peer referral methods. Targeted outreach included distributing flyers at local businesses and organizations where young PWUD may be present (eg, tobacco shops, laundromats, gas stations, and social service offices), referrals from staff from another study on PWUD in the target area, and hosting community cookouts that advertised the study. Those who were eligible and completed the survey also had the option to refer peers through emailed or text messaged electronic peer referral coupons. Participants received US \$10 for up to 3 eligible referrals who completed the survey. Study flyers and recruitment coupons had a URL for a study website hosted by WordPress [53], which had the link to the SurveyGizmo screening survey. The website also provided information for completing the screening assessment, informed consent, and survey. Flyers' text included a university and study logo and stated that participants who lived in the 5-county study area were needed for a study on rural health. The flyers did not disclose that the study was focused on drug use.

Informed consent was self-administered for both the online screening and the survey. The consent also informed participants that UDTs would be administered to a random subsample of participants. To demonstrate comprehension, participants were required to answer 4 questions correctly at the end of the consent form that covered the content of the informed consent. After informed consent, participants were asked how they would like to be compensated. Options included cash, money wire, gift card, or an e-gift card of US \$30. UDT compensation was US \$25 and was given in-person at the time of urine specimen collection.

Before beginning the full online survey, eligibility was assessed using the date of birth to capture age and quizzes that examined knowledge about opioids and the local community to verify substance use and residence, respectively. Before initiating recruitment, we conducted pilot tests of these quizzes with young adult PWUD living in the study area. Information gathered was used to make adjustments to the quizzes to maximize utility and clarity before participant enrollment.

Quiz to Verify Substance Use Eligibility

To verify substance use, people were asked questions about their use, followed by a quiz. First, people were asked to select all substances they had used to get high in the past 30 days from a list containing several opioids (eg, heroin, synthetic opioids, buprenorphine, methadone, and prescription opioids), nonopioids (eg, prescription sedatives or tranquilizers, cocaine, crack, methamphetamine, gabapentin, bath salts, and hallucinogens), and *other*, followed by a write-in response. Participants also had the option to select *none of these*. Those who had not used any substance to get high in the past 30 days were not quizzed and skipped the remaining substance use items.

People who reported using prescription opioids to get high were asked to specify which prescription opioid(s) they used using a checklist. People who reported using any opioid were then asked to specify which opioid they had used *most often* to get high in the past 30 days. Those who reported and specified which prescription opioid they had used were given the option to select that particular drug.

The drug quiz queried the opioid they reported using most often in the past 30 days. If they had used other nonopioids to get high, in addition to opioids, the *most often* follow-up question only listed opioids to ensure they were quizzed on a drug that related to eligibility criteria. Drug-specific opioid and nonopioid quizzes are described below.

Heroin Quiz

People who reported heroin as their most frequently used opioid in the past 30 days were administered a similar, 4-question quiz. First, they were asked what the most common size for a cap, or *one hit*, of heroin was in their county with the following response options: one-tenth of a gram (correct), one gram, five grams, and 20 grams. People were then asked how much 1 cap or *hit* of heroin cost in their town, with the following response options: US \$0-\$10, \$10-\$50 (correct), \$50-75, and more than \$75. Local law enforcement experts who arrange undercover drug purchases and local PWUD were consulted for information on *cap* size (1/10th of a gram or 100 mg) and heroin price (US \$20 to \$40 per cap).

Finally, people were asked to identify which photograph looked most like the heroin they buy in their county and were given 10 images as options, with 5 showing different types of powder heroin ranging from white to dark brown and 5 showing images that had textures and/or colors that would obviously not be heroin to a heroin user. People were required to get either the most common size or the cost for 1 cap of heroin correct to *pass* the heroin quiz. Image recognition was not included in the heroin quiz score, as it is possible that some people may only see heroin after it has been dissolved and heated for injection.

Prescription Opioid Quiz

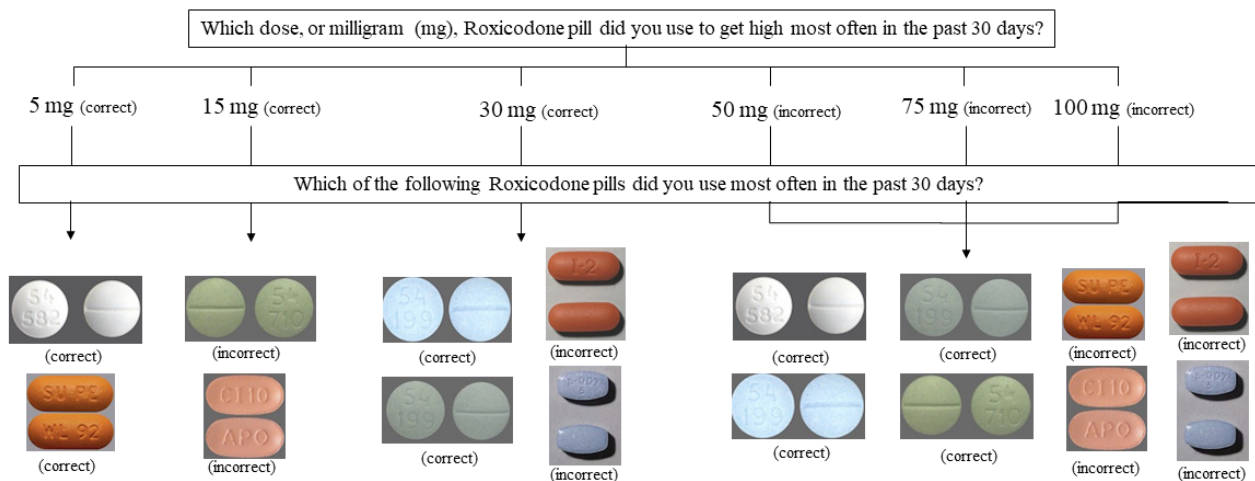
For nonmedical use of prescription opioids, buprenorphine, and methadone, quizzes involved multiple-choice questions about dose (ie, choosing the dose from a list of real and fake milligrams options) and appearance (ie, recognizing an image from a set of correct and incorrect images). Because most prescription opioid pills, lozenges, films, or tablets are made in

multiple doses and have different appearances depending on dose, formulation, and manufacturer, the quiz's branching and skip patterns had to account for each drug/dose combination. Questions had a varying number of response options depending on the number of actual doses and images that were possible, such that 50% of options were correct and 50% were incorrect. For example, as shown in Figure 1, Roxycodone is manufactured as 5, 15, and 30 mg pills; therefore, the dose question had 6 response options so that 50% of options were correct and 50% were incorrect. Similarly, sets of response options for questions on Roxycodone images for each dose contained 50% correct

responses. Incorrect dosage selection branched to an image question that provided images of all doses so that even if participants selected the incorrect dose, they still had the opportunity to identify the correct image.

People were also asked about the street price in an open-ended question. They were instructed to leave the answer blank if they did not know it. Because the study team was unable to gather information on street price for every possible prescription opioid, milligram, formulation, and manufacturer, this question was not included in the quiz score. People were only required to get either dose or image correct to *pass* the prescription opioid quiz.

Figure 1. Example sequence of questions from the online screening eligibility process for prescription opioid quiz for Roxycodone.



Synthetic Opioid Quiz

Because of the recent emergence and rapidly evolving nature of the synthetic opioid market, we could not program a scorable quiz for synthetic opioids. If a person reported using synthetic opioids, they were asked where people normally get synthetic opioids (online, gas stations, drug paraphernalia stores, or other), what type of substance synthetic opioids were (pills, powder, liquid, and other), and price for 1 dose. The answers were not scored, and people who reported synthetic opioids as their most commonly used drug were automatically deemed eligible for the survey if they completed the screener and were otherwise eligible.

Nonopioid Quiz

People who did not report opioid use received a brief quiz because if quizzes were only given to those who initially reported opioid use, it could serve as a clue to people about what type of drug use would qualify them for the study. Therefore, to avoid unmasking eligibility criteria, people who had not used an opioid (ie, methamphetamine, cocaine, bath salts, or hallucinogens) were administered a 3-question quiz on the nonopioid drug they reported using in the past 30 days. The quiz asked about the drug's color and texture (ie, pill, liquid, powder, rocks, or other), as well as an open-ended item on dose or common size for a bag of the drug. The nonopioid quizzes were not programmed to be scored.

Quiz to Verify Residential Eligibility

To verify residence in the 5-county area, people were asked which state and county they had slept in most often in the past 6 months and then were administered a 5-question quiz assessing their knowledge of that county. Quiz items for study area counties were drawn at random from a 10-question bank developed specifically for that county. A question bank was used so that if a person tried to coach another respondent as they took it simultaneously or at a later date or tried to take the screening survey multiple times until they passed, it would be harder to share and/or learn the answers.

Quiz items contained yes/no and multiple-choice questions with the latter having 4 or 5 response options. For each eligible county, county-specific quiz items queried topics that were known widely within the county but most likely were unknown to people who did not live in the county. A total of 6 of the 10 quiz item topics were the same across counties; however, the remaining 4 items in the bank varied across eligible counties based on what features were applicable and salient (see [Multimedia Appendix 1](#)). Questions and topics were chosen based on suggestions from community members who attended local recruitment events and from local community partners. People were required to get 3 out of 5 questions correct to *pass* the county quiz.

A generic county quiz was administered when individuals reported living outside the 5-county study area to help mask which counties were eligible. The generic county quiz was pulled from a 10-question bank that had similar content

presented in [Multimedia Appendix 1](#). Responses to these items were not scored, as correct answers for all possible noneligible counties were unknown and simply stating that they lived outside the 5-county area disqualified persons from the study.

Urine Drug Testing

A subsample (n=34) of survey participants who reported using opioids in the 24 hours before completing the screening were randomly selected to complete a 13-Panel iCup Drug Test within 3 days of the survey based on drug detection windows. The survey tool was programmed to randomly select participants for UDT if they completed the survey and reported using opioids in the past 24 hours. The iCup test is an extensive UDT for 13 different drugs including opiates (heroin and morphine), buprenorphine (Suboxone, Subutex, and Temgesic), methadone (Dolophine, Methadose, and Phytetone), oxycodone (Percocet, Percodan, OxyContin, and Tylox), and propoxyphene (Darvocet and Darvon), as well as various stimulants, sedatives, and other drugs [54]. According to the manufacturer, most drugs appear in urine 2 to 5 hours after use, and drug detection windows vary based on several factors including frequency of use, route of administration, body mass, and age. Participants who were randomized to receive a UDT were contacted by the study staff to schedule an appointment at a local venue to obtain the urine specimen.

Analysis

Descriptive statistics were used to describe results of the online eligibility screening algorithm and quizzes and to compare UDT results with self-reported opioid use. Nonparametric tests (eg, Kruskal-Wallis test and Spearman rank-order correlation) were performed because of non-normal distribution of outcome

variables to explore associations across subgroups using SPSS Statistics version 25.0 (SPSS Inc).

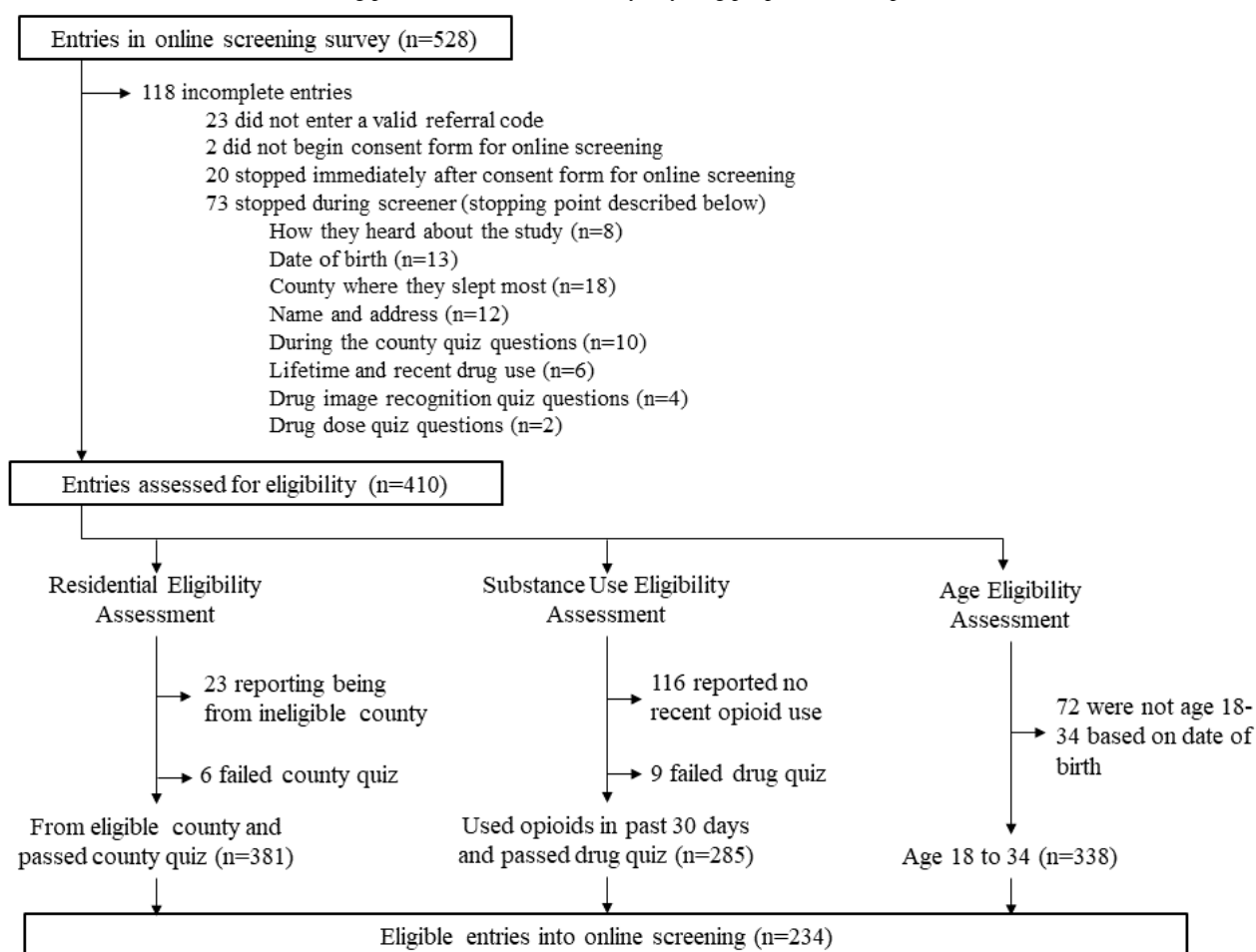
Ethics

All study procedures were approved by the University of Kentucky Institutional Review Board, and data were protected by a Federal Certificate of Confidentiality. To ensure anonymity, IP address and geolocation of the device used when completing the survey were not collected. All data were password-protected and stored on a secure server.

Results

Overview

[Figure 2](#) describes the results of the eligibility screening. In total, there were 528 entries in the online eligibility screening survey, 22.3% (118/528) of which were incomplete (see [Figure 2](#)). Among the complete entries, the median time required to complete the screening was 6.14 min (interquartile range: 3.65-8.82 min). Of the 410 complete entries, 57.1% (234/410) were deemed eligible. Over half (229/410, 55.9%) were male, and the average age was 30 years (SD 11 years). Data integrity (ie, fraud detection) and final survey sample characteristics of eligible participants are published elsewhere [53]. Most (116/176, 65.9%) of the ineligible entries were due to not reporting any recent opioid use, followed by 41% (72/176) who reported being outside the eligible age range (18-35 years) and 13.1% (23/176) reporting living outside the study area. Only 6.8% (12/176) of ineligible entries were classified as ineligible because of failing the county quiz (n=5) and/or drug quiz (n=7). It should be noted that ineligibility data presented in [Figure 2](#) are not exclusive; people may have been ineligible based on multiple criteria.

Figure 2. Outcomes of the online screening process from the online study of young people who use opioids.

Drug Quiz Results

In total, only 4 people failed the drug quiz for heroin, as a result of answering both the cap size and street price question incorrectly. Among the 168 people who passed the drug quiz for heroin, 167 (99.4%) recognized the image of powdered heroin, 159 (94.6%) answered the cap size question correctly, and 163 (97.0%) answered the street price question correctly. In total, 91.7% (154/168) answered the cap size and street price questions correctly. Because of the low variance on the quiz scores, we lacked the statistical power to examine variables associated with performance on the heroin quiz.

The most common prescription opioid that participants had used most frequently in the past 30 days and were, therefore, quizzed on was Percocet (n=18), followed by Norco (n=5), fentanyl (n=4), Roxicodone and Lortab (each with n=3), Tramadol and Tylox (each with n=2), and Opana and OxyContin (each with n=1). A total of 2 participants failed the drug quiz for prescription opioids, 1 for Percocet and 1 for Tylox. Among the 38 people who passed the drug quiz for a prescription opioid, 36 (95%) answered the dose question correctly, and 31 (82%) selected the correct image. Of those who selected incorrect prescription opioid images, 1 was for Norco and 6 were for Percocet. The 2 incorrect dose responses were also for the Percocet drug quiz.

In total, 74 people reported buprenorphine as their most frequently used drug in the past 30 days, with most (n=66) using buprenorphine pills. Among those quizzed about buprenorphine pills, 3 answered the dose and image questions incorrectly and failed the drug quiz. Of those who passed the drug quiz, 95% (60/63) answered the dose question and 92% (58/63) answered the image question correctly. In total, 84% (53/63) answered the dose and image questions correctly. Among those quizzed about buprenorphine strips, all passed the drug quiz, with 89% (8/9) answering both dose and image questions correctly.

A total of 4 people were quizzed on methadone, 1 on liquid methadone, and 3 on pills. No participant failed the methadone drug quiz. Only 1 person answered a methadone quiz question incorrectly, which was the methadone pill dose question.

County Quiz Results

A Kruskal-Wallis test was conducted to examine differences in the quiz score across the 5 counties in the study area. No statistically significant differences in quiz scores were found across the 5 counties ($\chi_4^2=6.9$, $P=.14$). Of the 6 parallel questions that were asked for every county in the study area (see [Multimedia Appendix 1](#)), the item querying smallest communities in the county was answered incorrectly most frequently, followed by if there was a jail or prison in the county, the local physical landmark specific to the county, and if there was a Walmart in the county. Among the 381 people who passed the county quiz for an eligible county, the average score was

4.9 (range 0-5) and most (91.1%) answered all 5 questions correctly.

Spearman rank-order correlation was used to investigate whether there was an association between length of residence in the county and county quiz score among those who were eligible and completed the survey. There was no statistically significant association between length of residence in the county and county quiz score ($r_s=.03$, $P=.74$). Of note, length of residence could not be assessed as a correlate to county quiz score among those who failed the county quiz because duration of residence was only collected from those who participated in the study.

Urine Drug Testing Results

Among the 44 individuals who were randomized to UDT, 34 completed the UDT within 3 days of their survey. Of these,

74% (25/34) tested positive for any opioid, including 27% (9/34) who tested positive for opiates (ie, heroin), 50% (17/34) who tested positive for buprenorphine, and 3% (1/34) who tested positive for oxycodone (see Table 1). Overall, 64.7% (22/34) tested positive for any stimulant. In addition, 6% (2/34) tested positive for benzodiazepine and 3% (1/34) for phencyclidine. Only 2 participants did not test positive for any drug.

Table 2 describes test results based on the opioid they reported (1) using most frequently in the past 30 days and (2) using in the past 24 hours. Slightly more than 50% (18/34) had urinalysis results that matched the opioid they reported using most frequently in the past 24 hours.

Table 1. Comparison of self-reported use of opioids with results of the 13-panel iCup urine drug test completed within 3 days of self-reported use.

Opioid used within past 24 hours ^a	Those with positive UDT ^b , n (%)	Days since survey completion, average (range) ^c	UDT detection window, days [54]	Detection threshold, ng/mL [54]
Heroin (n ^d =21)	8 (38)	0.22 (0-1)	2-4	2000
Buprenorphine (n ^d =9)	8 (89)	0.52 (0-3)	2-3	10
Percocet (oxycodone; n ^d =4)	1 (25)	0.75 (0-1)	2-4	100

^aParticipants had self-reported the opioid they used most often in the past 30 days and also reported use in the 24 hours before completing the screening.

^bUDT: urine drug test.

^cDays elapsed between survey completion and UDT completion. Zero means that the screening was performed the same day.

^dThe number of people who completed the UDT.

Table 2. Urine drug testing results of 13-panel iCup urine drug test completed within 3 days of self-reported use (N=34).

Drug	Positive UDT ^a , n (%)	UDT detection window, days [54]	Detection threshold, ng/mL [54]
Marijuana	18 (53)	15-30	50
Opioids	25 (74)	— ^b	—
Opiates (heroin, morphine)	9 (27)	2-4	2000
Methadone	0 (0)	3-5	300
Oxycodone	1 (3)	2-4	100
Propoxyphene	0 (0)	1-2	300
Buprenorphine	17 (50)	2-3	10
Stimulants	22 (65)	—	—
Methamphetamine	21 (62)	3-5	1000
Amphetamine	21 (62)	2-4	1000
Cocaine	3 (9)	2-4	300
Benzodiazepines	2 (6)	3-7	300
Phencyclidine	1 (3)	7-14	25
Barbiturates	0 (0)	4-7	300
Any drug (excluding marijuana and tricyclic antidepressant)	30 (83)	—	—

^aUDT: urine drug test.

^bNot applicable.

Discussion

Principal Findings

Web-based recruitment and data collection can be leveraged for research among hidden populations. However, tools for verifying behavioral and geographic eligibility criteria, such as recent substance use and residence, in Web-based research are lacking. This study demonstrated the utility of using online eligibility screening quizzes to verify substance use and residence in an online survey of young adult PWUD from rural Kentucky. In a random sample of participants who completed UDT within 3 days of their online screening, 73.5% (25/34) tested positive for an opioid, with drug detection windows ranging from 1 to 5 days. Only 2 did not test positive for any drug. In addition, most of those who reported recent opioid use (285/294, 97.0%) and living in the 5-county study area (381/387, 98.4%) were able to pass the respective quizzes.

Quizzes to verify substance use queried drug dose, price, and image recognition. People were able to offer accurate answers to these questions across opioid types. For example, among those who reported heroin as their most frequently used drug in the past 30 days, most (154/168, 91.7%) answered the cap size and street price questions correctly, and every participant except 1 was able to successfully recognize an image of powdered heroin. Most participants who passed a prescription opioid drug quiz were able to correctly answer dose and image questions (28/39, 71.8%). Of note, Percocet was the most common prescription opioid that participants reported using *most frequently* in the past 30 days and had a greater proportion of incorrect pill image and dose responses. During the study, researchers anecdotally discovered that the street name for Roxycodone (eg, Perc 30s) may have led people who were using Roxycodone to incorrectly select Percocet and subsequently be unable to correctly identify dose and pill images. Formula doses, pill images, and drug street names may vary across settings and should be considered when developing similar tools. PWUD within the setting may be a vital resource to ensure proper tool development. In addition, to avoid unmasking the eligibility criteria in studies focused on specific drug classes (such as opioids as done in this study), it is important to administer quiz questions for all drug classes.

People also performed well on quizzes that were used to verify their residence in the 5-county study area. Of those who reported being from an eligible county, 1.6% (6/387) failed the eligibility quiz. Questions that had the highest proportion of correct answers were those about businesses or facilities in the county (ie, whether there was a particular grocery store such as Kroger, Walmart, or local chains in their county, a particular pizza restaurant in their county). Questions that appeared to be most difficult for participants were multiple-choice items that asked them to identify the county's largest town/city and which among the 5 lists of small communities was located in their county. Furthermore, depending on the length of a study and turnover in communities, changes in local businesses and facilities may need to be considered when utilizing community-specific quizzes.

Community member input and pilot testing were essential to the development of the county quizzes. In this study, community partners who worked in local public health and social service agencies helped develop sets of 10 questions for each of the 5 eligible counties; quizzes were then piloted with local PWUD. Initially, quizzes contained questions on high school mascots and colors, but feedback from local PWUD revealed that those who moved to the area more recently may not know information about local schools, so the questions were revised. Pilot-testing results highlight the need to engage community members in the development of quizzes and to pilot-test quizzes in the target sample. These findings may also reveal the need for future studies to collect data on duration of residence in the screening instrument and to potentially vary the threshold for passing based on the length of residence. In addition, to minimize inapposite participation that could result from advertising online or, more broadly, where geographic ineligibility could be more problematic, study advertising should be targeted. In this study, community cookouts, flyers, and outreach by local study staff were used to advertise the study, which may have resulted in the low percentage (23/410, 5.6%) of screening survey participants who reported being from a county outside the eligible study area.

Limitations

Although using Web-based methods to screen and enroll young adult PWUD was successful in this study, there were limitations. Quizzes are limited in their ability to distinguish people who have ever used substances from those who have used recently, given that drug prices, doses, and appearances may not vary drastically over time. In addition, creating quizzes for nonprescription opioids such as heroin and synthetic opioids is more difficult because of lack of manufactured doses and potential inconsistencies in appearance. Quizzes for these drugs may, therefore, need to be more vague and consequently easier to pass. This study's small strata-specific sample sizes (ie, by drug and by county) limited its ability to detect correlates to quiz performance and precluded a more rigorous statistical comparison of quiz results with urine drug screen outcomes. Future research could examine differences in quiz performance by drug type and examine other correlates to quiz performance. Other analytic approaches such as factor analysis were not employed in this study because each quiz was slightly different across counties based on county features and for each drug based on dosages, pill manufacturers, and appearances. In future research involving a larger, more homogenous sample (ie, in 1 interested in use of a single drug) or more limited geographic area, psychometric properties of quizzes could be evaluated.

Narrow UDT detection windows limited our ability to compare test results with self-reported past 30-day substance use [54]. Future research could utilize hair, saliva, or blood tests that have longer detection windows and better capture eligibility recall periods [37]. Finally, technological issues could also create a barrier to participation or lead to inaccurate ineligibility. Informal conversations with participants revealed that some had difficulty entering their date of birth because of the appearance of the question on some smartphone devices; others experienced problems with loading image questions because of internet speed and connectivity. Of note, 48.3% (72/151) of

participants reported completing the survey on a smartphone, 28.9% (43/151) on a computer, 10.7% (16/151) on a tablet, and 12.1% (18/151) on some other device [55].

Clinical and Research Applicability

Innovative screening approaches are becoming increasingly important with the rise in Web-based research. Methods that utilize technology are, therefore, necessary both to ensure enrollment of truly eligible participants and to prevent fraudulent participation. Online quizzes to screen and enroll PWUD hold promise for future research as an alternative to more time- and resource-intensive approaches that could offset the advantages of Web-based methods. Online eligibility quizzes could also prove useful for studies that are not Web-based, as they could be used for eligibility screening and thereby reduce burden on staff of screening study participants through interviewer-administered approaches. Furthermore, as technology evolves, new methods for eligibility verification

may emerge, particularly in studies where participants are using smartphones. For example, image recognition software could be used to recognize injection stigmata in studies of people who inject drugs or to verify residence in a target community through photographs of landmarks. With advances in drug testing and remote diagnostic confirmation using smartphones through saliva- [56,57], urine- [57,58], and serum-based assays [57], smartphone-based testing also may be integrated into future online studies of PWUD. Geocaching [58] and global positioning system targeting technology such as those used in online gaming and gambling to validate that a patron is within authorized jurisdictional boundaries [59,60] may be used in the future to verify residential eligibility. Although new technologies are promising, until they are seamlessly integrated into survey platforms, strict data security measures are in place, and smartphone ownership is ubiquitous, quizzes to assess eligibility will continue to be an important tool for screening and enrollment of participants into online research.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Quiz questions used to verify residential eligibility in a 5-county study area.

[[PDF File \(Adobe PDF File\), 67KB - resprot_v8i6e12984_app1.pdf](#)]

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Abbreviations

ARC: Appalachian Regional Commission

CDC: Centers for Disease Control and Prevention

IP: internet protocol

MSM: men who have sex with men

PI: principal investigator

PWUD: people who use drugs

SAMHSA: Substance Abuse and Mental Health Services Administration

UDT: Urine Drug Testing

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Protocol

Protocol for the Development of a Behavioral Family Lifestyle Intervention Supported by Mobile Health to Improve Weight Self-Management in Children With Asthma and Obesity

David Fedele^{1*}, PhD, ABPP; Robert Lucero^{2,3*}, PhD, MPH, RN, FAAN; David Janicke¹, PhD, ABPP; Mutasim Abu-Hasan⁴, MD; Elizabeth McQuaid⁵, PhD, ABPP; Jon Moon⁶, PhD; Andrea Fidler¹, MS; Tanya Wallace-Farquharson⁷, MSN, RN; David Lindberg⁸, MS

¹Department of Clinical & Health Psychology, University of Florida, Gainesville, FL, United States

²Department of Family, Community, and Health System Science, University of Florida, Gainesville, FL, United States

³Center for Latin American Studies, University of Florida, Gainesville, FL, United States

⁴Department of Pediatrics, University of Florida, Gainesville, FL, United States

⁵Departments of Psychiatry and Human Behavior and Pediatrics, Brown University, Providence, RI, United States

⁶MEI Research, Ltd, Edina, MN, United States

⁷Department of Biobehavioral Nursing Science, University of Florida, Gainesville, FL, United States

⁸Department of Statistics, University of Florida, Gainesville, FL, United States

* these authors contributed equally

Corresponding Author:

David Fedele, PhD, ABPP

Department of Clinical & Health Psychology

University of Florida

101 S Newell Dr, Rm 3151

PO Box 100165

Gainesville, FL, 32610

United States

Phone: 1 352 294 5765

Email: dfedele@phhp.ufl.edu

Abstract

Background: Asthma is the most common chronic childhood illness and is a leading cause of emergency department visits in the United States. Obesity increases the risk of poor health outcomes, reduced quality of life, and increased health care expenditures among youth with asthma. Weight loss is crucial for improving asthma outcomes in children with obesity. Our study team developed the Childhood Health and Asthma Management Program (CHAMP), a 16-session behavioral family lifestyle intervention (BFI) for school-age children with asthma and obesity and evaluated CHAMP in a randomized controlled trial compared with attention control. There were medium effect sizes favoring CHAMP for changes in body mass index z-scores, asthma control, and lung function among completers (ie, those who attended ≥ 9 of 16 sessions). Despite high rates of satisfaction reported by families, attendance and trial attrition were suboptimal, which raised concerns regarding the feasibility of CHAMP. Qualitative feedback from participants indicated 3 areas for refinement: (1) a less burdensome intervention modality, (2) a more individually tailored intervention experience, and (3) that interventionists can better answer health-related questions.

Objective: We propose to improve upon our pilot intervention by developing the Mobile Childhood Health and Asthma Management Program (mCHAMP), a nurse-delivered BFI, delivered to individual families, and supported by a mobile health (mHealth) app. This study aims to (1) identify structural components of mCHAMP and (2) develop and test the usability of our mCHAMP app.

Methods: Participants will be recruited from an outpatient pediatric pulmonary clinic. We will identify the structural components of mCHAMP by conducting a needs assessment with parents of children with asthma and obesity. Subsequently, we will develop and test our mCHAMP app using an iterative process that includes usability testing with target users and pediatric nurses.

Results: This study was funded in 2018; 13 parents of children with asthma and obesity participated in the needs assessment. Preliminary themes from focus groups and individual meetings included barriers to engaging in health-promoting behaviors,

perceived relationships between asthma and obesity, facilitators to behavior change, and intervention preferences. Participatory design sessions and usability testing are expected to conclude in late 2019.

Conclusions: Outcomes from this study are expected to include an mHealth app designed with direct participation from the target audience and usability data from stakeholders as well as potential end users.

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KEYWORDS

asthma; obesity; child; family; program development

Introduction

Background

Asthma affects more than 8% of youth and is a leading cause of emergency department visits in the United States [1-3]. Recent evidence indicates that pediatric asthma and obesity are interrelated, with heightened weight status modifying asthma course [4]. Indeed, obesity places children with asthma at an increased risk for poor health outcomes, reduced quality of life, and increased health care expenditures [5-11]. Weight loss is critical for improving asthma outcomes in individuals with obesity [12]. Behavioral family lifestyle interventions (BFIs) are the most effective weight self-management interventions for children with obesity [13,14]. BFIs, grounded in social cognitive theory [15-17], help families acquire self-management skills to better regulate their dietary intake and physical activity behaviors, ultimately leading to reduced child adiposity [18,19].

Our study team recently developed the Childhood Health and Asthma Management Program (CHAMP), a tailored BFI for children with asthma and obesity [20]. Over a 4-month period, parent and child dyads were asked to attend 12 group-based sessions and 4 individual family sessions. Parent and child sessions occurred on weekday evenings, ran concurrently, and were designed to last approximately 90 min. Each session adhered to the following general structure: (1) a review of parent and child progress, (2) skills training and implementation, and (3) goal setting and encouragement. Most families who participated in the trial identified as African American (67%, 16/24) and reported an annual family income of less than US \$35,000. Preliminary pilot testing comparing CHAMP with a rigorous attention control produced mixed findings. CHAMP earned high participant satisfaction ratings and medium effect sizes favoring CHAMP for changes in body mass index (BMI) z-scores, asthma control, and lung function among completers [20]. However, consistent with other BFIs [21-23], intervention session attendance was challenging as families reported barriers to attending in-person groups, including travel distance, and scheduling conflicts. Furthermore, qualitative feedback indicated 3 clear areas for refinement: (1) a less burdensome intervention modality, (2) a more individually tailored intervention experience, and (3) interventionists that can better answer health-related questions.

Mobile health (mHealth) technologies are ubiquitous across sociodemographic strata [24]. Moreover, mHealth has emerged as an effective platform that can improve diet and physical activity in youth with obesity, facilitate the delivery of

personalized intervention content, and can address some of the time- and access-related barriers faced by families of children with asthma and obesity [25]. In addition, nurses have the requisite knowledge and skill set to educate, motivate, and successfully assist families to use behavioral weight self-management skills to facilitate health behavior change [26,27]. Their credibility with families and widespread integration into pediatric health care and community settings across the country increase the promise of downstream scalability. We posit that a nurse-delivered BFI, delivered to individual families and supported by mHealth, is the right approach to overcome attendance challenges associated with family and work schedules [26-29] and will be responsive to participant feedback from our pilot trial.

Study Aims

We propose to leverage lessons learned from our pilot trial to develop Mobile Childhood Asthma Management Program (mCHAMP), a nurse-delivered BFI supported by mHealth. To achieve this purpose, we will do the following:

1. Identify the structural components of mCHAMP using a valid collaborative approach for adapting evidenced-based interventions, known as the Assessment Decision Administration Production Topical Experts Integration Training Testing (ADAPT-ITT) model [30]. The first 2 phases of the ADAPT-ITT model, assessment and decision, will be used to guide the adaptation process. We will conduct a needs assessment with parents (n=20) of children with asthma and obesity to produce the principal components of mCHAMP. The modified intervention protocol will reflect and be responsive to the needs of families of children with asthma and obesity.
2. Develop and test our mCHAMP mobile app to enable a nurse-led BFI for children with asthma and obesity. Using an iterative process, we will develop (n=10) and conduct usability testing (n=10) of the mCHAMP app with parents of children with asthma and obesity [31]. We will then gather provider feedback on clinical implementation from pediatric nurses (n=5).

Methods

Study Design

We will use the ADAPT-ITT model to modify our existing CHAMP protocol and create the mCHAMP app. Table 1 (below) presents the timeline for activities to achieve the study aims.

Table 1. Twelve-month project timeline for study activities.

Activity	Months											
	1	2	3	4	5	6	7	8	9	10	11	12
Study preparation	✓ ^a	— ^b	—	—	—	—	—	—	—	—	—	—
Recruitment/needs assessment	✓	✓	—	—	—	—	—	—	—	—	—	—
Design sessions	—	✓	✓	—	—	—	—	—	—	—	—	—
mCHAMP ^c tool development	—	—	✓	✓	✓	✓	✓	—	—	—	—	—
Usability testing/provider feedback	—	—	—	—	—	—	—	✓	—	—	—	—
Data analysis	✓	✓	✓	—	—	—	—	✓	✓	—	—	—
mCHAMP final refinement	—	—	—	—	—	—	—	—	—	✓	—	—
Dissemination	—	—	—	—	—	—	—	—	—	—	✓	✓

^aActivity planned for corresponding month.

^bNot applicable.

^cmCHAMP: Mobile Childhood Health and Asthma Management Program.

Institutional review board approval and Information Technology security clearance was sought and initiated during the application review period. Any remaining study preparations will be completed in month 1, including hiring graduate research assistants and setting-up a participant reimbursement account. Participant recruitment and data collection will occur from months 1 to 3. Ongoing qualitative data analysis will occur in months 1 to 3. The research team will collaborate with MEI Research, Ltd during months 3 to 7 to develop the mCHAMP app. mCHAMP usability testing with parents and feedback from registered nurses will occur during month 8. Analysis of usability data and synthesis of registered nurse feedback will be conducted during months 8 and 9. MEI will make final refinements to the mCHAMP app based on usability and feedback results.

Participants

Inclusion and Exclusion Criteria

Caregiver participants must be parents or legal guardians of a child who (1) is between the ages of 6 and 12 years, (2) with a physician-verified current diagnosis of asthma for ≥ 6 months, (3) with a BMI ≥ 85 th percentile for biological sex and age as published by the Centers for Disease Control and Prevention [32], and (4) lives in the home with the parent. Parents must also speak and read English. There is no BMI requirement for participating parents/legal guardians. Child asthma, height, and weight will be verified by electronic medical record if recruited from the medical system. Parent report of child's height and weight will be used for individuals recruited outside the medical system. Parents will be excluded if they have a significant cognitive impairment or developmental delay that interferes with study completion. Nurse participants must be registered nurses who (1) provide care for children with asthma and (2) have worked in that capacity for 1 or more years.

Recruitment

Parent participants will be recruited from a pediatric pulmonary clinic, as well as local advertisements distributed through community organizations, physician offices, and schools. When

feasible, research staff will be available to briefly meet with potential participants during a scheduled clinic visit. In coordination with clinic staff, research staff will meet with interested participants to provide a study overview, complete in-person screening for eligibility, and invite participation. In the event that a family is unable to complete screening during a clinic visit, clinic or research staff will request permission for a member of the study team to contact patients for screening and document that consent in writing. A member of the study staff will then call interested participants to provide a study overview and invite participation. Nurse participants will be recruited from flyers and through professional networks.

Enrollment/Informed Consent

Participant enrollment date and the capacity of each study phase will determine which tasks (eg, focus group, design sessions, or usability testing) parents are asked to participate in. During informed consent, the available study tasks will be explicitly stated, and parents will have the option to select which task(s) they want to participate in. Participation in 1 research task does not preclude participation in additional research tasks.

All participants will be provided written informed consent regarding risks, benefits, confidentiality, incentives, and the name and phone numbers, so they may call if they have additional questions. We will receive both verbal and signature consent from participants to participate. Finally, additional informed consents will be obtained to audio-tape meetings for quality control purposes. Participants will be informed that the tapes will be used to transcribe their responses for full review and will not be used for anything other than research purposes.

Retention Plan

We did not have a well-defined retention plan for CHAMP. Thus, we developed the following retention strategies given the previously noted attendance difficulties and attrition in CHAMP. At the start of the study, we will aim to engage participants in a discussion surrounding the importance of their contributions to research. The study's requirements will be clearly and concisely conveyed to the participant. We will also discuss the impact of dropouts and the importance of returning for any

additional sessions, consider barriers that may impede participation, and work together to develop strategies to overcome the identified barriers. We will obtain several phone numbers (home, cell, and work) for each family to decrease the likelihood of attrition owing to changing residences, phones, or phone numbers. During this initial visit, we will also record the best time to call families and whether it is acceptable to call them at work. A tracking system will also be implemented to track participant sessions and log all contact attempts.

The day before the session, participants will be contacted via their preferred method of communication to review visit reminders and to confirm the appointment. For participants who do not answer, a voicemail will be left listing the date/time of the scheduled visit as well as instructions to return our call to confirm the appointment. Participants who miss a session will be called 5 min after the anticipated start time of the session. If a participant is still unable to be reached, a voicemail will be left asking the participant to call our study staff. If participants do not return the call within 2 days, the reestablishment of contact procedure detailed in the following paragraph will be implemented.

When a participant cannot be reached, they will be called 5 times to establish contact; calls will be made at varying times of day and days of the week. After 3 contact attempts, a secondary phone number will be called. Study staff will identify themselves, explain the reason for the call, and confirm the participant's current contact information. If no new phone numbers are obtained, the secondary contact will be asked to pass a message on to the participating family. Participants who cannot be contacted will be sent a letter reminding them of upcoming sessions and asking them to contact study staff.

Aim 1: Identify the Structural Components of Mobile Childhood Health and Asthma Management Program

In line with the ADAPT-ITT model [30], we will conduct assessment and decision phases using feedback from parents of children with asthma and obesity to design the mCHAMP.

Phase 1: Needs Assessment

We will recruit 20 parents of children with asthma and obesity to participate in 4 focus groups (between 4 and 8 parents per focus group). Each parent will participate in only 1 focus group. In the event that scheduling in-person focus groups is nonviable (eg, unable to identify shared availability across participants in the upcoming 3 weeks), we will conduct individual meetings with participants. Audio of all focus groups and individual meetings will be recorded. Focus groups and individual meetings will take place at the University of Florida (UF), a convenient community location, or over a video chat interface that enables compliance with the Health Insurance Portability and Accountability Act of 1996 (Zoom). Focus groups and individual meetings will last approximately 1 hour, and parents will be compensated US \$50 for their participation.

The purpose of these groups and individual meetings will be to identify what structure and components of our existing CHAMP protocol are most salient to individual families of children with asthma and obesity. Participants will complete a demographic questionnaire and technology use questionnaire. Then, we will

begin by explaining the purpose of the focus group and exploring broad question categories about asthma and weight self-management, which are as follows:

1. What changes, if any, have you or your family made because of your child's asthma?
2. What is your family's experience with trying to balance taking care of asthma and making healthy choices?
3. What things get in the way of your family being more active or eating healthier?

Next, we will introduce the intervention in its current form and seek feedback as follows:

1. What type of intervention content (eg, behavior monitoring, skills training, and goal setting) would be most feasible and helpful?
2. How can we be most helpful in teaching and practicing these skills with families?
3. How might a smartphone app be used to help families learn new skills, set goals, keep track of behaviors, and problem-solve things that get in the way?
4. How would you prefer to be in contact with a nurse interventionist (ie, face-to-face, telephone, and video conferencing)?
5. How many contacts do you think would allow you to learn the content?

Finally, we will summarize the main points of the discussion, ask for any comments or corrections, and ask whether we missed anything in our discussion.

Recordings of focus groups and individual meetings will be transcribed verbatim by a professional transcription service. We will enter transcribed files and expanded field notes into NVivo (QSR International). We will code and aggregate interviews using a theoretical thematic analysis approach to developing themes [33-35] and double-check for inconsistencies in the transcripts against the audio recordings. Our theoretical thematic analysis approach will use an a priori theoretical framework guided by social cognitive theory. We will mark comments identified to represent discrete thoughts or themes using a semantic analysis and use an essential realist approach to arrive at themes [33]. These patterns or themes will comprise the initial set of categories. DF and DJ and research staff will then recode the data using these categories. Any disagreements will be resolved based on consensus or a two-thirds agreement. We used empirical guidelines to establish our initial sample size goals [36]. We will recruit additional study participants if saturation is not achieved with the planned participant enrollment. We will organize major themes into summary tables to inform the decision phase.

Phase 1: Decision

We will develop an intervention protocol draft for mCHAMP using data from phase 1 and the collective expertise of the research team. Within the framework of BFIs for weight self-management, the study team will address a set of core questions related to key content and activities. When differences of opinion occur, we will apply a two-thirds consensus method to adopt the research team member's input into the intervention protocol draft.

Mobile Childhood Health and Asthma Management Program Content

The core questions related to key content are as follows:

1. What are the core behavioral weight self-management skills that should be provided as part of the intervention?
2. What content from our existing CHAMP protocol should be further adapted to address the needs of these families?
3. What additional content could we add on the basis of the needs of families of children with asthma and obesity?
4. How do we best position pediatric nurses to serve as interventionists?
5. What should be the overall number and type (face-to-face vs phone) of intervention contacts?

Mobile Childhood Health and Asthma Management Program Delivery

The core questions related to activities are as follows:

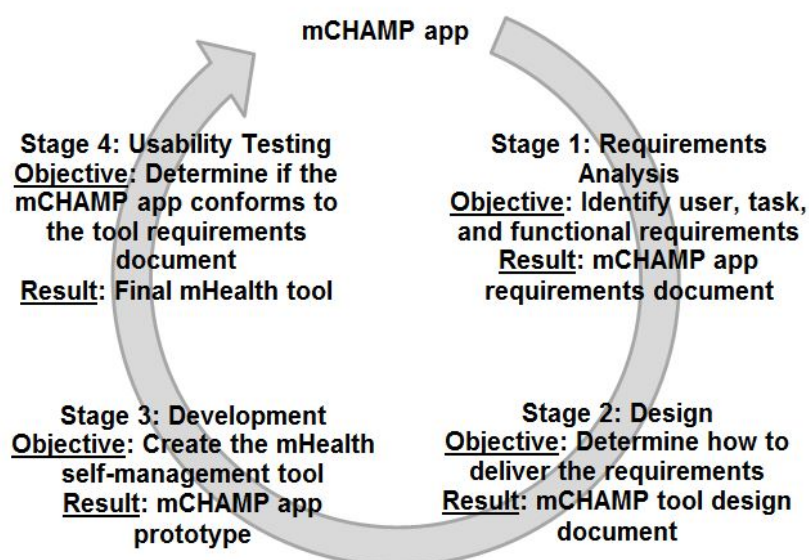
1. What is the best modality to deploy specific intervention content and tasks (eg, in-person, phone, or via the mCHAMP app)?

2. How can we best leverage the mCHAMP app to overcome attendance and participation barriers we encountered in our pilot study?

Aim 2: Mobile Health Weight Self-Management Tool Development

Figure 1 shows the life cycle for developing the mCHAMP app. The result will be an mHealth tool that will be integrated with the revised mCHAMP protocol for families of children with asthma and obesity. One of the lead authors (RL), who is an expert in user-centered design including usability testing, will direct and participate in the implementation of the consumer-centered participatory design (C²PD) approach that will be used to develop mCHAMP tool [31]. This approach has been used by Dr Lucero in other consumer health domains such as fall prevention among community-dwelling older adults and family caregiving of persons living with dementia to develop both personal computer- and app-based self-management tools [37-39].

Figure 1. Development process for the Mobile Childhood Health and Asthma Management Program (mCHAMP) app. mHealth: mobile health.



Stage 1: Requirements Analysis

The C²PD approach will be used to elicit user requirements [31]. Study participants and investigators focus on 4 specific domain requirements: (1) user characteristics and needs, (2) system content and functions, (3) content function and use, and (4) representation of content and function.

For this phase, we will recruit 10 parents of children (aged between 6 and 12 years) with asthma and obesity to participate in a series of 3 participatory design sessions (PDSs). There will be 2 separate design groups (n=5 per group), with each group meeting 3 times. Parents will be compensated US \$50 for their participation in each design session (up to US \$150 total). Participants will complete a demographic questionnaire and technology use questionnaire. Design sessions will be audio-recorded and will take place at UF, a location in the community, or over Zoom. In the event that scheduling group

sessions is not feasible, we will conduct individual meetings with participants. Participant time commitment and compensation will remain consistent regardless of design group method.

After each session, DF, RL, and DJ will debrief to note important system requirements. Examples of design session activities that have been implemented in our previous research include the following: interactive multiple-choice selection using visual cues, low-fidelity prototyping, interactive observation, and participant-designed 2-dimensional interfaces, photo elicitation, and constructing collages [37]. *PDS 1, user assessment*, is the process of identifying user characteristics, such as technology expertise and skills (eg, use of smartphone and tablet), comfort in interacting with technology, educational background, and preferences between visual and text to communicate information. *PDS 2, functional assessment*, is the process of identifying system goals of mCHAMP. Parents may

find it necessary for the mCHAMP app to contain a function that can be used to facilitate self-monitoring related to caloric intake. *PDS 3, representation and task assessment*, involves identifying preferred task structures and procedures, such as input and output formats of information and communication flow (ie, representation) and ways of searching, entering, accessing, or retrieving information (ie, task) from the app.

Recordings of design sessions will be transcribed verbatim by a professional transcription service. NVivo 11 software (QSR International) will be used to analyze the data. A descriptive content analysis will be conducted for each session to generate a list of user, functional, and representation and task

requirements. Two members of the research team (Fedele and Lucero) will read the transcripts to identify recurring or specific content. They will meet to review, clarify, and draw consensus on emerging content with input from the research team. The output of the analysis will be a set of requirements for the design of the mCHAMP app. On the basis of the requirements for the mCHAMP app, the research team will draft a requirements or design document to guide prototype development.

Stage 2: Design

We anticipate that the mCHAMP app used to support our BFI could include several components to support our revised intervention protocol (see [Table 2](#)).

Table 2. Potential mCHAMP intervention components.

Potential app component	Potential Functionality
Weight self-management education	Providing information on American Academy of Pediatrics recommendations for dietary, physical activity, and screen time; discussing how to build a home environment that promotes healthy dietary habits and engagement in physical activity (eg, stimulus control); providing education regarding the importance and safety of exercise for children with asthma and collaboratively brainstorming ways to increase physical activity in their family and community; discussing the importance of regularly self-monitoring dietary habits and physical activities; and providing feedback on behavioral parenting strategies (eg, positive reinforcement, differential attention, and contingency management) to overcome child resistance.
Remote monitoring	Ability for family and nurse to monitor the child's dietary habits (eg, servings of fruits and vegetables and sugar sweetened beverages), screen time, number of steps, nonstep-based activities (eg, swimming), and the child's weight.
Goal setting	Information on how to complete structured goal setting and action planning for the week using a SMART ^a goal framework.
Communication with nurses	Ability to send nurses questions regarding intervention content, review goal setting, and remote monitoring of weight self-management behaviors.

^aSMART: Specific, Measurable, Attainable, Relevant, Time-Bound.

Stage 3: Development

Existing technology provided by MEI Research, the technology partner, will be leveraged to develop mCHAMP through an iterative process [40]. This technology includes PiLR ecological momentary assessment (EMA) that is part of the patented PiLR Health system. PiLR EMA is a smartphone software that can deliver interactive, real-time surveys and intervention content that we are able to configure at the individual or group level. PiLR EMA compiles to native Android and iOS software for mobile devices to ensure that it functions in offline situations to record sensor data and provide assessments and content. PiLR EMA is supported and operated remotely by the PiLR system. PiLR is a cloud-based platform to collect, store, process, and report on objective behavioral data from surveys and multiple sensors. Real-time surveys and intervention content are designed through a Web portal and can be delivered by time, initiated by the participant, or initiated by sensor-based triggers. We will work with MEI Research to customize PiLR EMA to create an app specifically for mCHAMP. We will provide oversight to ensure fidelity of the design approach and adherence to usability principles.

Stage 4: Usability Testing

Once the mCHAMP app prototype has been developed, we will conduct usability evaluations with 10 parents of children with asthma and obesity. Usability testing will take place at UF.

Usability testing will be conducted individually with each parent and will last approximately 1 hour. Parents will be compensated US \$50 for their participation. Participants will complete a demographic questionnaire and technology use questionnaire. We will focus on measures related to the user as well as functions, representation of information, and tasks in the app. The usability guide will consist of a series of scenarios to test simple and complex features of the mHealth tool. Participants will be asked to think aloud as they use the prototype. Their verbalizations and the researcher's prompts and clarifications will be audio-recorded. We will assess the usability of the app via the following methods:

Usefulness

A functional analysis will inform the potential usefulness of the mCHAMP tool. Features wanted by parents will be compared with the following: (1) all of the features and content in the tool, (2) the features and content wanted by parents but not in the tool, and (3) the features and content included in the tool (ie, designer's model) but not in the user model (ie, parents). These comparisons will facilitate identifying what features and content should be included in the mCHAMP tool based on the needs of parents.

Usability

A representation and task analysis will evaluate how usable the mCHAMP tool is for families of children with asthma and

obesity. Representation analysis will be conducted to evaluate how usable the tool is for task completion. Specifically, the analysis will evaluate the ability of parents to recognize the built-in cues of the tool to support completing tasks. The more cues are recognized and used, the more usable the tool should be for parents. Proportions of cues will be calculated for each participant to characterize how well the tool can support end users. Task analysis will evaluate how usable the tool is. Two criteria will be used: (1) learnability: the ease of learning and relearning and (2) efficiency: the effort used to accomplish a task. *Learnability* will be characterized based on the count of errors and the count of hints and prompts needed to recover from errors faced by parents. *Efficiency* will be described by reporting the number of steps and the duration of time needed to accomplish each task. If the tool is difficult to learn and/or inefficient for any participant, we will identify problem tasks and modify the tool.

Satisfaction

The Post-Study e-Health Usability Questionnaire (PSHUQ [41]) will be used to evaluate parent satisfaction with the mCHAMP tool at the end of the usability testing session. The PSHUQ is an 18-item Likert-type scale ranging from 1 (*strongly agree*) to 7 (*strongly disagree*). The PSHUQ is composed of 2 subscales: (1) system usefulness—ease of completing task and (2) system quality—satisfaction with the quality of information and interface. The mean, SD, and variance for each of the individual items from the PSHUQ tool will be computed. An overall satisfaction score will be obtained by calculating the average scores for each parent across both subscales. Boxplots will be constructed for each of the individual items as well as the aggregate satisfaction to detect for outliers. If the aggregate satisfaction rating is greater than 3.5 on a scale of 1 (ie, positive rating) to 7 (ie, negative rating), or if any outliers are detected on any individual scale, we will review individual PSHUQ scores and consider modifications to the tool.

Phase 4: Provider Feedback

We will conduct semistructured interviews with pediatric nurses who provide care to 6- to 12-year-old children with asthma (n=5). We will explore what they perceive as potential barriers and facilitators of delivering our proposed mCHAMP intervention for their patient population. Nurses will complete informed consent before participating. Before the interview, nurse participants will have access to a prototype of mCHAMP, and study staff will explain the project and its goals. Specific questions include the following:

1. Does mCHAMP capture intervention content that would be useful for your patients?
2. How could we engage nurses in using the mCHAMP app and delivering the BFI for their patients?
3. How would the mCHAMP app and BFI fit in your typical clinic workflow?
4. What, if any, modifications could we make to mCHAMP to reduce barriers to implementation?

Individual semistructured interviews will be scheduled to last approximately 1 hour. Male and female providers of any race

and ethnicity will be invited to participate in the interview. Interviews will be conducted in-person and will be audio-recorded. Participants will also complete a demographic questionnaire and technology use questionnaire. Nurses will be compensated US \$100 for their participation. Data generated from these interviews will inform future refinements of mCHAMP in advance of future research directions (eg, pilot efficacy testing).

Results

This study was funded in 2018, and recruitment started in September 2018. At this time, 13 parents of children with asthma and obesity have been recruited from an outpatient pediatric pulmonary clinic and consented for participation in the needs assessment; 7 parents participated in focus groups, each comprising 2 to 3 individuals. Due to the scheduling conflicts, 6 parents participated in individual interviews. Interviews were coded using a theoretical thematic analysis approach [33]. Parents reported barriers to engaging in health-promoting behaviors (eg, time constraints, medication side effects, individual preferences, and mood) as well as facilitators to behavior change (eg, family collaboration, goal setting, and monitoring behaviors). Participants also discussed perceived relationships between asthma and obesity and described their intervention preferences (eg, frequency of contact, method of contact, and nurse involvement).

A total of 10 participants have also consented for participation in the PDSs and usability testing, which is expected to conclude in 2019. By the end of the study, we plan to develop a highly usable, useful, easy-to-use mHealth app, mCHAMP, that can enable parents to self-manage their child's asthma and obesity health-related behaviors. The first results are expected to be submitted for publication in late 2019.

Discussion

BFIs are the gold standard for promoting effective weight self-management in children [13,14]. Our team recently developed a tailored BFI for children with asthma and obesity. Although results indicated changes in weight and asthma outcomes were promising for completers, attendance was suboptimal and multiple barriers prevented families from attending in-person groups [20]. mHealth is uniquely positioned to address previously observed attendance challenges [28,29], deliver individualized content, and has demonstrated improvements in dietary intake and physical activity in youth with obesity [25]. To our knowledge, this is the first study to develop a nurse-delivered BFI supported by an mHealth app and tailored to the needs of children with comorbid asthma and obesity. Products of this study are expected to include an mHealth app designed by the target audience, initial usability data from stakeholders as well as target users, and a refined nurse-delivered self-management intervention protocol. This study is also expected to demonstrate an innovative approach to integrating multiple intervention development and adaptation frameworks.

Conflicts of Interest

JM is an employee of MEI Research, which supplied software used in the study.

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Abbreviations

- ADAPT-ITT:** Assessment Decision Administration Production Topical Experts Integration Training Testing
BFI: behavioral family lifestyle intervention
BMI: body mass index
C2PD: consumer-centered participatory design
CHAMP: Childhood Health and Asthma Management Program
EMA: ecological momentary assessment
mCHAMP: Mobile Childhood Health and Asthma Management Program
mHealth: mobile health

PDSs: participatory design sessions

PSHUQ: Post-Study e-Health Usability Questionnaire

UF: University of Florida

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Protocol

Understanding Pregnancy and Postpartum Health Using Ecological Momentary Assessment and Mobile Technology: Protocol for the Postpartum Mothers Mobile Study

Dara D Mendez¹, MPH, PhD; Sarah A Sanders², MPH; Hassan A Karimi³, MSc, PhD; Pedram Gharani³, MSc; Stephen L Rathbun⁴, MSc, PhD; Tiffany L Gary-Webb^{1,2}, MHS, PhD; Meredith L Wallace⁵, PhD; John J Gianakas¹, BSc; Lora E Burke⁶, MPH, PhD; Esa M Davis⁷, MPH, MD

¹Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, United States

²Behavioral and Community Health Sciences, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, United States

³Geoinformatics Laboratory, School of Computing and Information, University of Pittsburgh, Pittsburgh, PA, United States

⁴Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia, Athens, GA, United States

⁵Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, United States

⁶Department of Health and Community Systems, School of Nursing, University of Pittsburgh, Pittsburgh, PA, United States

⁷Division of General Internal Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, United States

Corresponding Author:

Dara D Mendez, MPH, PhD

Department of Epidemiology

Graduate School of Public Health

University of Pittsburgh

130 De Soto Street

5130 Public Health

Pittsburgh, PA, 15261

United States

Phone: 1 412 648 5664

Fax: 1 412 624 7397

Email: ddm11@pitt.edu

Abstract

Background: There are significant racial disparities in pregnancy and postpartum health outcomes, including postpartum weight retention and cardiometabolic risk. These racial disparities are a result of a complex interplay between contextual, environmental, behavioral, and psychosocial factors.

Objective: This protocol provides a description of the development and infrastructure for the Postpartum Mothers Mobile Study (PMOMS), designed to better capture women's daily experiences and exposures from late pregnancy through 1 year postpartum. The primary aims of PMOMS are to understand the contextual, psychosocial, and behavioral factors contributing to racial disparities in postpartum weight and cardiometabolic health, with a focus on the daily experiences of stress and racism, as well as contextual forms of stress (eg, neighborhood stress and structural racism).

Methods: PMOMS is a longitudinal observation study that is ancillary to an existing randomized control trial, GDM² (Comparison of Two Screening Strategies for Gestational Diabetes). PMOMS uses an efficient and cost-effective approach for recruitment by leveraging the infrastructure of GDM², facilitating enrollment of participants while consolidating staff support from both studies. The primary data collection method is ecological momentary assessment (EMA) and through smart technology (ie, smartphones and scales). The development of the study includes: (1) the pilot phase and development of the smartphone app; (2) feedback and further development of the app including selection of key measures; and (3) implementation, recruitment, and retention.

Results: PMOMS aims to recruit 350 participants during pregnancy, to be followed through the first year after delivery. Recruitment and data collection started in December 2017 and are expected to continue through September 2020. Initial results are expected in December 2020. As of early May 2019, PMOMS recruited a total of 305 participants. Key strengths and features of PMOMS have included data collection via smartphone technology to reduce the burden of multiple on-site visits, low attrition rate because of participation in an ongoing trial in which women are already motivated and enrolled, high EMA survey completion

and the use of EMA as a unique data collection method to understand daily experiences, and shorter than expected timeframe for enrollment because of the infrastructure of the GDM² trial.

Conclusions: This protocol outlines the development of the PMOMS, one of the first published studies to use an ongoing EMA and mobile technology protocol during pregnancy and throughout 1 year postpartum to understand the health of childbearing populations and enduring racial disparities in postpartum weight and cardiometabolic health. Our findings will contribute to the improvement of data collection methods, particularly the role of EMA in capturing multiple exposures and knowledge in real time. Furthermore, the results of the study will inform future studies investigating weight and cardiometabolic health during pregnancy and the postpartum period, including how social determinants produce population disparities in these outcomes.

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KEYWORDS

ecological momentary assessment (EMA); wireless technology; remote sensing technology; maternal health; pregnancy; postpartum; body weight; health status disparities; health equity

Introduction

Research has consistently shown a racial disparity in postpartum weight retention, where black women are more likely to retain or gain weight after delivery compared with white women even when entering pregnancy at similar weights [1-4]. Multiple studies have attributed this disparity to individual-level factors, such as breastfeeding behavior [5,6], exposure to stressors [7], or diet and exercise [8,9], but these findings do not fully explain the racial disparity. Furthermore, there is a dearth of literature specifically addressing how contexts and environments intersect with individual-level factors in reproducing racial disparities. Given that stressful exposures to racism and related forms of oppression and discrimination are unique to black women and related to adverse perinatal outcomes [10], it is important to specifically understand how these stressors contribute to the disparity in postpartum weight retention and related cardiometabolic risks in the context of pregnancy.

The Postpartum Mobile Mothers Study (PMOMS) is an innovative longitudinal study designed to understand the contextual, behavioral, psychosocial, and clinical factors related to racial disparities in postpartum weight and cardiometabolic health. PMOMS includes pregnant populations recruited during midpregnancy and followed up through the first year postpartum and is ancillary to the Comparison of Two Screening Strategies for Gestational Diabetes (GDM²) trial [11]. PMOMS participants complete daily surveys via smartphone technology, weigh themselves via Bluetooth-enabled scales, and attend follow-up visits for anthropometric measurements. In this paper, we describe how PMOMS expands on the feasibility of using mobile technology in behavioral research via ecological momentary assessment (EMA) methods to understand women's experiences and exposures in their natural environment via real-time measurements of psychosocial (eg, stress and racism), behavioral (eg, physical activity), and contextual (eg, location linked to neighborhood and environmental data) factors.

EMA is a well-known method in studying hypothesized environmental effects on human behavior and has been shown to be an effective method for regular or daily data collection [12]. EMA offers a way to understand experiences and exposures in real time, and often in the participants' natural

environments [13]. Mobile devices, such as smartphones, have become optimal vehicles for remote data collection or the collection of data in an environment that is not a controlled laboratory setting, including EMA data collection. When compared with data collection in a laboratory setting, remote, real-time data collection eliminates the need for long-term recall, considers the context in which people are responding, is consistent and reliable, has ecological validity, and provides opportunities for more data points [12,14]. In 1 study, physiological data collected via EMA to capture cardiovascular health, specifically blood pressure, produced different results from that collected in a laboratory context [15]. In addition, collecting EMA data has been shown to be feasible and accessible in various populations, with high participant satisfaction, and some studies showing completion rates of up to 89% [16-18].

There are several examples of EMA methods being used in clinical and public health research among childbearing or pregnant populations, the populations of focus for this study. Several studies included interventions focused on managing gestational weight gain and gestational diabetes [19-24]. For example, 2 studies [19,25] demonstrated how wireless glucometers contributed real-time blood glucose measurements, which helped to tailor a mobile app's feedback to participants at risk for gestational diabetes. Observational studies, although fewer in number, have also demonstrated the feasibility and accuracy of using mobile technologies, including smartphones, to facilitate EMA data collection in a parous population [17,26,27].

One of the key EMA measures of interest in PMOMS includes reported experiences of racism, with a focus on interpersonal racism—including, microaggressions [28,29]. Several studies have used EMA approaches to specifically measure experiences of racism, discrimination, and other forms of marginalization [30-36], but none of these previous studies using EMA methods specifically addressed health during and after pregnancy. Furthermore, only one of these studies tracked EMA measurements over several months [31], whereas the others ranged between 3 days and 3 weeks [32-35]. Some studies used portable electronic devices to maintain data entries [31,36], whereas more recent studies incorporated smartphones [33-35]

to understand various experiences of racism and discrimination. EMA data collected via mobile technology in this study allows us to query everyday experiences and momentary occurrences in a participant's natural settings that may contribute to chronic exposure to racism.

Another key approach applied in this study is geographic momentary assessment (GMA), an extension of EMA, which measures location and environment in real time, providing an avenue to capture multiple environmental exposures over time. Geographic positioning systems (GPSs) are built into most modern smartphones, which allows for regular access to location information [37]. GMA methods allow researchers to match data collection points with the participant's geographical location (ie, their natural environment) along with self-reported measures of contexts. The current GMA literature focuses mainly on behaviors such as substance use, where context, location, and environment may have a tremendous influence on outcomes. For example, some studies have assessed eating behaviors and substance use alongside measures of mental health and stress as mediators or predictors of these behaviors [37-40]. To date, no GMA studies have focused on childbearing populations, pregnancy, or the postpartum period.

This paper outlines the various processes and steps involved in designing and executing PMOMS, including how PMOMS is ancillary to an ongoing trial, GDM²; the use of mobile technology; applications of EMA methods; and longitudinal follow-up. Details of the research development process, infrastructure, challenges encountered, and lessons learned are also described.

Methods

Overview

We outline the GDM² trial as the primary study in which PMOMS approaches and recruits potential participants; original research that contributed to the development of the present PMOMS methodology; the pilot studies conducted to confirm the feasibility of EMA methods among pregnant and postpartum women (ie, the PregEMA and PostpartumEMA pilot studies); and the technological infrastructure necessary for direct communication with participants and collection and transmission of participant data and related security measures.

Comparison of the Two Screening Strategies for Gestational Diabetes (GDM²) Trial: Parent Study

The key methodological and infrastructural element in PMOMS is its partnership with a parent study: the Comparison of Two Screening Strategies for Gestational Diabetes (GDM²) trial [11,41]. The GDM² trial was designed to examine 2 testing strategies for screening and diagnosing gestational diabetes and to follow select women and infants through 12 months after delivery to assess metabolic risk profiles and infant growth. Given the similar study objectives and observation periods, PMOMS is an ancillary study to GDM² and recruits directly from the parent study. GDM² is as an excellent platform for PMOMS recruitment, including the interstudy collaboration,

and is crucial to the success of PMOMS. Recruitment for GDM² began in July 2015. Participants in the GDM² trial are recruited and requested for consent during pregnancy, between 19 and 29 weeks' gestation. After enrollment, participants are asked to attend 2 study visits during pregnancy to complete laboratory work, anthropometric measures, and brief questionnaires.

Exemplar and Pilot Studies

The Advancing Real-time Data Collection with Adaptive Sampling and Innovative Technologies (EMPOWER) study served as an exemplary longitudinal EMA study for PMOMS as it was designed to understand factors related to relapse (of weight) among individuals enrolled in a weight loss intervention over 12 months [18]. The EMPOWER study incorporated EMA methods that provided guidance for PMOMS, but it also served as a precedent for the importance of longitudinal data collection regarding weight loss and retention. Although the PMOMS structure and population differ from those of the EMPOWER study, the findings helped to justify this long-term protocol [18]. The EMPOWER study findings revealed an attrition rate of 13% (n=19) [18]. In addition, some of the key measures applied in PMOMS were generated based on constructs from EMPOWER, which are to be detailed in a later section.

Furthermore, 2 pilot studies were conducted among a cohort of GDM² participants as a means to demonstrate feasibility of recruitment, data collection, and technology infrastructure. The PregEMA pilot study [42] was conducted during October 2015 to January 2016 as an ancillary study to the GDM² trial in a sample of pregnant women [11] to determine the feasibility of EMA/GMA data collection among pregnant women via Web-based surveys accessed via smartphones over a 4-week period. Feedback from pilot participants' exit interviews provided valuable insight into the study elements, such as the maximum tolerable number of EMA prompts delivered in 1 day or the content of the survey questions. This pilot also demonstrated the feasibility of recruiting participants already enrolled in the parent study (GDM² trial). Findings from this pilot and the lessons learned are detailed elsewhere [42].

These same participants were also approached to participate in an extension of the pilot study, which involved responding to additional EMA surveys during the first 12 weeks of the postpartum period (PostpartumEMA pilot) and reporting their weight as given on a scale provided by the study. The pilot extension further demonstrated the feasibility of participants responding to regular EMA prompts for longer periods of time and after childbirth. These surveys included key questions about participants' physical and emotional health during the postpartum period, along with self-reported weight measurements.

The approaches employed in the pilot studies [42] provided insight about the feasibility of using EMA and mobile technology to learn about women's pregnancies and health in real time and in their natural environments. For example, the pilot demonstrated the utility of a Web-based versus phone-based app for collecting self-reported data of daily events and experiences, coupled with the collection of location data. The pilot data indicated that women felt an average of 1 survey

per day was not overburdensome and that receiving additional surveys, depending on content, would not add more of a burden. Finally, the pilot studies were the starting point for the source population, measures, infrastructure, and tools in PMOMS.

Postpartum Mothers Mobile Study Population: Screening, Recruitment, and Follow-Up

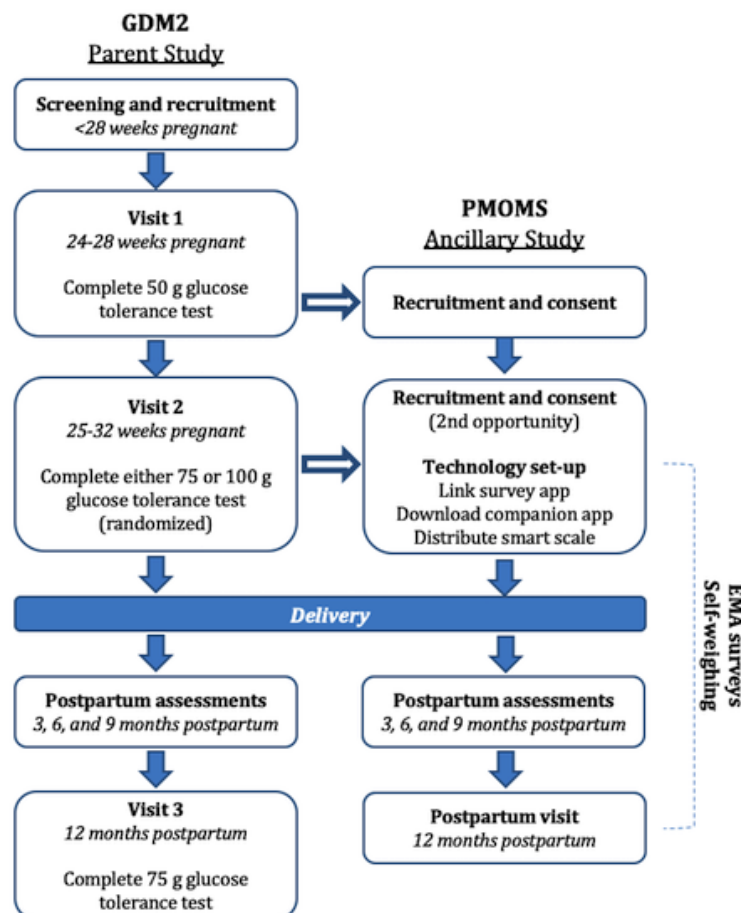
As previously described, PMOMS benefitted from the study infrastructure established by GDM², given the parent study’s eligibility criteria and research aims. Figure 1 shows the key research activities and points of participant interaction from the GDM² trial in relation to PMOMS. The first visit involves obtaining written informed consent to participate in GDM², with consenting participants completing a nonfasting 50 g glucose tolerance test (GTT). During the hour that participants are waiting to have their blood glucose drawn, PMOMS staff approach GDM² participants to potentially recruit and consent into PMOMS. All eligible GDM² participants are asked to return for a second visit 1 to 2 weeks later, representing another opportunity to recruit participants into the PMOMS if they did not provide consent during the first visit.

Specific to the research activities for PMOMS, the second GDM² visit is primarily used to provide the consented PMOMS

participants with study materials (eg, smart scale and smartphone), additional instructions, and further information after screening is complete. During the second GDM² visit, participants have about 1 to 2 hours of downtime when they are waiting to complete the 75- and 100-g oral GTTs. This visit allows ample time for setup and orientation of participants to the PMOMS devices.

A portion of women recruited into the GDM² trial are not followed up after delivery because of the parent study’s sampling method for postpartum follow-up (ie, only a portion of the women with normal glucose results) [11,41]. Consequently, GDM² will not conduct postpartum telephone surveys or call these participants back for a third visit (eg, 12 months postpartum). To maintain continuity and postpartum follow-up of all participants recruited into PMOMS, we implemented a study protocol similar to that of GDM² for postpartum follow-up, as illustrated in Figure 1. This will ensure that all women recruited into PMOMS are followed through 12 months postpartum, regardless of whether the GDM² trial follows these women after delivery. The follow-up measures include telephone-administered surveys completed at 3, 6, and 9 months postpartum, as well as the 12-month postpartum follow-up visit at the clinic.

Figure 1. General flow of activities and data collection for the Postpartum Mothers Mobile Study (PMOMS), including the points where research activities for PMOMS and the Comparison of Two Screening Strategies for Gestational Diabetes (GDM²) trial intersect, as indicated by the arrows. Note that PMOMS replicates GDM² protocols for the postpartum assessments and final study visit. EMA: ecological momentary assessment.



Smartphones, Smart Scales, and Compensation for Postpartum Mothers Mobile Study

PMOMS is designed to use smart technologies as the main tools for data collection and communication. Participants use smartphones to complete surveys on a daily basis via the PMOMS Web-based app, as well as Bluetooth-enabled smart scales for collecting weight. The process and infrastructure for these tools are described in more detail later.

PMOMS offers participants the option of using their own mobile device or to obtain a new smartphone in the event that their personal phone is not compatible with the study infrastructure or limited in its ability to complete daily surveys. We determine the compatibility of their personal phone with a basic technology screening questionnaire, which asks the participant about their smartphone usage, access to Wi-Fi at home and/or work, and whether or not they pay for an unlimited data plan. For example, if a participant expresses having an outdated mobile phone or inadequate service connection at home, our researchers recommend that they accept a new smartphone to participate in the study.

Each participant receives a smart scale, which is Bluetooth and Wi-fi enabled. It has a companion smartphone app. The Bluetooth and wireless features enable direct communication with the user's app, logging weight and body composition data automatically and often in real time. Any weight data collected while the participant is *offline* is stored and later updated in the database when a wireless connection is available. Previous studies have validated the use of smart scales in research settings [43-46], and additional studies cite the use of other smart devices that assess anthropometric measures, such as a Bluetooth-enabled glucometer [47,48].

PMOMS compensation includes a combination of direct payments and options for receiving a new smartphone. Participants have 2 options with regard to the smartphone: (1) use their personal phone to facilitate data collection or (2) accept a new smartphone from our study as their primary device. The study finances the smartphones distributed under the second option, including an unlimited data plan, talk, and text for the duration of the study. Participants become eligible for additional monetary compensation at various points in the study, contingent on their completion of a set percentage of surveys. For participants not selected for GDM² follow-up in the postpartum period, PMOMS compensates them using the same rates as the parent study. These details are reported elsewhere [11,41]. At the conclusion of PMOMS, participants are able to keep the smart scale as well as the smartphone provided by the study (if applicable).

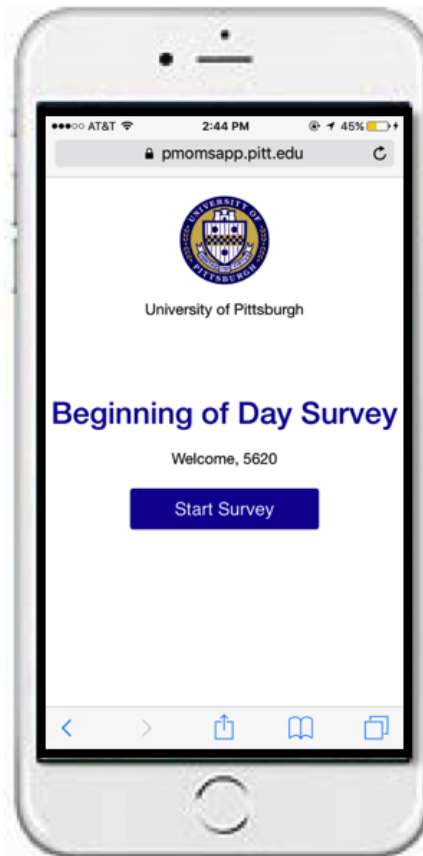
Daily Ecological Momentary Assessment Data Collection Protocols

PMOMS applies 2 types of EMA data collection methods to administer surveys to participants: *signal-contingent* and *time-contingent* prompts. *Signal-contingent* responses, also known as *random*, are prompted according to a known random sampling design to obtain a representative sample of the participants' time in the study; this is described in more detail in the next section. *Time-contingent* responses are elicited at fixed times during the day, labeled as *beginning of day* (BOD) or *end of day* (EOD) prompts. These *time-contingent* prompts are programmed according to participant preference in the PMOMS, with the only requirement being that the BOD prompt occurs at least 9 hours before the EOD prompt. Figure 2 below is an example of how the app appears to a participant on their smartphone.

PMOMS does not include *event-contingent* responses, which are initiated by the participant. In the context of the EMPOWER study (described earlier), researchers included these *event-contingent* prompts as primary outcomes typically within moments of a predefined event (eg, in EMPOWER, being tempted to eat outside of meal/diet plan); but this is not the focus of PMOMS [18]. Low participant utilization of these responses in the EMPOWER study further justified the decision not to incorporate *event-contingent* responses into PMOMS [18].

Nevertheless, PMOMS prioritized the development of a response infrastructure for participants that expressed feelings of depression or thoughts of harming themselves or others in *signal-contingent* assessments. This would not qualify as an *event-contingent* response, as it is not prompted by the participant. Instead, this inquiry into participant mood or depression occurs within a specific item in a BOD survey, which is then followed up by the study team member when appropriate. In the case of a participant expressing their need for emotional support, but not expressing the impulse to harm oneself or another, the survey app alerts study investigators such that the participant may receive proper follow-up, including the phone number for a local crisis hotline, called Resolve Crisis Network [49]. If a participant was to express any impulse to hurt themselves or others, study investigators would be alerted to contact the crisis hotline directly. In addition, any confirmation of depression or potential for self-harm would be reported to the participant's healthcare provider via the electronic medical record system.

Figure 2. Recreated screenshot of Postpartum Mothers Mobile Study app prompting a participant to complete their beginning of day survey.



Sampling Design for Ecological Momentary Assessment Prompts

The delivery of survey prompts was carefully programmed according to a specific sampling design. The frequency of EMA sampling for PMOMS was informed by the time scale of temporal dependence in study variables, the relative importance of variables to study aims, and the need to reduce participant burden. Sampling too frequently, for example, will not only increase the burden on study participants but may also result in redundant data because of temporal correlation in participant responses. However, the precision (SEs) of estimated mean levels of temporally varying study outcomes, and model parameters that depend on those outcomes, decrease with decreasing sampling frequency. PMOMS researchers modeled their EMA sampling approach after the study by Shiffman [50], who partitioned variables that influence behavior into 3 categories based on time scales at which they vary from *enduring* traits, which are relatively stable, to *momentary* states, which are volatile and transient. In between the 2 extremes, there are *background conditions* “which are neither as stable as traits nor as volatile as states” [50].

To better understand the sampling frame applied in the EMA context more generally, and in PMOMS specifically, it is helpful to describe the underlying statistical properties. The volatility of an outcome may be described by its variance, whereas its stability may be described by the range of temporal correlation beyond which observations are uncorrelated. Borrowing from geostatistical methods [51], both volatility and temporal dependence in a time-varying outcome $Y(t)$ at time t may be

described through the variogram $2\gamma(r)$, a function of the lag time between pairs of observations of that outcome r units of time apart. The variogram $2\gamma(r)$ is defined to be equal to the mean of the squared difference $[Y(t+r) - Y(t)]^2$ between observations $Y(t)$ and $Y(t+r)$ that are r units of time apart. The variogram $2\gamma(r)$ is generally an increasing function of time lag r between observations (Figure 3), leveling off at an asymptote when the distance r attains the range of temporal correlation. Sampling at intervals closer than the range will result in redundant observations as they are temporally correlated: the higher the sampling frequency, the greater that redundancy.

The height of the plateau, or asymptote, is twice the variance, and so can be regarded as a measure of volatility. If the outcome $Y(t)$ varies continuously over time, and there is no measurement error in its observations, then the variogram will approach zero as the lag distance r approaches zero. In many cases, however, the variogram will approach a value greater than zero, the so-called nugget effect, as lag distance r approaches zero. This nugget effect can be attributed to measurement error or small-scale discontinuities in the data that might arise. For example, abrupt changes in psychological states attributed to discrete events in a participant’s day, such as receipt of good or bad news, might cause this effect. For some time-varying variables, the nugget may be close to the sill, in which case, observations can be treated as approximately independent outcomes.

The variogram can be estimated using the classical variogram estimator, where the sum is the overall pairs of observations

$Y(s)$ and $Y(t)$ approximately r apart in time and N_r is the number of such pairs of observations [51]:

$$2\gamma(r) = 1/N_r \sum (Y(s) - Y(t))^2$$

To inform the processes and EMA sampling frame for PMOMS, data from the EMPOWER study [18] were used for 2 reasons: EMPOWER served as an exemplar study in its approach to EMA data collection, as previously described; and several of the core constructs and measures from EMPOWER were applied in PMOMS. Using EMPOWER data, variograms were separately estimated for each participant in the study. On the left-hand side of Figure 4, a spaghetti plot of the variogram estimates is presented for “How confident are you that, if you have an urge to go off your healthy lifestyle plan, you can resist the urge?”, a measure of self-efficacy using a 10-point Likert scale in the EMPOWER study. Subjects show a wide variation in their time scales, especially with respect to the sills, suggesting that the volatility of self-efficacy depends on the study participant.

In addition, 4 common patterns are illustrated in the plot on the right-hand side of Figure 4. The variogram for participant A

shows a short range of temporal dependence of about 3 days, suggesting that answers 3 or fewer days apart are redundant. There is a substantial nugget effect of 2.5, suggesting that there is considerable variation in self-reported confidence within days, and the sill is about 4.4, yielding an estimated variance of 2.2 for this participant. The variogram for participant B was typical of many of the participants, remaining close to zero at all lag distances. This suggests that this participant’s self-reported level of self-efficacy/confidence was nearly constant throughout the study; close examination confirms that 88.0% of the time, the participant rated confidence as 8, and 11.7% of time, it was rated as 7. Participant C showed a cyclic pattern, with peaks 7 days apart, suggesting that the participant’s confidence depends on the day of the week. Finally, the variogram for participant D continues to increase with increasing lag distances up to 100 days; such variograms suggest a long-term trend in the level of self-efficacy/confidence. These measures in EMPOWER related to self-efficacy/confidence are similar to measures included in PMOMS; hence, the rationale for examining temporal trends and patterns as a means to inform the sampling strategies and frequency for PMOMS EMA measures.

Figure 3. Plot of the variogram $2\gamma(r)$, an increasing function of lag time r between pairs of observations of a specified outcome.

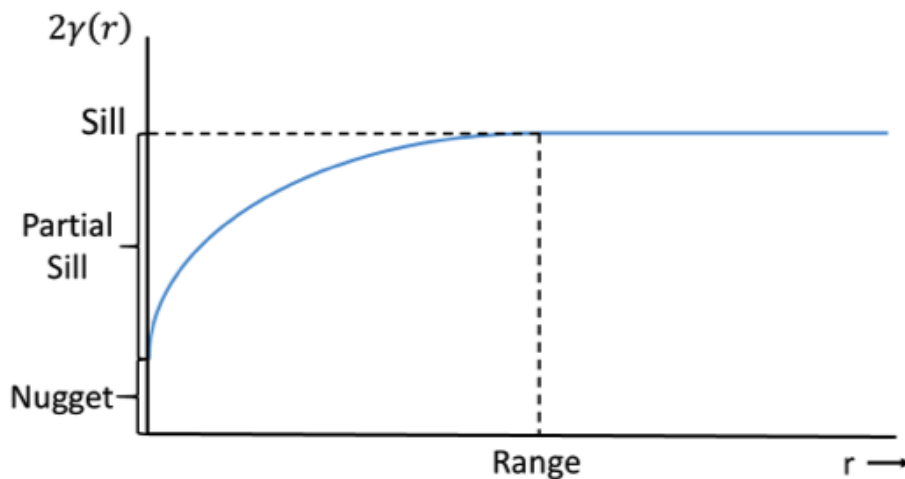
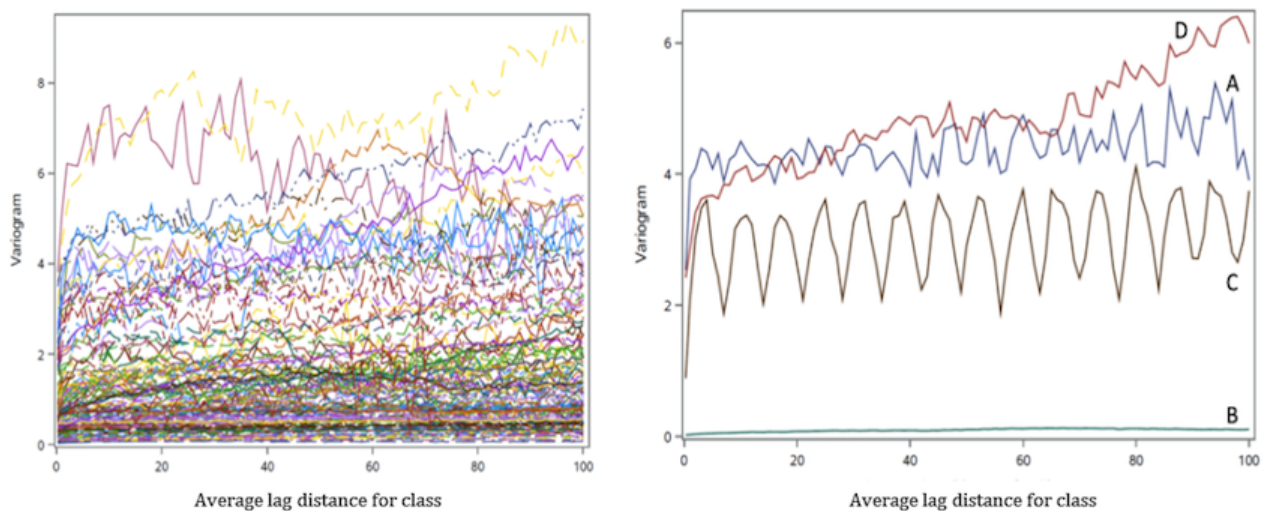


Figure 4. Left panel: a spaghetti plot of the variograms for confidence from random assessments of each of the Advancing Real-Time Data Collection with Adaptive Sampling and Innovative Technologies participants. Right panel: variograms for 4 select participants (A-D).



On the basis of previous studies and analyses of EMA data from EMPOWER, mood constructs (eg, anger, depression, and enthusiasm) have ranges of temporal correlation of less than 1 day; sleep variables have ranges of 1.6 to 2.8 days; and self-efficacy variables have ranges of 7.8 to 9.8 days [18]. These results suggest that mood shows great volatility and so should be sampled frequently, whereas self-efficacy is relatively stable and need not be sampled as frequently. On the basis of previous work [18], we targeted a mean of 1 random assessment per day in addition to the BOD and EOD surveys. The random assessment times are selected according to a self-correcting point process [52], yielding a mean of 1 assessment per day, a sampling frequency compatible with the above variogram analyses. This means that some days may deliver 0 random prompts, whereas other days can range between 1 and 3 random prompts. The self-correcting process yields a more regularly spaced pattern of random prompts and less variability in the number of random prompts per day than completely random prompts, thus reducing burden on the study participants.

To further reduce burden on the study participants, a double-sampling design [53] was implemented, under which questions regarded as being critical to study aims and important covariates (eg, racism, discrimination, self-efficacy, control, and stress) are asked during all random assessments, whereas a subset is to be asked only in randomly selected assessments (eg, mood, general wellness, and depression). Initial assessment probabilities for the latter are set to 50%.

Questions of interest can make the EOD surveys lengthy as they address the days' physical activities, diet, and breastfeeding behaviors (postpartum only). As a result, randomized block designs were implemented as a means to query subsets of questions in each EOD survey. The prenatal period was partitioned into 28-day blocks, starting on the first Monday following enrollment, and ending at the time at which women go into labor. In each 28-day block, 4 weekend days and 10 weekdays are selected for randomized EMA items that cover the additional food-related and physical activity survey content. Half of the selected weekend days and half of the selected weekdays were randomly assigned to assessments focused on food-related questions, whereas the remainder of the selected days were physical activity assessment questions. Given the additional survey items related to breastfeeding, we use a 42-day block to cycle through the questions asked in EOD surveys to accommodate for the additional content during the postpartum period. A total of 4 weekend days and 10 weekdays are selected

in this block to cover both food-related and physical activity questions. Similarly, 4 additional weekend days and 10 weekdays are selected to cover food-related and breastfeeding questions. Finally, the remaining 4 weekend days and 10 weekdays are assigned physical activity and breastfeeding questions.

The participants have a break from answering any prompts from delivery through 7 days postpartum, to allow them time to become acclimated to their new family circumstances. Postpartum assessments continue after that 7-day period

Ecological Momentary Assessment Survey Questions

We assess numerous constructs and measures in the BOD, EOD, and random prompts, as illustrated in Table 1. These measures were selected based on their hypothesized associations with postpartum weight retention and, specifically, contributors to the racial disparities. In many cases, these previously validated scales (eg, Gendered Racial Microaggressions Scale) have not been applied in an EMA context; therefore, PMOMS is attempting to apply such measures and constructs in ways that previous studies have not. By assessing the participants' experiences through these EMA measures longitudinally, PMOMS expects to gain a more nuanced understanding of how contextual, behavioral, and psychosocial factors intersect to explain changes in postpartum weight and cardiometabolic health and, more specifically, how they contribute to existing racial disparities.

Racism and discrimination are measured in multiple ways, including the specific construct identified in Table 1. The participants also answer a series of 12 items related to microaggressions, based on the Gendered Racial Microaggressions Scale [28,29], experienced that day such as, "Receive negative comments about my skin tone," "Someone made me feel exotic because of my race or gender," and "Someone made a sexually inappropriate comment towards me." If they answer yes to any of the items, follow-up questions will inquire about their feelings, their reactions, and the location of the interaction.

In addition to self-weighting (described further below), participants are asked questions about context such as "Where are you located?" and "Who are you with?" Each prompt also asks for permission to capture GPS location (geospatial data and approaches are also described further). These 3 context-related measures are asked in all survey prompts, including BOD, EOD, and random.

Table 1. Primary variables and covariates assessed in ecological momentary assessment prompts, with examples.

Construct	Delivery	Measurement example
Sleep [54]	BOD ^a	How long (in minutes) did it take you to fall asleep last night?
Diet [55]	BOD, EOD ^b	How many meals did you eat today?
Sedentary/physical activity [56]	EOD	How many hours did you spend sitting today?
Racism [31]	Random	How often were you treated with less courtesy than other people because of your race? (0=never; 1=almost never; 2=sometimes; 3=fairly often; 4=almost every day).
Stress [57]	Random	How often have you felt nervous or stressed? (0=never; 1=almost never; 2=sometimes; 3=fairly often; 4=very often).
Control [57]	Random	How often have you felt you were able to control important things in your life? (0=never; 1=almost never; 2=sometimes; 3=fairly often; 4=very often).
Self-efficacy [57]	Random	How often have you felt confident about your ability to handle your personal problems? (0=never; 1=almost never; 2=sometimes; 3=fairly often; 4=very often).
Depression [58]	Random	Have you felt depressed today? (yes or no)
Mood	Random	How are you feeling? (eg, content, tired, hungry).
Support	Random	Please rate the level of support you have to care for yourself. (0-4).
Breastfeeding	Random	Did you breastfeed today? (yes or no).

^aBOD: beginning of day.

^bEOD: end of day.

Non-Ecological Momentary Assessment Survey Questions

In addition to the many EMA-based surveys, PMOMS also incorporates surveys into the app to conduct assessments that are not temporally or ecologically based. These *non-EMA* prompts are delivered subsequent to BOD surveys at specific milestones throughout the study. Table 2 describes these non-EMA surveys.

In addition to data collection via smartphones and scales, key measures and constructs are collected via the larger GDM² trial.

This includes a series of questionnaires during the GDM² screening process, baseline (during visit 1), randomization visit (visit 2), delivery visit, and at 12 months postpartum (visit 3). As described in the section *PMOMS Recruitment, Retention, and Follow-up*, PMOMS researchers replicate the same postpartum protocol for any participant not selected for follow-up by GDM². The survey measures collected during the GDM² study visits and telephone calls address stress, mood, depression, physical activity, diet (eg, 24-hour dietary recall), and demographic information. Additional measures of pregnancy and infant health outcomes are abstracted from the electronic medical records.

Table 2. Timing and content of non-ecological momentary assessment surveys delivered after beginning of day prompts throughout the study.

Delivery period	Constructs measured
14 days after study enrollment	<ul style="list-style-type: none"> • Technical issues with devices or app • Burden of EMA^a prompts • Experiences of discrimination over lifetime [31]
Day 8 after delivery	<ul style="list-style-type: none"> • Anxiety in interpersonal relationships • Social support • Use of social media to connect with peers • Breastfeeding initiation
Every 3, 6, and 9 months after delivery	<ul style="list-style-type: none"> • Burden of EMA prompts • Issues not being addressed in surveys • Participant behaviors related to weight loss
After final study visit (1 year postpartum)	<ul style="list-style-type: none"> • Participant history of residence(s) • Workplace/employment • Social support • Satisfaction with Postpartum Mothers Mobile Study

^aEMA: ecological momentary assessment.

Self-Monitoring With Smart Scales and Health Mate App

Although the smart scale and app provide a convenient platform, researchers have little control over how participants choose to use the devices' additional features. One instance of this occurred during study development, when the smart scale manufacturers added a *pregnancy mode* to their app, including additional counseling and reminders that correspond to the user's gestational age. If the pregnancy mode is activated, the app will present dietary recommendations or advice on gestational weight gain that could influence a participant's behavior and could subsequently bias the study outcomes. Consequently, although we do not have direct control over access to this information, we provide instructions upon enrollment for the participants to avoid using this feature because of limited information about the sources and validity of the health and behavioral information provided to them.

Via the PMOMS app, we prompt all the participants, starting each Friday and throughout the weekend, to remind them to weigh themselves with the question, "Were you able to weigh yourself and get a weight?" If they answer no, then we ask them to "Please describe why." Response options include, "Scale is not working properly" and "I did not want to weigh myself." Early on in the study development, we identified the potential influence of monitoring one's weight on the participant's behavior during the study and, thus, their outcome measurements. The participants are only prompted to step on the scale weekly; however, the participants may choose to weigh themselves more often, as the scale is available to them in their homes. The Self-Monitoring and Recording Using Technology trial investigators [59] described self-monitoring as the *cornerstone* of behavioral treatment. Consequently, participant behaviors related to self-weighing and perinatal weight management are taken into account when evaluating factors that are hypothesized to affect weight and cardiometabolic measurements, as described in the previous section regarding non-EMA surveys.

Postpartum Mothers Mobile Study Technology and Infrastructure

The PMOMS Web-based app has 3 core components: data collection, data management, and data analytics. Each component is designed to maximize the study aims, particularly the unique features of EMA data collection throughout pregnancy, as well as leverage the Bluetooth technology in the smart scale for repeated weight measures. This section provides additional detail on the technical infrastructure established by PMOMS to ensure efficient and secure data collection.

The technology infrastructure has 5 major modules: (1) an administration module to invite participants to the study, manage and modify participants' profiles, and authenticate PMOMS for using the scale; (2) a Web-based survey module that contains specific questions related to participants' circumstances at different locations and times; (3) a database management module for storing and managing the collected data as well as generating parameters for the survey using the scheduled tasks; (4) a

random value generator module to provide constrained random times for random assessments and EOD block group questions; and (5) a data retriever module to fetch body measurement data from the third-party scale database.

App Architecture and Data Flow

PMOMS uses a mobile app based on a client-server architecture with 4 tiers: presentation, logic, database, and scale (Figure 5).

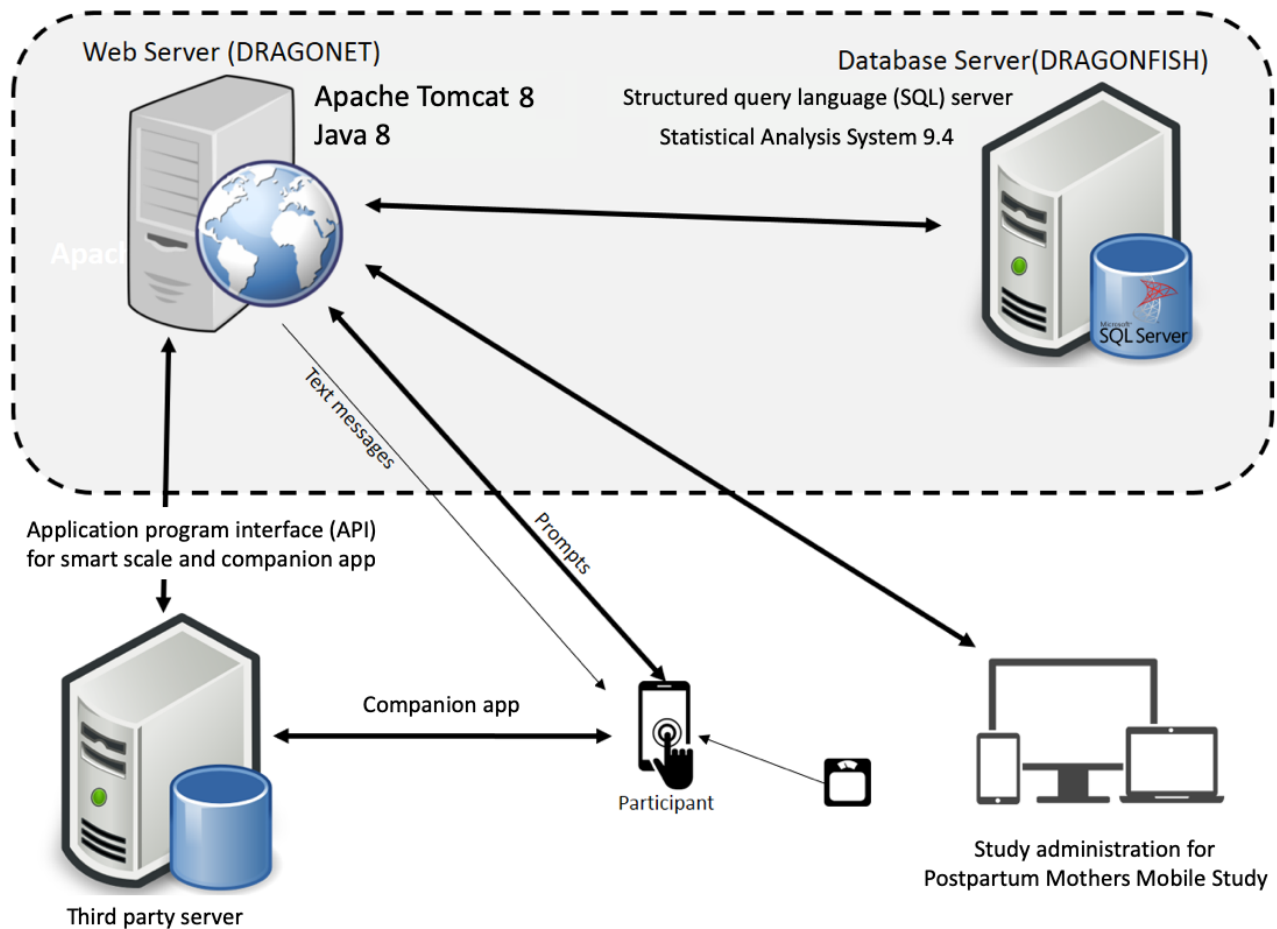
The presentation tier consists of interfaces used to communicate the surveys, management panel, data, and responses of the system to end users of the app, including participants and staff. The content that is communicated with the end user consists of both static and dynamic information; an example of the latter includes survey questions based on stage of participants and time. The administrative interfaces are designed for desktops and tablets, allowing administration staff to manage participants' information.

Communication between the users' phones and the server is secured through the transport layer security protocol, previously known as the secure sockets layer protocol, whereas communication between the servers is secured using the firewall system implemented by the Computing Services and Systems Development office within the University of Pittsburgh. These interfaces for participants (ie, smartphones) and staff (ie, tablet and desktop) are shown in Figure 5.

The logic tier includes the essential logic to ensure that all functions in PMOMS are performed consistently and according to the design specifications. Furthermore, rules and algorithms for evaluating participants' circumstances and for compiling the questionnaires are all conducted in this tier. See the logic tier (ie, Dragonet) in Figure 5. Surveys are received by participants at scheduled times, so the data go from the logic tier to presentation tier (smartphone). For the purpose of loading scheduled surveys on the participants' smartphones, a text message containing a URL linking the surveys is sent to the stored contact information for participants. Reminders about the survey are sent to respondents if they do not complete the surveys within a specified amount of time. In the case of time-contingent prompts (eg, BOD and EOD surveys), participants have 30 min to complete the survey once it is delivered; signal-contingent prompts (eg, random) allow participants 60 min for completion. The URL expires after these time periods, which triggers a text message indicating cancellation of the survey to be sent to the participant. If a participant does not start the survey while it is valid, a record of *not attempted* is automatically entered into the database and the survey is no longer available. However, a survey that was started or ongoing, but not submitted in the time window, is still valid for submission for an additional hour. Survey responses received in the logic tier are then processed for storage in the database tier.

The database tier contains a database management system for storing and managing all data collected in PMOMS. Data collected and managed in this tier are participants' information and responses to the surveys. See the database tier (ie, Dragonfish) in Figure 5.

Figure 5. The 4-tier architecture of Postpartum Mothers Mobile Study application and technology infrastructure.



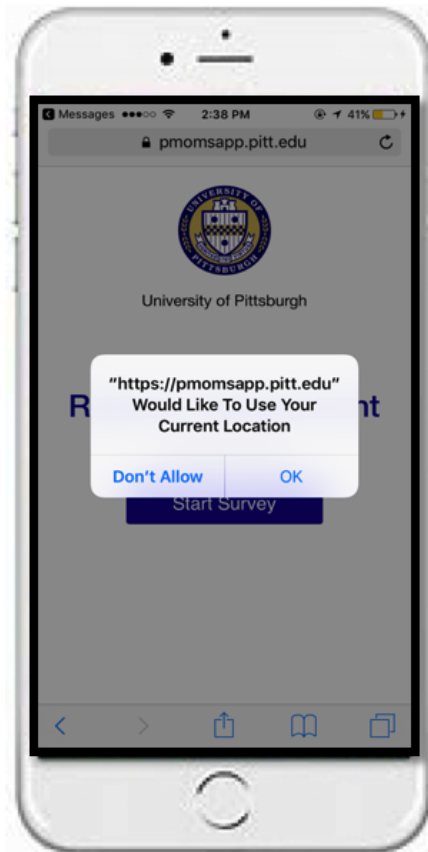
Data received from the smart scale by the presentation tier, through Wi-Fi or Bluetooth connection with the scale, is then sent to the scale tier, which consists of a third-party database, maintained by the producers of the smart scale and accompanying app, as a repository of body measurements of PMOMS participants from the smart scale. As the PMOMS team is authorized by participants to access their data, token keys are generated and stored in the database. The required and authorized data are transferred from this tier to the database tier on a regular basis using the OAuth framework, which is an open protocol allowing for limited but secure communication between multiple applications [60]. Finally, the database tier retrieves the weight data from the scale tier. See the scale tier in Figure 5.

Geolocation

As described previously, the Web-based, platform-independent app includes GPS capabilities, requesting participant permission to record GPS coordinates whenever any survey prompt is received. Figure 6 illustrates how the app requests permission. Once granted, the participant's device location is provided to the app through the HTML5 Geolocation application programming interface. To protect the participant's privacy, location data are transmitted through a secure connection.

Although other studies have attempted to match GMA data with timestamps for EMA responses [39,61], PMOMS staff developed a Web app that delivers EMA prompts and collects GPS coordinates simultaneously.

Figure 6. Recreated screenshot of Postpartum Mothers Mobile Study survey app requesting permission to collect geolocation data.



Data Management

The database tier of PMOMS is responsible for storing and managing data, which are mostly the responses to the various survey questions that are either required or optional. All participants must answer the required questions, and the optional questions can be skipped and are recorded as missing values in the database.

For efficient data management, the missing values are coded in different ways indicating the reason for their absence. Example codes are *not applicable*, *missed*, *not asked*, and *unknown*. These missing data can be used for generating reports to track the level of participation and monitor the integrity of the database. In addition to the storage of data in the database, a copy of the data is stored in a flat file for cross-validation of the responses and as a backup in case of server crashes.

Overview of Analytical Strategy: Understanding Postpartum Weight Change

PMOMS aims to predict postpartum weight retention in part from mean levels of time-varying variables $x(t)$ attained using EMA according to the formula:

$$\bar{x}(T) = \frac{1}{T} \int_0^T x(t) dt$$

Here, the integral is over the sets of time either during pregnancy or postpartum (or the entire study period), and $\bar{x}(T)$ may be regarded as a population mean where the population includes all points in time in the interval $[0, T]$.

Random assessment provides a representative sample of times from which design-unbiased estimates [62] of $\bar{x}(T)$ may be obtained, where $\Pi(t)$ is the sampling intensity at time t , and the sum is overall random assessments S_T in the interval [63]. Missing data may be addressed using the weighted estimator, where $1 - q(t)$ is the probability that an observation at time t is missing.

If data are missing completely at random, then $q(t)$ is constant and may be estimated empirically by the proportion of data that are not missing. Otherwise, $q(t)$ may be estimated (eg, using a regression model) as a function of the observed data. Then the mean level of the time-varying variable may be estimated using:

$$\bar{x}(T) = \frac{1}{T \sum_{t \in S_T} \Pi(t) q(t)} \sum_{t \in S_T} x(t) \Pi(t) q(t)$$

The EMA sampling intensity, targeting a mean of 1 random assessment per day (as described previously), was used to balance the precision of estimating mean values of EMA predictors against the burden of study participants. With respect to the latter, burdensome EMA assessments may not only adversely impact compliance with EMA assessments and quality of responses to those assessments but also act as an intervention impacting participant behavior. As it estimates $\bar{x}(T)$ with error, replacing with $\bar{x}(T)$ can result in biased estimates of regression coefficients in both linear and nonlinear models [64,65]. This measurement error is negligible if the variance of $\bar{x}(T)$ is small within subjects compared with the variance of $\bar{x}(T)$ between subjects.

Secondary data analyses will include prediction of EMA outcomes using linear mixed-effects and generalized linear mixed models, including random subject effects. Such models typically assume that the within-subjects variance component does not depend on subject. The variogram analyses, including the analyses described earlier of the EMPOWER data, suggest that there is considerable variation in the within-subjects variance among subjects. Therefore, we plan to construct mixed-effects models in which the within-subjects variance depends on the participant.

Results

By November 2017, the PMOMS app was completed based on the prototype from the previous pilot studies and extensive testing with volunteers and study staff. PMOMS recruitment and data collection began December 2017 with an expectation to continue recruitment through September 2019 and conclude data collection in September 2020. Initial results are expected December 2020. As of early May 2019, PMOMS screened and approached 356 participants and 305 consented to participate. Out of those, 284 have been issued devices (smartphones and/or smart scales) and have been entered into the PMOMS technology systems to begin completing EMA surveys and collecting weight data. So far, 266 participants have given birth and are engaged in postpartum assessments and follow-up. On the basis of baseline data generated from GDM² in April 2019 that were available for 238 participants, 63% of the population was white; 25% was black; 4% was Asian; 3% identified as multiracial; and the remaining identified as Native Hawaiian, American Indian, or another racial category (not specified). Out of the 238 participants, 7.2% identified as Hispanic/Latino.

As of early May 2019, the attrition rate was approximately 15% because of withdrawal from GDM² or PMOMS for various reasons including moving to new locations, health challenges, or lack of interest in continued participation. PMOMS continuously monitors study recruitment and attrition and has instituted procedures to continue engaging participants, such as check-in calls to discuss any technology challenges, breaks from continuous EMA prompts as needed, and a *Contact Us* button within the app for reporting technological challenges. In addition, a scale back of EMA surveys will be implemented to further reduce participant burden. On the basis of data generated in May 2019 (approximately 17 months after study recruitment began), survey completion rates during the first 4 weeks of study participation were 77.7% overall (76.4% for BOD, 78.6% for EOD, and 78.2% for random). The overall survey completion rates during the entire pregnancy period were 76.6% (74.3% for BOD, 77.8% for EOD, and 77.7% for random) and declined

slightly to 69.5% at 1 month postpartum, 66.2% at 2 months postpartum, 64.2% at 3 months postpartum, 61.8% at 4 months postpartum, 62% at 5 months postpartum. We do not report completion rates at 6 months and higher because of smaller sample sizes at that time period.

Discussion

The PMOMS includes multiple processes for study initiation, development, and implementation. This study is unique in that it attempts to engage populations during late pregnancy and through 1 year postpartum to enhance our understanding of racial disparities in postpartum weight and cardiometabolic health by leveraging an existing trial aimed to understand how GDM² testing strategies and outcomes may influence gestational diabetes, metabolic issues in after pregnancy, and infant outcomes. The work generated from PMOMS coupled with GDM² can also provide insight into health outcomes over the life course irrespective of pregnancy status.

A key strength of this study is the implementation of novel measurements of stress, discrimination, behavior, and context. We apply an intensive EMA protocol that calls for daily participation over an average of 15 months per woman. To our knowledge, this is the first study to specifically engage women over this length of time, using an EMA app via mobile technology. Through a period of development and internal testing, we were able to maximize data collection and minimize error. In addition, the use of the smart scale to capture weight allows for measurements of weight over time and during time periods that have not been captured by previous studies. Finally, it serves to highlight the PMOMS protocol's leveraging of recruitment infrastructure in GDM², which facilitates the enrollment of participants by consolidating staff support from the 2 studies, resulting in a less costly and more efficient protocol.

The PMOMS design and app have utility not only among pregnant populations and related to weight and cardiometabolic health but also among other populations and health conditions, particularly in understanding phenomenon that may change frequently or that change over time. The knowledge gained can help identify factors that influence obesity and cardiovascular disease disparities for women, inform the refinement of existing interventions, and provide insights for the development of novel approaches that incorporate evolving technology that permits timely, bidirectional communication between women, support systems, and providers throughout pregnancy and during the postpartum period.

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Authors' Contributions

DDM was responsible for the development of the research study, writing, and edits. SAS was responsible for leading writing and editing. All authors were responsible for writing, editing, and final approval of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BOD: beginning of day

EMA: ecological momentary assessment

EMPOWER: Advancing Real-time Data Collection with Adaptive Sampling and Innovative Technologies

EOD: end of day

GDM²: Comparison of Two Screening Strategies for Gestational Diabetes

GMA: geographic momentary assessment

GPS: geographic positioning system

GTT: glucose tolerance test

PMOMS: Postpartum Mobile Mothers Study

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Protocol

Uniform Noting for International Application of the Tumor-Stroma Ratio as an Easy Diagnostic Tool: Protocol for a Multicenter Prospective Cohort Study

Marloes Smit¹, MD; Gabi van Pelt¹, BSc; Annet Roodvoets², MSc; Elma Meershoek-Klein Kranenbarg², MSc; Hein Putter³, MSc, PhD; Rob Tollenaar¹, MD, PhD; J Han van Krieken⁴, MD, PhD; Wilma Mesker¹, PhD

¹Department of Surgery, Leiden University Medical Center, Leiden, Netherlands

²Datacenter Surgery, Leiden University Medical Center, Leiden, Netherlands

³Department of Medical Statistics, Leiden University Medical Center, Leiden, Netherlands

⁴Department of Pathology, Radboud University Medical Center, Nijmegen, Netherlands

Corresponding Author:

Wilma Mesker, PhD

Department of Surgery

Leiden University Medical Center

Albinusdreef 2

Leiden, 2333 ZA

Netherlands

Phone: 31 715264005

Email: W.E.Mesker@lumc.nl

Abstract

Background: Colon cancer treatment is dependent on the stage at diagnosis. The current Tumor-Node-Metastasis (TNM) staging for the selection of patients for adjuvant chemotherapy needs additional prognostic and predictive biomarkers. Better decision making for chemotherapy will result in reducing over- and undertreatment. We developed a new, easy-to-apply, practice-changing method to select colon cancer patients for adjuvant chemotherapy: the tumor-stroma ratio (TSR). The TSR distinguishes within stage II-III patients who will likely benefit from adjuvant chemotherapy and those who will not.

Objective: The aim of the study was to add, in addition to the TNM classification, the TSR to current routine pathology evaluation. Pathologists will be instructed for scoring the TSR in combination with a quality assessment program. An international multicenter study will validate the parameter prospectively.

Methods: The study is designed for future implementation of the TSR to the current TNM guidelines, using routinely Haematoxylin- and Eosin-stained tumor tissue sections. In part 1 of the study, an electronic learning (e-learning) module with a quality assessment program using the European Society of Pathology framework will be developed. This module will be used to assess the reliability and reproducibility of the TSR, conducted by national and international pathologists. Part 2 will involve the validation of the TSR in a prospective cohort of colon cancer p-stage II-III patients in a multicenter setting. In total, 1500 patients will be included.

Results: The results of part 1 will be expected in the first half of 2019. For part 2, the inclusion of patients in the prospective study, which started at the end of 2018, will take 3 years with an additional follow-up after another 3 years.

Conclusions: The main endpoints of this study are as follows: in part 1, trained (international) pathologists who are able to reliably score the TSR, resulting in low intra- and interobserver variation; in part 2, confirmation of significant survival differences for patients with a stroma-high tumor versus patients with a stroma-low tumor. On the basis of these findings, a modification in current treatment guidelines will be suggested.

Trial Registration: Netherlands Trial Register NTR7270; <https://www.trialregister.nl/trial/7072>

International Registered Report Identifier (IRRID): DERR1-10.2196/13464

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KEYWORDS

tumor-stroma ratio; colon cancer; pathology; observer variation; prospective study

Introduction

Background

Despite complete resection of the primary tumor and surrounding lymph nodes, colon cancer patients often develop recurrence of disease, caused by the remaining micrometastases. These can be treated with chemotherapy. However, as micrometastases are difficult to detect, treatment guidelines are usually based on tumor characteristics related to disease progression and survival, such as depth of invasion and lymph node metastasis. The current guidelines advise to give adjuvant chemotherapy to patients with stage III colon carcinoma and patients with stage II and one or more high-risk factors [1]. Only a part of the patients who are treated with chemotherapy will actually benefit. Furthermore, there is also substantial undertreatment because 25% of the stage II patients, who do not receive adjuvant chemotherapy, will develop recurrence or metastasis within 5 years [2]. Some patients with stage IIIA receive adjuvant chemotherapy, whereas in some cases, the prognosis is better compared with patients with stage IIB disease [1]. The selection of colon cancer patients for adjuvant treatment should be further improved to establish an optimal treatment regimen for each patient.

Over the last decade, the microenvironment or stromal (ie, nonepithelial) component of tumors has been studied intensively. There is increasing evidence that the tumor stroma plays an important role in the biological behavior of tumors, their growth, ability to metastasize, but also their response or resistance to anticancer drugs [3-6]. Tumors that are rich in stroma behave in a more aggressive way compared with tumors with little stroma [2,7].

Tumor-Stroma Ratio

The tumor-stroma ratio (TSR) parameter is based on the amount of stroma within the primary tumor and can be determined, without extra costs, during routine pathology assessment. Using the TSR, stage II/III stroma-high (high-risk) patients can be adequately registered for treatment with chemotherapy, whereas for the (elderly) patients with stage III and stroma-low, further discussion is needed as to whether adjuvant therapy will benefit these patients. New guidelines for patient management will have consequences for better patient management leading to a more optimal selection for adjuvant chemotherapy with a potential reduction in costs.

A high stroma percentage (>50%) is an unfavorable prognostic factor. The TSR has been validated in various international studies with high interobserver agreements [2,7-12]. The TSR was discussed by the TNM Evaluation Committee, the Union for International Cancer Control, and the College of American Pathologists. They stated that our observations are important

and novel and have the potential to be added to the TNM staging algorithm as prognosticator. They advocated validation in a prospective multicenter study and development of consensus agreement and a quality assessment program. This protocol elaborates on this recommendation.

Objectives

The overall objective is the addition of the TSR to current routine pathology next to the TNM classification for clinical decision making.

Primary objective for each part of the project:

1. Part 1: To evaluate and improve the reliability and reproducibility of pathologists specifically instructed for TSR scoring.
2. Part 2: To confirm the prognostic power of the method to select patients at risk for the development of recurrence of disease resulting in high-level evidence for adaptation of guidelines.

Methods

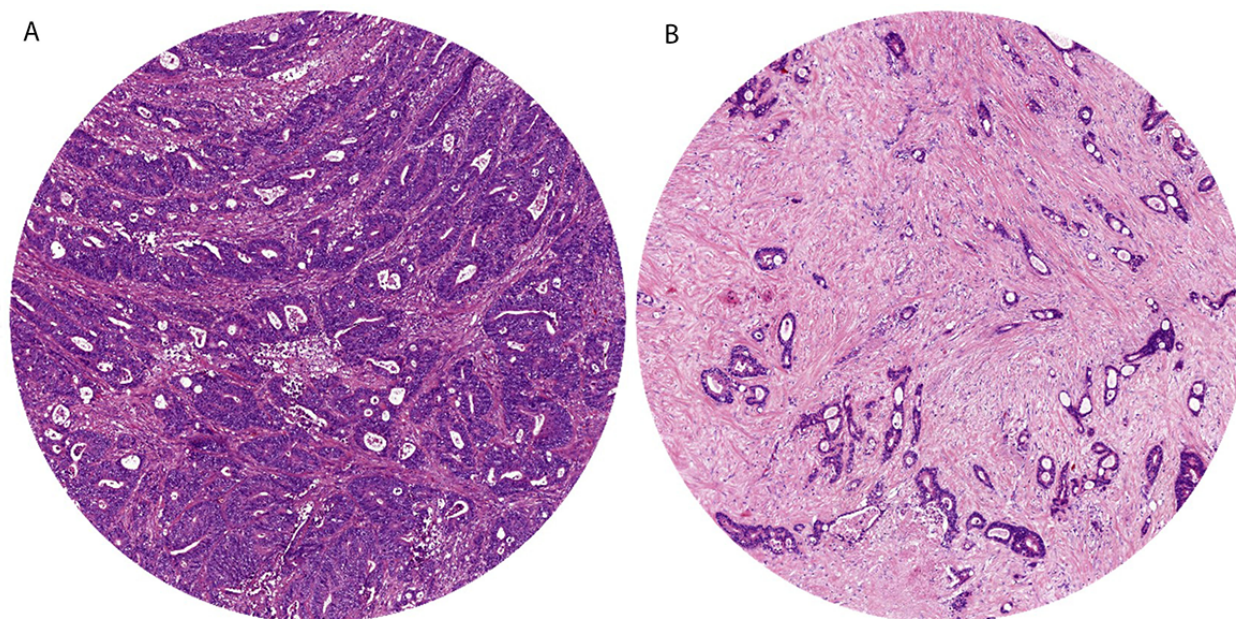
Histopathological Scoring of the Tumor-Stroma Ratio

For the evaluation of the TSR, Haematoxylin and Eosin (H&E)-stained sections of the primary colon carcinoma, used in routine pathology to determine the T-stage (ie, the deepest part of the tumor), are analyzed using conventional microscopy. Areas with the largest amount of stroma are selected using a 2.5x or 5x objective. An area where both tumor and stromal tissue are present within this vision site is selected using a 10x objective. Tumor cells have to be present at all borders of the selected image field. Mucinous tumors, although more difficult, can also be scored; an area containing mucus may be used. However, the volume of mucus should be excluded when determining the TSR. Other challenging cases can be tumors with abundant necrosis and/or muscle tissue in between tumor glands. Necrotic areas or muscle tissue should be avoided in the scoring procedure. It is not necessary to score the TSR at the invasive front, picking a field with as much stroma as possible is more accurate.

Stroma-high is defined as >50% stromal area and stroma-low, as ≤50% stromal area in the histological section (Figure 1). This cut-off has been determined a priori with maximum discriminative power [2,7,9]. Even if there is only one image field with a stroma-high score, this image field is decisive to categorize the patient as stroma-high.

The scoring protocol is available in an instruction movie on the Uniform Noting for International application of the Tumor-stroma ratio as Easy Diagnostic tool (UNITED) study website [13] and in written form published by our group [14].

Figure 1. Examples of stroma-low colon cancer (A) and stroma-high colon cancer (B).



Study Design

Part 1 will consist of an electronic learning (e-learning) module which has been developed with a quality assessment program in the framework of the European Society of Pathology (ESP) External Quality Assessment program. Using this module, a reliability and reproducibility study on H&E-stained tumor tissues will be conducted among national and international pathologists.

Part 2 will involve validation in a prospective cohort of colon cancer stage II-III patients within this multicenter setting. The inclusion is expected to take 3 years, with a 3-year follow-up period.

Patient Description

In the UNITED study, all patients are diagnosed with pathological stage (p-stage) II or p-stage III colon cancer. For e-learning, H&E-stained slides of stage II-III colon cancer patients were selected in a retrospective manner. Material was obtained from the archive of the Department of Pathology of the Leiden University Medical Center (LUMC).

Part 1: The E-Learning Module

An e-learning module has been developed in the framework of the ESP. The software used for the e-learning is PathXL Tutor version 6.1.1.1. (Philips). This is a Web-based software that can be accessed worldwide. Participating pathologists receive specific user credentials for access to the e-learning sets. The workflow is shown in [Figure 2](#) and includes an introduction film with the technical instructions. Hereafter, the participating pathologists may start the e-learning by analyzing the training set containing 40 cases.

TSR scores of participating pathologists will be compared with a reference score (consisting of 3 observers at the LUMC). If a pathologist does not pass a set (interobserver variability $\kappa < .70$), he or she is asked to re-analyze the set. If need be, the instruction video and protocol can be studied again. If a pathologist passes the set ($\kappa \geq .70$), the pathologist is able to continue to the next set of 40 slides. The test set will be repeated after 2 months, thereafter inter- and intraobserver variability are determined. The pathologists are unaware of any clinical information or previous scoring.

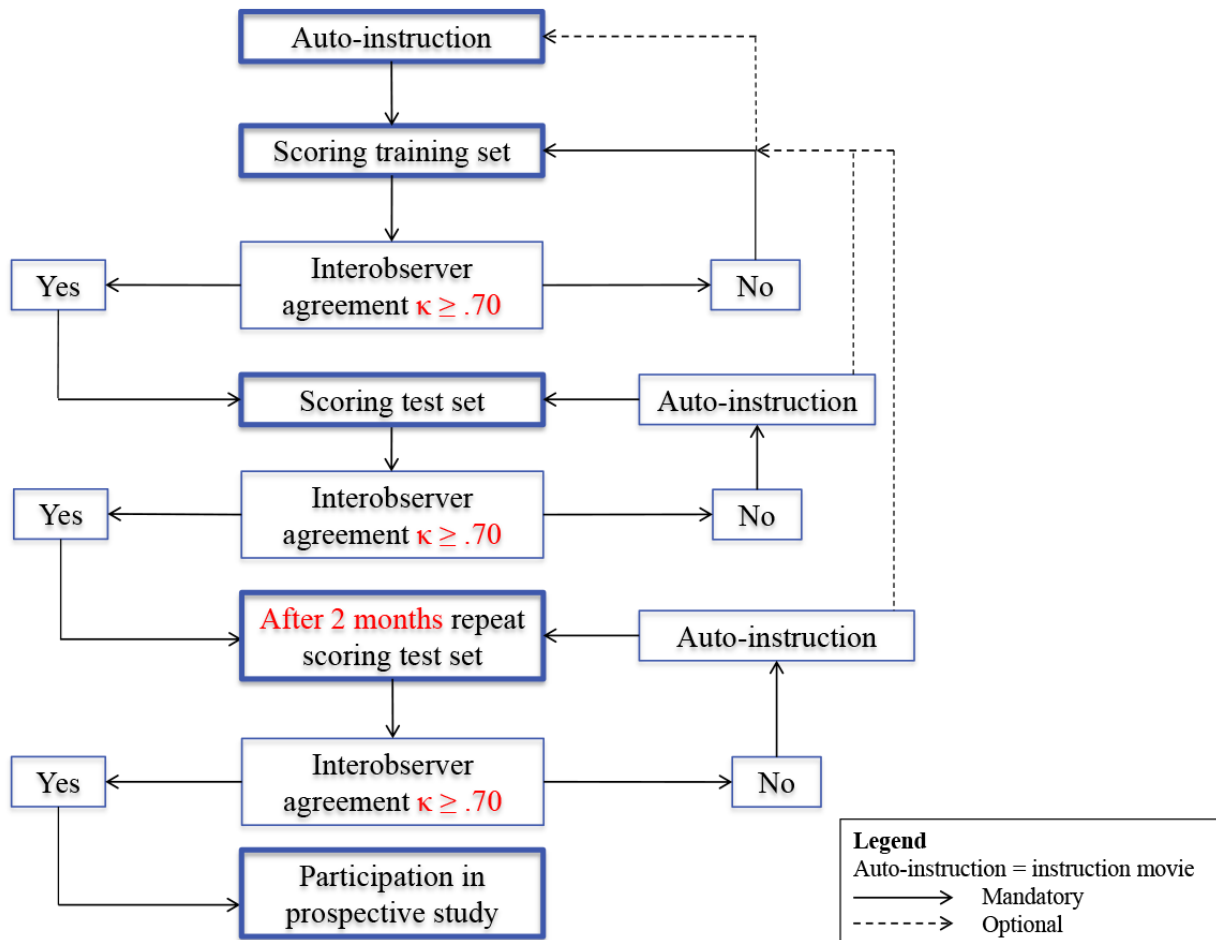
The quality of TSR scoring by the participating pathologists will be monitored on a yearly basis by offering control series.

Part 2: Validation of the Tumor-Stroma Ratio in a Prospective Study

After finishing the e-learning, the pathologist is well instructed to score TSR in the daily routine. To validate the TSR prospectively, a multicenter study is set up. The study aims to include, in the participating centers, a total of 1500 colon cancer patients who have undergone complete curative resection (R0 resection), independent of receiving adjuvant chemotherapy according to actual guidelines.

Recruitment of Patients and Consent

Each consecutive eligible patient with a clinical stage I/II/III tumor will be informed about the study by their physician or research nurse. After informed consent, the pathologist is notified that the TSR can be determined. All patients, independent of gender and family history, are invited to participate. Medical history is no reason for exclusion, apart from malignancies within 10 years before the current colon carcinoma. [Textboxes 1](#) and [2](#) describe the inclusion and exclusion criteria.

Figure 2. Flowchart for the instruction of participating pathologists using the e-learning module.**Textbox 1.** Patient inclusion criteria.

- Histologically proven colon carcinoma
- Complete curative resection (R0 resection)
- Clinical stage I (T1-2, N0, M0), II (T3-4, N0, M0) or III (any T, N1-2, M0)
- Aged ≥ 18 years
- Written informed consent

Textbox 2. Patient exclusion criteria.

- Neo-adjuvant treatment; this influences the amount of tumor and stroma, by fibrosis formation
- Any malignancy within 10 years before the current colon carcinoma (except for basal cell carcinoma or cervical carcinoma in situ) or any colon carcinoma in history; owing to prolonged treatment or metastasis from earlier primary tumors that can influence the current colon carcinoma prognosis. Basal cell carcinoma and cervical carcinoma in situ do not have metastatic capacity
- Multiple synchronous colon tumors; patients with synchronous tumors are likely to have a worse prognosis and need a different approach for treatment
- Rectum tumors; these are defined as separate entities. Prognosis and treatment is different compared with colon tumors

Additional exclusion after surgery:

- p-stage I or stage IV; p-stage I is excluded as these patients will not receive adjuvant treatment. Stage IV patients are excluded as these patients are palliatively treated
- Deceased within 3 months after surgery; patients who die within 3 months after surgery die most often owing to comorbidity or surgical complications

Safety Reporting and Risk Analysis

The patient material to be analyzed in this study is a conventional H&E-stained histological section of the primary tumor, obtained during the routine pathology process. The method is without any additional intervention and the study does not have consequences for the treatment of patients. Therefore, the safety or health of participating subjects will not be jeopardized in any way by this study. Consequently, no adverse events, serious adverse events, or suspected unexpected serious adverse events will occur owing to the study. A data safety monitoring board is not indicated.

Data Storage

The LUMC Datacenter, Department of Surgery, is the Central Datacenter and responsible for supply of electronic Case Report Forms, study database, generation of queries within the database, and central monitoring.

Data will be stored in Castor Electronic Data Capture (Castor EDC; Castor, Amsterdam, the Netherlands) [15]. Castor EDC is a cloud-based electronic data capture platform, easy-to-use by researchers worldwide and highly secured. Data can be easily captured; therefore, data are of high quality and reusable. Data and documents will be stored for at least 15 years.

Statistical Analysis

Statistical analysis will be performed using IBM SPSS Statistics version 25.0 in collaboration with the Department of Medical Statistics of the LUMC.

Part 1

For the analysis of the inter- and intraobserver variability, Cohen kappa coefficient will be used.

Part 2

Sample Size Calculation

For the prospective cohort, a sample size calculation has been performed for both stages based on earlier research findings [2,7].

- p-stage II patients: with a hazard ratio (HR) of 2.0, adjusted for TNM, and a known percentage of stroma-high patients in p-stage II of 20% to 25% [2,7], 114 recurrence events with 90% power are necessary. To achieve 114 recurrence events based on an event rate of 0.0575 per year (leading to a 5-year probability of 75% and 3-year recurrence probability of 84.2%), this leads to 722 patients.
- p-stage III patients: with an HR of 2.0, adjusted for TNM, and a known percentage of stroma-high patients in stage III of 30% to 35% [2,7], 97 recurrence events with 90% power are necessary. To achieve 97 recurrence events based on an event rate of 0.081 per year (leading to a 5-year probability of 66.7% and 3-year recurrence probability of 78.4%), this leads to 450 patients.

To obtain 1172 evaluable p-stage II/III, approximately 1500 (+25%) patients will be registered, as all p-stage I and stage IV patients will be excluded.

Statistical Analysis

Survival analysis will be performed using Kaplan-Meier survival analysis and differences in survival distributions will be tested using Log Rank statistics. The Cox proportional hazard model is used to determine the HR of explanatory variables for overall and disease-free survival (OS and DFS, respectively).

OS is defined as the time period between the date of surgery and the date of death from any cause or the date of the last follow-up. DFS is defined as the time between the date of surgery and the date of any recurrence (local, regional, or distant metastasis), date of new primary tumor, or date of death (any cause). If no event occurs, DFS is calculated as the time period until the date of last follow-up.

Ethical Considerations

This project is registered with the Netherlands Trial Registry (NTR 7270). It will be conducted according to the Declaration of Helsinki, Forteza, Brazil, October 2013.

As this research plan uses existing H&E-stained sections, conventionally prepared for routine diagnostics, there is no risk for the patient, and we expect no problems with the regulatory authorities in the collaborating countries.

The UNITED study protocol has been approved by the Medical Research Ethics Committee (MREC) of the LUMC, study number p17.302. Before inclusion of patients in participating countries, the protocol will be endorsed by the MREC of each participating hospital.

Informed consent will be obtained from each eligible patient in oral and written form before surgery.

Results

Part 1

The e-learning started mid-2018 and the first results will be expected in the first half of 2019. The results will be presented within 6 to 12 months after the last pathologist has completed the e-learning module.

Part 2

The first patients were included at the end of 2018. In total, 1500 patients are needed, and the expected inclusion time is about 3 years. A follow-up of 3 years is required. In late 2023, the first results are expected, and they will be presented within 12 to 18 months after the last follow-up.

Discussion

The UNITED study has been developed to implement the TSR in routine pathology, in addition to the TNM classification and other known risk factors as an extra indicator for medical treatment decision making.

Earlier research validated the prognostic value of TSR in retrospective cohort studies. With the UNITED study, we aim to validate the prognostic value of the TSR in a prospective way.

The results of the e-learning will contribute to a standardized method and specifically trained pathologists. With the yearly quality assessments, the quality of the scoring method will be monitored and guaranteed.

Beside the tumor characteristics, as described in the TNM classification, to determine the p-stage, the microenvironment of the tumor is an important factor as well. The microenvironment of a tumor is a wide spread of different cell types. More tumor characteristics in the microenvironment are studied, such as tumor budding [16-21], Immunoscore [22-24], and desmoplastic reaction [19,25,26]. They are all independent prognostic biomarkers for survival [16-26]. Outside this protocol, we aim to study the relation between the different (microenvironment) biomarkers to better understand the role

of the microenvironment and to further improve patient selection for adjuvant treatment.

Treatment decision making in oncology is a multidisciplinary process where medical oncologists play a pivotal role. These professionals will also be involved by the introduction of the TSR in daily clinical practice.

In conclusion, the UNITED study will, for the first time, evaluate the TSR in a prospective cohort to prove its prognostic value in stage II/III colon cancer. After completion of the UNITED study, the TSR will have the highest level of evidence for a prognostic marker and should be ready to use in the daily practice of all gastroenterology pathologists and also ready to play a role in clinical decision making.

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Conflicts of Interest

None declared.

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Abbreviations

Castor EDC: Castor Electronic Data Capture

DFS: disease-free survival

e-learning: electronic learning

ESP: European Society of Pathology

H&E: Haematoxylin and Eosin

HR: hazard ratio

LUMC: Leiden University Medical Center

MREC: Medical Research Ethics Committee

OS: overall survival

p-stage: pathological stage

TNM: Tumor-Node-Metastasis

TSR: tumor-stroma ratio

UNITED: Uniform Noting for International application of the Tumor-stroma ratio as Easy Diagnostic tool

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Protocol

Integration of Gender-Affirming Primary Care and Peer Navigation With HIV Prevention and Treatment Services to Improve the Health of Transgender Women: Protocol for a Prospective Longitudinal Cohort Study

Javier R Lama¹, MD, MPH; Kenneth H Mayer², MD; Amaya G Perez-Brumer³, MSc, PhD; Leyla Huerta⁴, BS; Hugo Sanchez⁴, BS; Jesse L Clark⁵, MD, MSc; Jorge Sanchez⁶, MD, MPH; Sari L Reisner^{2,7,8}, ScD

¹Asociacion Civil Impacta Salud y Educacion, Lima, Peru

²The Fenway Institute, Boston, MA, United States

³Department of Sociomedical Sciences, Mailman School of Public Health, Columbia University, New York, NY, United States

⁴Epicentro, Lima, Peru

⁵Department of Medicine, Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, United States

⁶Centro de Investigaciones Tecnológicas, Biomedicas y Medioambientales, Universidad Nacional Mayor de San Marcos, Lima, Peru

⁷Division of General Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA, United States

⁸Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, United States

Corresponding Author:

Javier R Lama, MD, MPH

Asociacion Civil Impacta Salud y Educacion

Av Almirante Miguel Grau 1010

Lima, 15063

Peru

Phone: 51 1 206 7800 ext 407

Email: jrlama@impactaperu.org

Abstract

Background: Public health strategies are urgently needed to improve HIV disparities among transgender women, including holistic intervention approaches that address those health needs prioritized by the community. Hormone therapy is the primary method by which many transgender women medically achieve gender affirmation. Peer navigation has been shown to be effective to engage and retain underserved populations living with HIV in stable primary medical care.

Objective: This study aims to assess the feasibility and acceptability of an integrated innovative HIV service delivery model designed to improve HIV prevention and care by combining gender-affirming primary care and peer navigation with HIV prevention and treatment services.

Methods: A 12-month, nonrandomized, single-arm cohort study was implemented in Lima, Peru, among adult individuals, assigned a male sex at birth, who identified themselves as transgender women, regardless of initiation or completion of medical gender affirmation, and who were unaware of their HIV serostatus or were living with HIV but not engaged in HIV treatment. HIV-negative participants received quarterly HIV testing and were offered to initiate pre-exposure prophylaxis. HIV-positive participants were offered to initiate antiretroviral treatment and underwent quarterly plasma HIV-1 RNA and peripheral CD4+ lymphocyte cell count monitoring. All participants received feminizing hormone therapy and adherence counseling and education on their use. Peer health navigation facilitated retention in care by visiting participants at home, work, or socialization venues, or by contacting them by social media and phone.

Results: Patient recruitment started in October 2016 and finished in March 2017. The cohort ended follow-up on March 2018. Data analysis is currently underway.

Conclusions: Innovative and culturally sensitive strategies to improve access to HIV prevention and treatment services for transgender women are vital to curb the burden of HIV epidemic for this key population. Findings of this intervention will inform future policies and research, including evaluation of its efficacy in a randomized controlled trial.

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KEYWORDS

transgender persons; culturally competent care; patient navigation; HIV; retention in care; health services; Peru

Introduction

Globally, transgender women (TW) are at a high risk for HIV infection, with a pooled 19.1% prevalence and a 48.8-fold increased odds of HIV compared with the general adult population [1]. Public health strategies are urgently needed to improve global HIV disparities among TW, including intervention approaches that address those health needs prioritized by the community [2]. In Peru, TW are disproportionately burdened by the HIV epidemic, with HIV prevalence estimates ranging from 30% to close to 45% [3-5] compared with less than 1% in the general population [6]. About 22,500 TW live in Lima (personal communication by Segura et al, 2010), the national capital and regional center, which is home to 80% of Peru's HIV epidemic [7], making it a key site for HIV interventions in Latin America. Improving access to HIV prevention and treatment services for TW in Peru is vital to curb the burden of HIV epidemic for this key population [8].

Gender affirmation is defined as the process of being recognized in one's internal felt gender and sense of oneself as having a particular gender identity [9,10]. Access to gender affirmation has been conceptualized across multiple domains: social (eg, *passing* in one's desired gender role, acceptance and use of preferred pronouns or name, and wearing desired clothes associated with gender identity), medical (eg, hormone therapy or surgery), and legal (eg, legal name change, change of birth certificate sex or passport/ID reflecting gender identity) [11]. Not all types of affirmation are needed or desired by transgender individuals. Hormone therapy is the primary method by which many TW medically achieve gender affirmation [12], as some consider body modification an important step in aligning their outward physical gender presentation with their internal felt sense of their gender [10]. The implementation of gender-affirming care has been shown to improve psychological well-being among TW [11,13]. Furthermore, studies suggest that the integration of gender-affirmative care, including delivery of feminizing hormone therapy, may facilitate TW engagement in HIV care [14,15]. Integrating hormone therapy with HIV prevention and care may increase patient-provider trust, provide an opportunity for patients and providers to discuss what is known about drug-drug interactions between antiretroviral medications and hormones shown to impede HIV prevention and treatment uptake and adherence among TW, foster positive interactions, reduce barriers to obtaining needed services, and support ongoing engagement and retention in HIV care [15,16].

Further evidence from Peru highlights lack of medical training and insufficient culturally competent clinical services to implement feminizing hormone therapy for TW [17]. As a result, gender affirmation procedures are usually performed outside the health system in informal peer-delivered systems [4]. In this setting, trained TW community members, as educators and/or

peer navigators, could improve gender-affirming medical care and also be involved into and support HIV service delivery programs, as research demonstrated the effectiveness of peer navigation to engage and retain underserved populations living with HIV in stable primary medical care [18].

In recent years, the concept of an HIV treatment cascade has emerged as a way to identify gaps in the continuum of how well people living with HIV are engaged in medical care. It consists of 5 main steps, including diagnosis, linkage to care, retention in care, adherence to antiretroviral therapy, and viral suppression [19]. Similarly, an HIV prevention cascade model has been proposed to assist in the implementation and monitoring of HIV prevention programs by identifying gaps in the steps required for effective use of prevention methods, including motivation, access, and effective use in a priority population that would benefit from the prevention method [20].

The *Féminas* (the plural form of *Fémina* in Spanish, meaning *Feminine* in English) study was designed to assess the feasibility and acceptability of a service delivery model designed to improve the HIV treatment and prevention cascades among TW in Lima, Peru, by integrating HIV prevention and care services with gender-affirming transgender medical care supported by peer navigation. The study was grounded in an implementation science framework, which aimed to test and translate research to promote evidence-based practices for improving health and well-being [21,22]. Specific design considerations were given to elements that could be replicated by different institutions, including the Ministry of Health, nongovernmental organizations and community-based organizations (CBOs) providing HIV prevention and care for TW, and/or researchers seeking to develop health interventions culturally tailored to the needs of TW. A mixed-methods formative research study was conducted to explore barriers and facilitators to implementing the proposed model of care. Perceived acceptability of the integrated care model was high among TW (n=48) and health care professionals (n=19) alike. Barriers for implementation included stigma, lack of provider training or Peruvian guidelines regarding optimal TW care, and service delivery obstacles (eg, legal documents, spatial placement of clinics, and hours of operation). The hiring of TW staff was identified as a key facilitator for engagement in health care [17,23]. These findings informed that working in partnership with local TW and health care provider organizations is critical to overcoming existing barriers to successful implementation of an integrated HIV prevention and treatment services and gender-affirmative medical care model for TW in Peru.

Methods

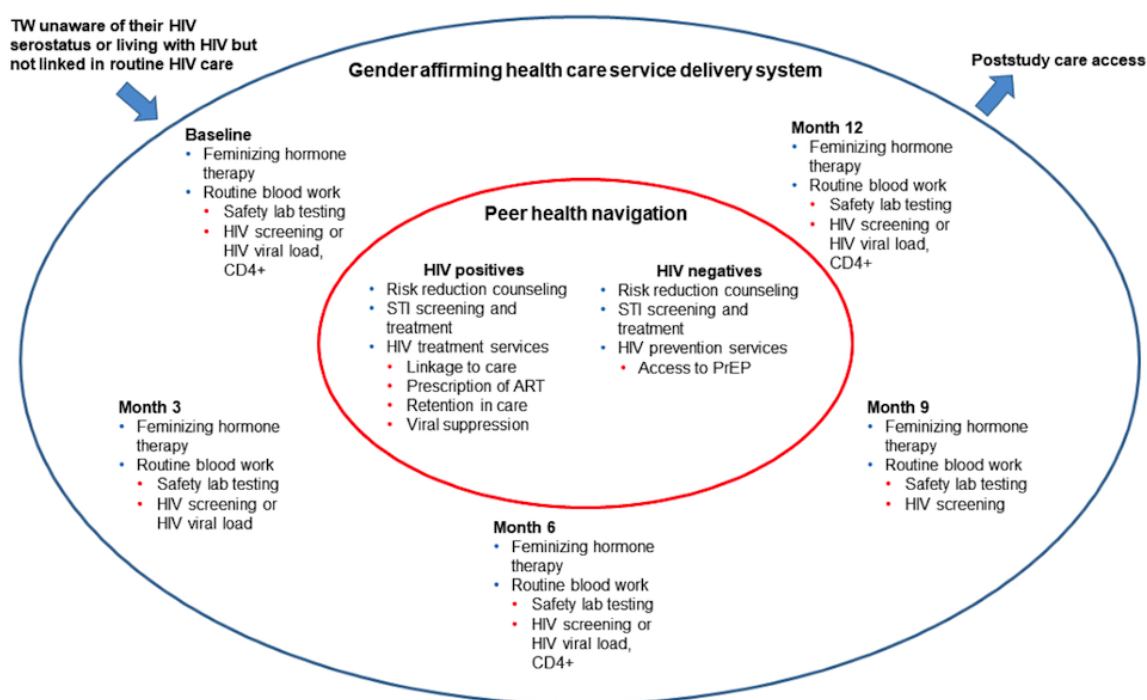
Study Design

Between October 1, 2016 and March 31, 2017, a 12-month, nonrandomized, single-arm cohort study was enrolled in Lima, Peru, to assess the feasibility and acceptability of integrating routine HIV prevention and treatment services with gender-affirming care (ie, feminizing hormone therapy) supported by TW community peer health navigators (Figure 1).

The study was led by Asociacion Civil Impacta Salud y Educacion (IMPACTA), a nongovernmental HIV research

organization, in partnership with Epicentro, a CBO that provides low-cost HIV and sexually transmitted infection (STI) testing and care, community services, and hosts volunteer-driven community activities, which served as a research site for all study operations. The Fenway Institute at Fenway Health, a leading center of transgender clinical care, training, education, and research in Boston, Massachusetts, United States, served as a research partner. Fenway Health's informed consent model of transgender care and community-based transgender health research [24] were the basis for the *Féminas* intervention in Lima, Peru.

Figure 1. Schematic of gender-affirming health care and peer navigation to improve the HIV prevention and treatment cascades. ART: antiretroviral therapy; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection; TW transgender women.



Entry Criteria

Adult individuals, aged 18 years or older, assigned a male sex at birth, who identified themselves as TW or on the trans-feminine continuum (eg, *trans*, *travesti*, *transgender*, or *transsexual*), regardless of initiation or completion of medical gender affirmation procedures, and who were unaware of their HIV serostatus or were living with HIV but not engaged in HIV treatment, were eligible to participate.

Community Engagement and Education

To enhance community engagement and for following principles of Good Participatory Practice to ensure ethical and scientific integrity [25,26], a Task Force composed of TW community representatives was convened for the study. The Task Force, acting as a community advisory board, informed the investigators on community issues, advised on study design, supported development of educational programs and campaigns, and facilitated collaborations with the study population. The Task Force also played a pivotal role in creating the *Féminas* house, as a separate stand-alone community facility and space for health care, support, and community programming placed

at Epicentro. Community mobilization activities conducted at this setting were coordinated by a member of the TW community. Tailored annual community engagement and education plans were designed in advance of study implementation to include the following: (1) formative research for stakeholder identification and educational material validation; (2) community awareness activities; and (3) study communication, including development of educational materials, community consultations, and communication of study results.

Training

Formative research informed the development of training plans to educate study providers, peer health navigators, and community stakeholders on the hormone therapy intervention. TW community representatives and health care providers received medical education training in health care needs, services, and strategies including a gender-affirmative approach to transgender medical care, feminizing hormone therapy, managing HIV infection, and the peer health navigation to improve linkage and retention in care.

Recruitment

Purposive sampling was used to recruit potential participants. Peer recruiters conducted outreach work by visiting TW-specific socialization venues, including discotheques, bars, erotic movie theaters, sex work areas, beauty parlors, volleyball courts, and others. In the field, recruiters approached their peers and asked for their verbal consent to receive information about the study design and criteria for participation. Flyers containing educational material and contact information were distributed after these informative meetings to refer potential participants to the research site for screening. This recruitment strategy was complemented by social media initiatives to promote study participation.

Screening

Counselors explained the study objectives to volunteers and obtained written informed consent to be screened for participation, HIV and STI testing, sample storage for future testing in ancillary studies, and contact for future studies. Participants underwent a computer-assisted self-interview (CASI) to assess demographics, gender identity, sexual

orientation and role, sexual risk behavior, previous HIV testing and diagnosis, history of body enhancement procedures and hormone therapy use, life expectations, problems and barriers perceived because of being TW, HIV testing history, and prior engagement in care, if HIV positive. Counselors assisted participants in cases of computer unfamiliarity or literacy challenges. Physicians obtained a brief medical history and performed a targeted physical examination. A peripheral blood sample was obtained for assessment of HIV, syphilis, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, as well as hematology and biochemistry laboratory tests. Participants underwent oropharyngeal and rectal swabbing and provided a urine sample for the diagnosis of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infection. An anal cytobrush was used to assess the presence of cytological abnormalities induced by human papillomavirus infection. Participants were asked to provide 2 sputum samples and undergo a chest x-ray to rule out active tuberculosis. Volunteers were convened to return to the research site in 2 weeks for the provision of results and enrollment if they were eligible and agreed to participate (Table 1).

Table 1. Study schedule of events.

Procedures	Screening	Postentry evaluations (months) ^a												
		0	1	2	3	4	5	6	7	8	9	10	11	12
Informed consent	X ^b	X	— ^c	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Medication history	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Clinical assessment	X	—	X	—	X	—	—	X	—	—	X	—	—	X
Complete physical exam	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Targeted physical exam		—	X	—	X	—	—	X	—	—	X	—	—	X
Computer-assisted self-interview	X	—	—	—	X	—	—	X	—	—	X	—	—	X
Complete blood count	X	—	X	—	X	—	—	X	—	—	—	—	—	X
Liver and renal function tests	X	—	X	—	X	—	—	X	—	—	—	—	—	X
Fasting glucose and lipids		X	—	—	—	—	—	X	—	—	—	—	—	X
Estradiol and total testosterone		X	—	—	X	—	—	X	—	—	—	—	—	X
Chest x ray and sputum samples	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Risk reduction counseling, condoms, and lubricants	X	X	—	—	X	—	—	X	—	—	X	—	—	X
Sampling for <i>Neisseria gonorrhoeae</i> and <i>Chlamydia trachomatis</i> testing	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Sampling for anal cytological abnormalities	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Syphilis serology	X	—	—	—	X	—	—	X	—	—	X	—	—	X
Hepatitis B and hepatitis C serology	X	—	—	—	—	—	—	—	—	—	—	—	—	—
HIV serology	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Care of HIV negative		—	—	—	—	—	—	—	—	—	—	—	—	—
HIV serology		—	—	—	X	—	—	X	—	—	X	—	—	X
Pre-exposure prophylaxis dispensation		X	X	—	X	—	—	X	—	—	X	—	—	X
Care of HIV positive		—	—	—	—	—	—	—	—	—	—	—	—	—
CD4+ cell count		X	—	—	—	—	—	X	—	—	—	—	—	X
HIV-1 RNA		X	—	—	X	—	—	X	—	—	—	—	—	X
Antiretroviral treatment dispensation		X	X	—	X	—	—	X	—	—	X	—	—	X
Feminizing hormone therapy		—	—	—	—	—	—	—	—	—	—	—	—	—
Adherence counseling and education		X	X	—	X	—	—	X	—	—	X	—	—	X
Dispensation		X	X	X	X	X	X	X	X	X	X	X	X	X
Peer health navigation support	X	X	X	X	X	X	X	X	X	X	X	X	X	X

^aVisits to occur every 30 days \pm 5 days.

^bThe procedure is indicated at the specific study visit.

^cNot applicable.

Enrollment

Peer health navigators remained in contact with screened participants and facilitated their return to the research site for enrollment. At the site, a physician assessed eligibility, which included TW who resided in Lima and had normal hematology and biochemistry laboratory results. Individuals presenting with active tuberculosis; history of pancreatitis; severe or depending alcohol or drug consumption; severe medical comorbidity; reporting the use of immunosuppressive, nephrotoxic, or hepatotoxic therapy; or having any other health condition that

in the opinion of the investigator would interfere with the evaluation of the study objectives were excluded. Volunteers received a detailed explanation of the risks and benefits of the medical intervention. Consenting participants underwent a CASI questionnaire, which included questions about personal and social network support for resilience to societal stigma and discrimination, hormone therapy expectations, and housing. A peripheral blood sample was obtained for assessment of baseline fasting glucose and lipids, estradiol, and total testosterone levels. All participants were prescribed and dispensed feminizing

hormone therapy and invited to initiate HIV prevention and care as described in Table 1.

Follow-Up

Participants were asked to return to research site for study visits at months 1, 3, 6, 9, and 12, which included clinical and laboratory safety assessment, and hormone therapy adherence counseling and education following standard protocols [27]. At quarterly visits, participants underwent HIV (for those negatives) and syphilis testing, and answered a CASI questionnaire on gender identity and body image sexual risk behavior, substance use, attitudes toward HIV testing, personal and social network support, hormone therapy expectations, mental health, adherence to hormone therapy, and involvement in TW community building activities (Table 1). The occurrence of laboratory grade ≥ 2 and clinical grade ≥ 3 adverse events were monitored in all follow-up visits. All participants were instructed to report the occurrence of unintended effects of the study at any time. Peer health navigation facilitated retention in care and promoted adherence to study procedures, HIV prevention and care, and hormone therapy by visiting participants at home, work or socialization venues, or by contacting them by social media and phone.

Regimen for Feminizing Hormone Therapy

Hormone therapy followed Fenway Health's protocol providing medical care of transgender persons [27]. Hormones were dispensed on site on a monthly basis. Follow-up dosages were individualized in response to clinical efficacy or the occurrence of adverse events. Estradiol valerate was initiated at 2 mg PO daily and increased to 4 mg after 4 to 12 weeks. Antiandrogen therapy with spironolactone started at a dose of 50 mg daily and indicated to be increased every 4 weeks to 200 mg daily.

HIV and Sexually Transmitted Infection Prevention and Care

All participants received risk reduction counseling, condoms, and lubricants when tested for HIV and/or STI. Participants diagnosed with HIV infection were invited to be linked to HIV care at IMPACTA, placed 4 blocks away from the research site Epicentro, where local standard care was offered, including initiation of antiretroviral therapy (ART) and assessment of baseline and quarterly plasma HIV-1 RNA and CD4+ lymphocyte cell count monitoring [28]. HIV-negative participants were invited to initiate standard HIV pre-exposure prophylaxis (PrEP) with daily oral emtricitabine/tenofovir disoproxil fumarate [29], which was available at the research site at no cost. Participants diagnosed with STI received international standard treatment and those susceptible to HBV were referred for vaccination [30].

Peer Health Navigation

Socially well-connected community members representing the diverse subcultures of TW in the city and with preexisting knowledge of local HIV and related social resources were convened and provided with skills and confidence to help TW self-manage their health care needs with the ultimate goal to facilitate engagement in study procedures and retention in follow-up. Training in peer navigation followed Fenway Health's protocol for HIV system navigation [18]. Navigators were

trained in several widely used frameworks, including the strengths-based perspective from social work practice, motivational interviewing, and stages of change. The strengths-based approach identifies, supports, and builds on patients' individual capacities, competencies, values, and hopes toward the goal of personal empowerment and resilience. Motivational interviewing is a theory-based, empirically valid approach that helps to change behaviors by examining and overcoming ambivalence that keeps many people from changing. Similar to motivational interviewing, the transtheoretical (*stages of change*) model provides a way to assess patients' readiness to adopt health-promoting behaviors. In addition to the initial 3-day training workshop, navigators received 4-hour monthly re-training sessions, in which barriers and facilitators experienced by navigating the system were shared and discussed [18].

Laboratory Procedures

HIV antibody screening was conducted on whole blood using Determine HIV-1/2 (Alere, Waltham, MA), a point-of-care third-generation HIV antibody test. Positive samples were sent for confirmatory testing by means of indirect immunofluorescence to the Peru National Institute of Health (NIH), unless a previous positive confirmatory result was identified in the Peru NIH database. Plasma HIV-1 RNA and CD4+ T-cell count assessments were also conducted at the Peru NIH. Antibodies to *Treponema pallidum* were detected using a rapid plasma reagin test (RPR Quicktest, Stanbio, Boerne, TX) and confirmed by a *T. pallidum* particle agglutination assay (DR0530, TPPA Test, Oxoid Limited, Basingstoke, UK). Both HBV (HBsAg, anti-HBc, and anti-HBs) and anti-HCV serologies were tested by means of chemoluminescent microparticle immunoassay (Architect, Abbott, Abbott Park, IL). *N. gonorrhoeae* and *C. trachomatis* infections were diagnosed by GeneXpert CT/NG (Cepheid, Sunnyvale, CA). Cytological slides were manually colored using standard Papanicolaou staining. Sputum testing for tuberculosis used the Ziehl-Neelsen stain. Hematology (XS-1000i Sysmex America, Inc, Lincolnshire, IL), biochemistry (IFCC Vitros, Ortho Clinical Diagnostics, Raritan, NJ), and hormone (Cobas E-601, Roche Diagnostics, Indianapolis, IN) tests were assessed automatically. Unless previously specified, all tests other than hepatitis serology and hormone tests (at Anglolib laboratory) were conducted at the IMPACTA PERU Clinical Trials Unit Laboratory. All test results were provided to participants within a period of 14 days.

Endpoints

Endpoints at baseline were as follows: (1) proportion of participants who had ever been tested for HIV and (2) proportion of participants newly diagnosed as HIV positive. At the end of the intervention (12-month follow-up), the endpoints were (1) proportion of HIV-negative participants at baseline who were motivated, accessed, and effectively underwent quarterly HIV testing, used condoms or PrEP [20] and (2) proportion of HIV-positive participants at baseline who linked to and were retained in care, adhered to ART, and resulted in viral suppression [19]. Occurrence of study endpoints were assessed

by an endpoint adjudication committee composed by the protocol team, led by the 3 study principal investigators.

Data Management and Monitoring

All participants' data were anonymized but not deidentified. All participants were identified with a unique alphanumeric code. The link between the participants' codes and identification was restricted to the study coordinator. It was stored in an electronic file and double password protected. Data were monitored for completeness, consistency, and accuracy, as well as for the occurrence of adverse events, in a biweekly basis by a protocol team led by the 3 study principal investigators.

Statistical Considerations

The target enrollment was 220 TW for a total of 200 completers (>90% retention during 12-months of follow-up) (Table 2). On the basis of these estimated percentages and assuming a moderate correlation across measurements ($\rho=.30$) [31], the

power to detect statistically significant differences across follow-up for all HIV cascade outcomes is greater than 0.80. Quantitative analyses will be implemented in Stata SE 13.0 (Stata Corp, College Station, TX) software using 2-tailed tests of significance, with statistical significance at the alpha .05 level. A generalized estimating equation (GEE) approach will be used [31-33] with robust standard errors, which is an extension of regression analysis that properly accounts for repeated measures. Descriptive statistics will be obtained to summarize all variables. Bivariate tests (t tests/chi-square adjusted longitudinally using GEE) will examine changes in the proportion of TW across outcomes of interest, followed by multivariable longitudinal models adjusted for covariates (eg, age). GEE models use the number of observations as data points over time (5 visits \times 200 TW=1000 observations). Multiple imputation [34,35] will be used assuming missingness is completely random.

Table 2. Projected sample sizes across HIV prevention and treatment cascade outcomes (N=200).

Cascade stage	Baseline, n (%)	12-months, n (%)	Difference in proportions	Outcomes
HIV test and risk reduction counseling in past 3 months	75 (37.5)	195 (95.0)	57.5	Increase in the proportion of TW who know their HIV status
HIV positive	46 (23.0)	66 (33.0)	10.0	Identify new HIV infections in TW
Linked to care	22 (47.8)	66 (100.0)	52.2	Increase in the proportion of HIV-positive TW linked to care
Retained in care	9 (40.9)	60 (90.9)	50.0	Increase in the proportion of HIV-positive TW retained in care and treatment
Adhered to ART ^a	11 (50.0)	60 (90.9)	40.9	Increase in the proportion of HIV-positive TW prescribed ART
Viral suppressed	5 (45.5)	50 (83.3)	37.8	Increase in the proportion of HIV positive TW who are virally suppressed
HIV negative	154 (77.0)	134 (67.0)	10.0	Identify high-risk HIV-uninfected TW
Completed referrals to HIV prevention services	35 (22.7)	70 (52.2)	29.5	Link high-risk HIV-uninfected TW to HIV prevention services, including access to pre-exposure prophylaxis
STI ^b screening, risk reduction counseling, and treatment in past 3 months	50 (25.0)	200 (100.0)	75.0	Increase in the proportion of TW screened and treated for STIs

^aART: antiretroviral therapy.

^bSTI: sexually transmitted infection.

Secondary analyses characterizing patterns of HIV virologic suppression over time will also be implemented. HIV cascade outcomes are also time to event data beyond the achievement of the dichotomous outcomes we propose. Therefore, data that allow us to capture the time at which an event of particular interest occurred (ie, virological suppression) will be collected. Patterns of change in biomarkers (ie, CD4+ cell count decrease) or the association between the primary endpoint and features of the longitudinal profiles are of interest. We will conduct joint modeling that enables longitudinal repeated biomarker measurements and survival processes to be modeled simultaneously while taking into account the association between them [36-38]. The random effects model for longitudinal data will be included in the survival model. Joint modeling provides less biased estimates and more efficient

inferences than a 2-stage modeling approach [39-41]. We will use SAS 9.4 (SAS Institute Inc, Cary, NC) [42]. The joint modeling approach is well suited for our study because there is no control group (which is best suited for implementation science), and within-person change across time is being assessed.

Protection of Human Subjects

All participants were reimbursed approximately US \$13 in local currency (40 Soles) at each study visit. The study protocol and its amendments, informed consent forms, and recruitment and educational materials were approved by the IMPACTA's Institutional Bioethics Committee in compliance with all applicable Peruvian and US Federal regulations governing the protection of human subjects. All participants provided written

informed consent for study screening and participation, receiving feminizing hormone therapy, HIV and STI testing, sample storage for future testing, and contact for future studies. The study protocol is registered at Peru National Institute of Health (Registro Nacional de Investigaciones en Salud EI00000345; dated on May 29, 2018) and Clinicaltrials.gov (Registration Number: NCT03757117; dated on November 28, 2018).

Poststudy Care Access

At the end of the intervention, all participants will be invited to continue receiving HIV and STI prevention and treatment at IMPACTA or referred to health care centers of the Peru Ministry of Health to receive it. It is expected that by time the study ends, feminizing hormone therapy will become available at public health care centers as part of the Ministry of Health policies to provide integrated HIV prevention and care to TW [43].

Dissemination

When intervention is near completion, the study team will prepare communication plans for disseminating and interpreting study results. We will host a preparatory activity of study results as a forum on the implications of the intervention targeting Ministry of Health representatives and the scientific and community stakeholders. In this forum, we will present a draft version *Best Practices* for dissemination of integrated TW health care services and ask audience for input that will be further incorporated. Thereafter, we will prepare the TW community for the disclosure of the results in a participant appreciation event.

Results

Patient recruitment started in October 2016 and final inclusion was March 2017. The cohort ended follow-up in March 2018. Data analysis is currently underway, and the first results are expected to be submitted for publication in June 2019.

Discussion

The *Féminas* study will investigate the feasibility and acceptability of an innovative service delivery model that integrates HIV prevention and treatment services with gender-affirming transgender medical care supported by peer navigation to improve the HIV prevention and care cascades among TW in Lima, Peru. To our knowledge, interventional research has not yet combined these 3 aspects to assess HIV outcomes across 12-months of prospective follow-up for TW primary medical care. The competent provision of feminizing hormones along with colocalized services targeting the HIV prevention and treatment cascades, supported by peer navigation, appears to be an attractive model for TW and an important aspect for future implementation of these services to address the HIV epidemic for TW.

For the success of the intervention, transgender community engagement is essential [17,23]. We promoted community mobilization through the implementation of community engagement and education plans, which were structured by members of the TW community in response to their health needs. Study procedures were implemented at a culturally

competent CBO accustomed to regularly providing services for TW residents in Lima. The TW Task Force was particularly crucial in the beginning of the project to gather input on the study design and implementation and offer a vision of the model that would be maximally responsive to the needs of the population.

The coordinator of the *Féminas* house had a challenging role, given her proximity to the community and the many demands placed upon her in terms of the project and by her peers. It is vital that the TW community is represented in the staff, particularly in a leading role such as coordinator [44]. At the same time, caution is warranted so as not to tokenize or overburden this individual in her professional work as a transgender peer. The coordinator position must have supportive and ongoing supervision that is gender affirming with a person (or people) knowledgeable about TW communities and not necessarily within trans communities, preferably clinical supervision. This supervision needs to include ongoing assistance troubleshooting any number of challenging situations that can arise between the personal and professional aspects of project coordination and strategizing how best to manage *insider* trans women community politics with other peer leaders and organizations.

Peer navigation is vital for the *Féminas* model of care [18]. At every initial and subsequent point of contact and visit, participants have social, medical, legal, and other needs, which necessitate referrals and assistance. The peer health navigation takes a great deal of staff time and effort, much more than originally anticipated and budgeted given the many challenges and barriers to services facing TW in Lima in the broader context of social exclusion and economic marginalization. In HIV service models, peer health navigators generally have a caseload of 20 to 40 HIV-positive individuals, depending on the number of complex needs individuals they are supporting and availability and quality of health care services and systems [45,46]. For the *Féminas* model, a maximum of 25 TW peers per navigator would be ideal. Appropriate and realistic staffing and effort for peer health navigation is an important future consideration for the model. In addition, there are many types of and approaches to peer navigation; however, surprisingly few curricula exist to operationalize and skill-build TW peer health navigators. Compiling and disseminating a manualized curriculum to train on peer health navigation represents an important next step.

Our study has several limitations. First, as a pilot single-arm study without a standard-of-care arm, this interventional research cannot assess the effectiveness of the intervention. Nevertheless, this study will play a key role in the development or refinement of a potential future intervention that we anticipate could be tested for efficacy in a later trial [47]. Second, purposive sampling was used to convene potential participants to the study; therefore, study participants do not necessarily represent the TW community in Lima. Sampling may have been biased by the peer recruiters' knowledge of, and access to, different subgroups of TW. In addition, HIV-positive TW already in care were not included in the study. Thus, we will not be able to assess whether an integrated model of gender-affirming

hormones and HIV care can improve HIV cascade outcomes for TW living with HIV and already receiving care.

The anticipated challenges inherent in studying at-risk populations include high participant attrition and low enrollment, as well as high rates of loss to follow-up. We have built a system robust against attrition through comprehensive collection of information on how to locate and contact participants, active tracking and engagement of participants between appointments using peer navigation, and reimbursement to minimize loss to

follow-up. The study will gather information about retention efforts for TW in Lima, including diverse strategies to minimize attrition. It is anticipated that integration and colocalization of hormones and HIV prevention and care will support TW retention and facilitate engagement in the study [48].

Findings from this implementation science study will inform future policies and research, including evaluation of the efficacy of the *Féminas* intervention in a future randomized controlled trial.

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Authors' Contributions

JRL, KHM, JS, and SLR conceptualized and designed the study. JRL, KHM, AGP-B, LH, HS, JLC, JS, and SLR wrote the study protocol. JRL, KHM, AGP-B, JLC, and SLR drafted the manuscript. All authors read and approved the final version of the manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Study protocol funder's original peer-review reports.

[[PDF File \(Adobe PDF File\), 42KB - resprot_v8i6e14091_app1.pdf](#)]

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Abbreviations

- ART:** antiretroviral therapy
- CASI:** computer-assisted self-interview
- CBO:** community-based organization
- GEE:** generalized estimating equation
- HBV:** hepatitis B virus
- HCV:** hepatitis C virus
- IMPACTA:** Asociacion Civil Impacta Salud y Educacion
- NIH:** National Institute of Health
- PrEP:** pre-exposure prophylaxis

STI: sexually transmitted infection

TW: transgender women

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Protocol

Enhancing Diabetes Self-Management Through Collection and Visualization of Data From Multiple Mobile Health Technologies: Protocol for a Development and Feasibility Trial

Ryan J Shaw^{1,2}, RN, PhD; Angel Barnes¹, BSN, RN; Dori Steinberg¹, RD, PhD; Jacqueline Vaughn¹, BSN, RN; Anna Diane¹, BSN, RN; Erica Levine¹, MPH; Allison Vorderstrasse³, DNSc, APRN; Matthew J Crowley^{4,5}, MD; Eleanor Wood⁶, BS; Daniel Hatch¹, PhD; Allison Lewinski⁴, RN, PhD; Meilin Jiang⁷, MS; Janee Stevenson¹, MSN, RN; Qing Yang¹, PhD

¹Duke University School of Nursing, Durham, NC, United States

²Center for Applied Genomics & Precision Medicine, Duke University School of Medicine, Durham, NC, United States

³New York University Rory Meyers College of Nursing, New York, NY, United States

⁴Center of Innovation to Accelerate Discovery and Practice Transformation, Durham Veterans Affairs Medical Center, Durham, NC, United States

⁵Division of Endocrinology, Diabetes and Metabolism, Duke University School of Medicine, Durham, NC, United States

⁶Pratt School of Engineering, Duke University, Durham, NC, United States

⁷Duke University School of Medicine, Durham, NC, United States

Corresponding Author:

Ryan J Shaw, RN, PhD

Duke University School of Nursing

307 Trent Dr, DUMC 3322

Durham, NC, 27710

United States

Phone: 1 9196849434

Email: ryan.shaw@duke.edu

Abstract

Background: Self-management is integral for control of type 2 diabetes mellitus (T2DM). Patient self-management is improved when they receive real-time information on their health status and behaviors and ongoing facilitation from health professionals. However, timely information for these behaviors is notably absent in the health care system. Providing real-time data could help improve patient understanding of the dynamics of their illness and assist clinicians in developing targeted approaches to improve health outcomes and in delivering personalized care when and where it is most needed. Mobile technologies (eg, wearables, apps, and connected scales) have the potential to make these patient-provider interactions a reality. What strategies might best help patients overcome self-management challenges using self-generated diabetes-related data? How might clinicians effectively guide patient self-management with the advantage of real-time data?

Objective: This study aims to describe the protocol for an ongoing study (June 2016-May 2019) that examines trajectories of symptoms, health behaviors, and associated challenges among individuals with T2DM utilizing multiple mobile technologies, including a wireless body scale, wireless glucometer, and a wrist-worn accelerometer over a 6-month period.

Methods: We are conducting an explanatory sequential mixed methods study of 60 patients with T2DM recruited from a primary care clinic. Patients were asked to track relevant clinical data for 6 months using a wireless body scale, wireless glucometer, a wrist-worn accelerometer, and a medication adherence text message (short message service, SMS) survey. Data generated from the devices were then analyzed and visualized. A subset of patients is currently being interviewed to discuss their challenges and successes in diabetes self-management, and they are being shown visualizations of their own data. Following the data collection period, we will conduct interviews with study clinicians to explore ways in which they might collaborate with patients.

Results: This study has received regulatory approval. Patient enrollment ongoing with a sample size of 60 patients is complete, and up to 20 clinicians will be enrolled. At the patient level, data collection is complete, but data analysis is pending. At the clinician level, data collection is currently ongoing.

Conclusions: This study seeks to expand the use of mobile technologies to generate real-time data to enhance self-management strategies. It also seeks to obtain both patient and provider perspectives on using real-time data to develop algorithms for software

that will facilitate real-time self-management strategies. We expect that the findings of this study will offer important insight into how to support patients and providers using real-time data to manage a complex chronic illness.

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KEYWORDS

self-management; technology; type 2 diabetes

Introduction

Background

As most of diabetes care occurs in outpatient settings and involves ongoing patient self-management, mobile health (mHealth) technologies may greatly improve diabetes management and health outcomes. mHealth involves the use of mobile devices to support continuous health monitoring and healthy behaviors [1]. Mobile devices include mobile phones and sensors that are worn, carried, placed in the physical environment, or accessed by individuals during normal daily activities [2]. These devices allow reporting of patient data such as blood glucose through a wireless glucometer, weight through a cellular-enabled scale, and physical activity through a wireless accelerometer in near real-time in the patient's daily environment. Moreover, these data can be transmitted to clinicians and health systems and may lead to the development of precision health strategies [3].

According to the Pew Research center, more than 92% of US adults own a cell phone, and more than 77% own a smartphone [4]. Furthermore, 84% of low-income individuals in the United States now own a cell phone, and almost 70% own a smartphone. Low-income racial/ethnic minorities are actually more likely than low-income whites to own mobile devices and to use features such as SMS (short message service) text messaging or smartphone apps [4]. Research demonstrates that mHealth tools are useful for diabetes self-management [5,6] including collaborative decision making between providers and patients [7]. Thus, mHealth technologies have great potential to facilitate wide delivery of diabetes treatment and enhance the development of self-management tools for diverse populations.

The study protocol described in this manuscript extends current research by using multiple mHealth technologies to provide diabetes-related data to help patients and their clinicians better understand illness dynamics and develops personalized approaches through data visualization to improve health outcomes in type 2 diabetes mellitus (T2DM). Specifically, we describe methods for identifying precision health strategies to help patients self-manage using multiple types of self-generated diabetes-related data. We will also demonstrate how clinicians can help guide near real-time patient self-management by collecting and aggregating streams of health data from multiple

mobile technologies and then creating a variety of data visualizations that we present to both participants and clinicians. Our goal is to understand what kinds of visualizations patients of varying backgrounds and clinicians need. Furthermore, we describe more about the need for understanding what kind of alerts patients might find useful to self-manage their diabetes. These alerts, or algorithms, will be developed from health data from the mobile technologies and associated electronic health record (EHR) data from patients.

Aims

The aims of this project are to examine the feasibility and utility of having patients self-monitor multiple types of diabetes-related data (blood glucose, weight, physical activity, medication adherence) using mHealth technologies (wireless glucometer, cellular-enabled body scale, wrist-worn accelerometer, and medication adherence SMS text message surveys). This will allow us to examine trajectories of diabetes-related variables (blood glucose, weight, physical activity, medication adherence) and challenges in self-management that patients face at points in time. We are also exploring the challenges and successes of patients self-managing diabetes using mHealth technologies through interviews and data visualizations. And finally, we are exploring clinicians' perspectives and input on using these data to develop algorithms for software that will facilitate patient self-monitoring and meet near real-time self-management needs. Results from this study will be used for the integration of data from mHealth tools into EHRs and for developing new models of care delivery to support diabetes management.

Conceptual Framework

The study protocol is supported by the adaptive leadership framework [8], which divides health challenges into 2 types: technical and adaptive [9,10]. Technical challenges such as how and when to measure blood sugar and what the appropriate medication dosages are to manage diabetes are addressed by the clinician with technical solutions. Adaptive challenges require the patient to adjust to new conditions and do the work of learning and making behavioral changes, for example, incorporating exercise into everyday life. Adaptive leadership is the work that clinicians do to help patients perform this work [11]. Using multiple types of self-generated diabetes self-monitoring data, clinicians can support patients in near real time to respond to adaptive challenges.

Figure 1. Mobile health in a collaborative work relationship.

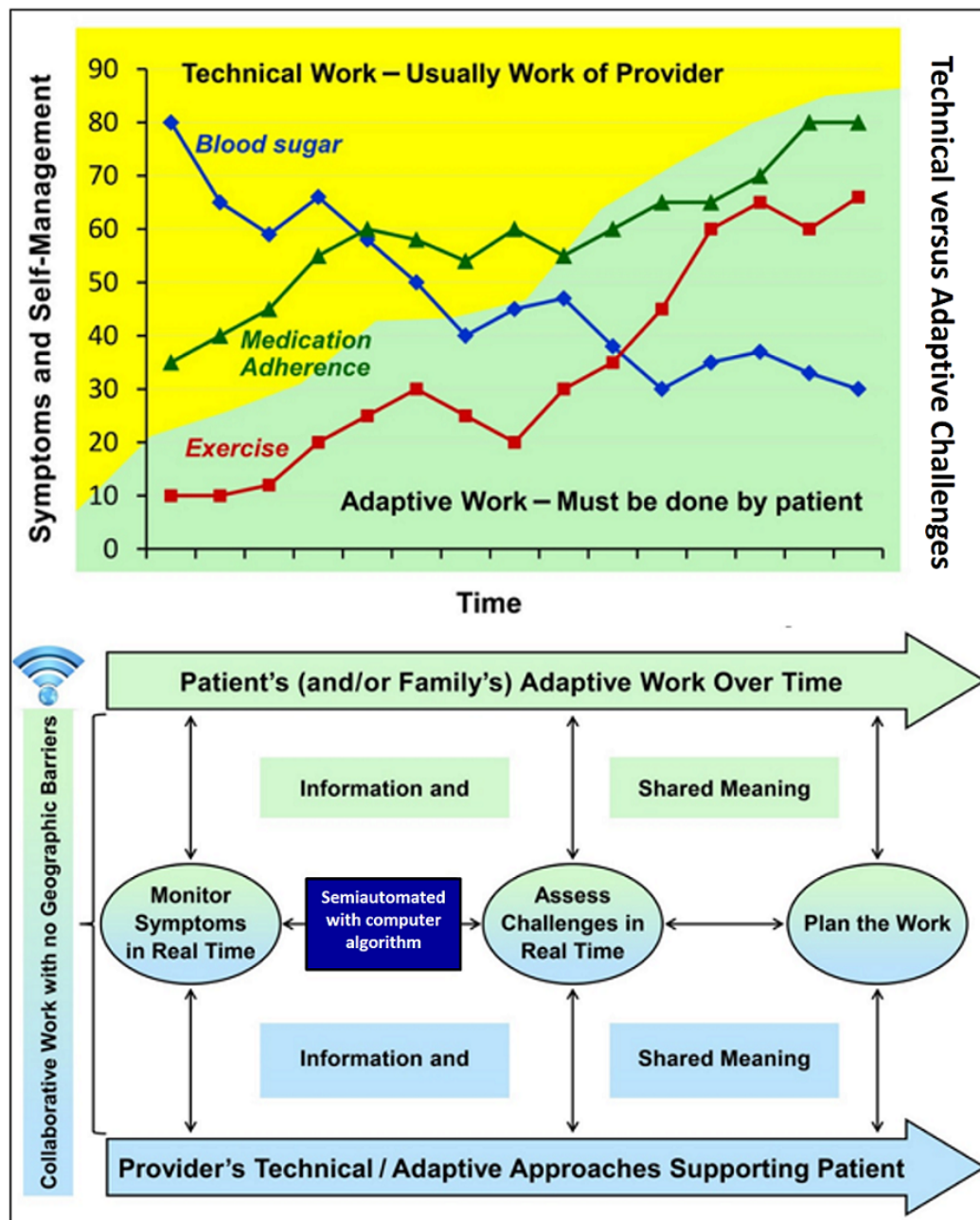


Figure 1 (adapted from National Institute of Nursing Research 1P30NR014139-01) shows how mobile technologies might help patients monitor behavioral, symptom, and biophysical trajectories. These trajectories, shown in the top half of the model, suggest these variables are dynamic. For example, when patients are able to overcome challenges in scheduling exercise and medication adherence, these behaviors increase, and their blood sugars are likely to decrease. The goal of adaptive leadership is for clinicians to address technical challenges, such as finding the appropriate medications and dosages, and also to help patients address adaptive challenges such as lifestyle changes by facilitating their adaptive work for self-management. Over time, as patients address the challenges of self-management and their adaptive work increases, the amount of technical work

needed by clinicians will decrease. The trajectories of the signs and symptoms of T2DM, such as high blood sugar, will also decrease. The lower half of the model illustrates that mobile technology can provide important information to be used in the collaborative work-relationship to facilitate both the adaptive work of patients and the technical and adaptive approaches used by clinicians to support patients. According to this framework, patients and clinicians collaborate to monitor symptom dynamics and self-management techniques. Together, they assess adaptive challenges and plan the technical and adaptive work needed to help patients meet their diabetes goals such as weight loss, medication adherence, and so forth. We considered this framework when designing the protocol described below including the questions we ask both patients and providers.

Methods

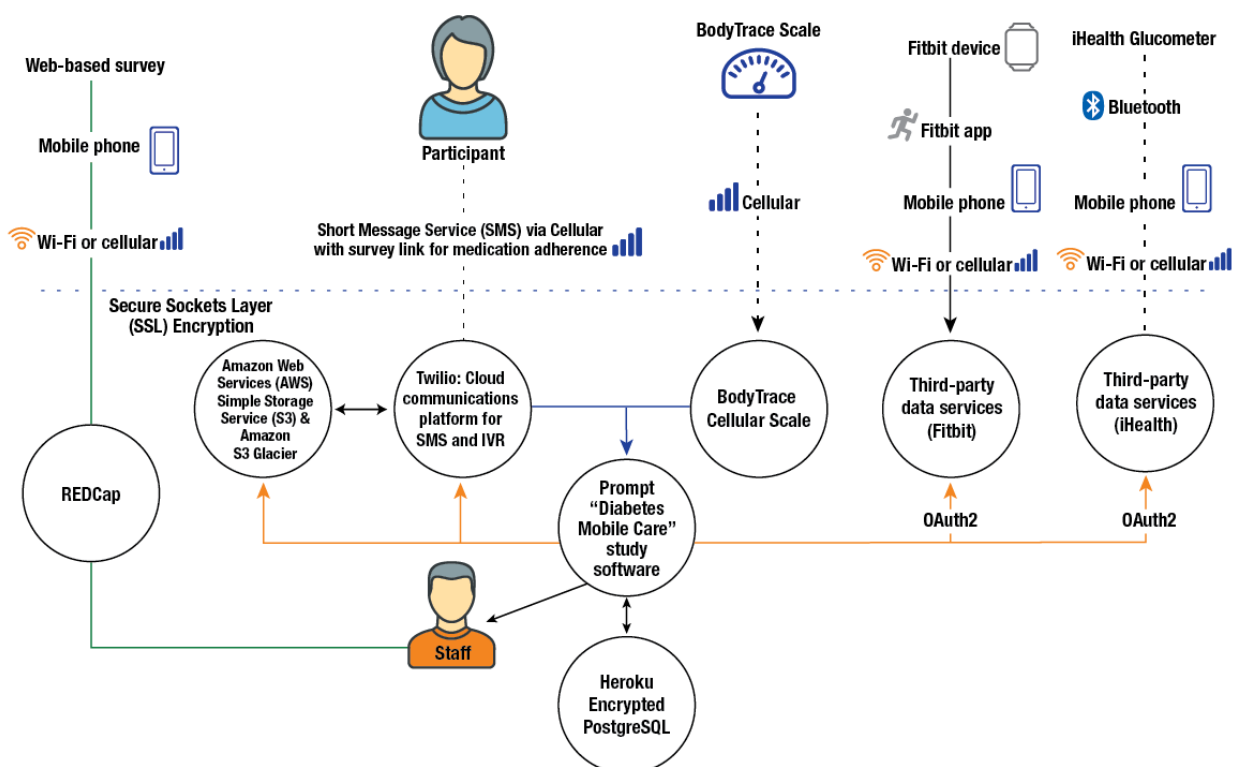
Study Phase 1: Software Development

We began with software development (Figure 2). For Phase 1, we selected consumer-friendly devices that patients could easily use for their diabetes self-management. We chose a wireless glucometer by iHealth, a wrist-worn accelerometer by Fitbit, and a cellular-enabled scale by BodyTrace. Using Prompt, a research platform designed to collect, analyze, and message patients about mHealth data [12], we programmed the ability to pull in data from these respective companies via their application programming interfaces (APIs). Every day, Prompt uses an authentication token to request data via each API for each participant in the study. Those data are collected over the course of the study and stored in a secure database. A study coordinator is also able to view data in aggregate that participants transmit over time. In addition, Prompt was programmed to send out a scheduled SMS text message with a survey link every 2 weeks. This link allowed participants to complete a short survey about their medication adherence via their phones in the Web-based Research Electronic Data Capture (REDCap) Web-based platform hosted at Duke University [13]. REDCap is a secure, Web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Study Phase 2: Data Collection

Following software development, we received institutional review board (IRB) approval for phase 2. In this phase, we are conducting a mixed methods explanatory sequential designed study [14] for which we recruited 60 adults (aged ≥18 years) with T2DM. This is a 2-phase design where quantitative data are collected and followed by qualitative data collection. Patients were recruited from a primary care clinic associated with an academic medical center in the southeastern United States and through local advertisements. Eligible participants met the following inclusion criteria: (1) aged ≥18 years, (2) able to speak and read English, (3) diagnosed with T2DM, (4) told by their primary care provider to monitor their blood sugar, (5) own and use a smartphone, (6) capable of giving informed consent, and (7) able to travel for study enrollment. Participants were excluded if they had a preexisting severe medical condition(s) that would interfere with study participation (eg, renal failure, severe orthopedic conditions or joint replacement scheduled within six months, paralysis, or cancer). A proactive effort was made to enroll patients at various stages of diabetes mellitus, with treatment regimens including both oral and injectable medications were included. We purposefully targeted patients with a range of diabetes severity and included at least 25 patients with a hemoglobin A_{1c} (HbA_{1c}) >7.5%. Patients were not required to have Wi-Fi or in-home internet; a smartphone with an internet connection was adequate. All other devices (eg, glucometer, cellular-enabled scale, and accelerometer) were provided to patients. Patients were excluded if they (1) had active dementia or psychiatric illness, (2) resided in a nursing home, or (3) were participating in another self-management study.

Figure 2. Data flow connecting participant device data to study software. IVR: interactive voice response.



We used a study recruiter to identify patients by reviewing EHRs at primary care clinics. Eligible participants received a letter inviting them to participate. Those who were interested contacted the study recruiter and were screened over the phone. Baseline appointments were scheduled. We also used Web advertisements and posted flyers to recruit half of our participants from the local community.

Sample Size

Our goal is to obtain information critical to plan a larger trial and to understand how to use data from these trials in clinical practice. Accordingly, our sample size is based on our aims to determine feasibility and acceptability on using these devices and getting feedback from multiple stakeholders involved with their use, not on power to detect significant effects of self-monitoring on outcomes (eg, weight, HbA_{1c}, and exercise). Our sample size of 60 patients is designed to provide a sufficient number of participants to obtain high retention rates, means, and variance estimates of end points that can be used to design and power the future trial. Our sample size of up to 20 clinician interviews is based upon estimates that we will likely reach data saturation within 12 or more interviews [15].

Baseline Appointment

To minimize participant burden, the baseline appointment occurred following a clinic visit or at a time deemed convenient for participants. During the in-person appointment, the recruiter (1) obtained signed informed consent, (2) administered surveys to record demographic factors, (3) measured patients' health literacy using the Rapid Estimate of Adult Literacy in Medicine [16] and electronic health (eHealth) literacy on the use of information technology for health using the eHealth Literacy Scale [17], (4) evaluated patients' perceived usefulness and ease of use of mobile technologies, (5) measured patients' exercise frequency using the Godin Leisure-Time Exercise Questionnaire [18], and (6) collected data from patients' EHRs (ie, HbA_{1c}, height, weight, blood pressure, heart rate, and medications). We collected demographic data including race/ethnicity, marital status, income (categorical), educational attainment, employment, age, sex, and duration of disease. These data allowed us to evaluate differences in the data collected by characteristics or groups of patients and to perform subgroup analyses.

Study details and expectations were discussed during the appointment and included risks and costs that participants might incur from using cell phone data and SMS text messages. The study recruiter helped patients set up the mobile technologies, including 2 associated glucometer and accelerometer smartphone apps, and answered any questions. The research assistant also instructed patients how to monitor and record progress. If patients needed follow-up then a call was placed by the recruiter to participants to address questions about the devices and study procedures and to provide a reorientation if needed. Participants were given a study number to call if they had questions or

problems with the study. A research assistant was available to participants throughout the study to provide technical support.

Daily Monitoring

Patient weight, physical activity, and blood glucose were self-monitored via devices provided at baseline (Table 1). Patients were asked to monitor weight daily using a cellular-enabled scale by BodyTrace that connected to a cellular network. Patients were advised to weigh daily because more frequent weighing promotes better weight outcomes than less frequent weighing [19,20]. Patients also received a Fitbit Alta, a reliable and validated triaxial accelerometer for exercise monitoring [21,22]. Participants were instructed to wear the Fitbit daily. The Fitbit tracked daily number of steps taken, distance traveled, and intensity of exercise and provided feedback on these data points to patients. The devices could be worn in the shower or while swimming and were to be worn 24 hours/day and removed only to recharge the battery once per week or when indicated. The Fitbit was tethered to the Fitbit app on the participants' smartphone via Bluetooth.

Glucose readings were tracked using a Food and Drug Administration–approved glucometer by iHealth (model BG5). Participants were instructed to monitor glucose based on the recommendations from their doctor. Like the Fitbit, the glucometer was tethered to a companion smartphone app via Bluetooth, which acted as an automatic logbook to store readings, notes, and medication dosages. Patients were given a 6-month supply of test strips for the device.

In addition to data tracking on the devices, patients received an SMS text message every 2 weeks with a link to a survey on medication adherence (over the previous week) that they completed via their smartphone. Participants clicked on the survey link, which took them to a Web-based survey in a REDCap database. We used a 3-item measure of nonadherence by Voils et al [23]. Participants were asked if over the past 7 days they (1) took all doses of my diabetes medication, (2) missed or skipped at least one dose of my diabetes medication, and (3) were not able to take all of my medication. Response options ranged from *never* (0) to *always* (5; Cronbach alpha=.84) [23]. Response items were scored to assess the extent of nonadherence.

Those who failed to transmit data for a period of 7 days or longer were contacted over the phone by a research assistant to encourage reconnection with the study. If there was no response, the participant was contacted again via phone call or email 1 week later. Nonresponse at that time was considered elective withdrawal from the study. We attempted to contact any participants who withdrew to discuss their reasons for withdrawal. However, no more than 2 follow-up phone calls were made. We asked participants at baseline to please notify us of travel or other situations during which they were not able to transmit data. We made exceptions for participants who were on vacation or traveling. All mobile devices remained active until the end of the study to allow for reconnection at any point.

Table 1. Mobile devices and data collection

Data	Instrument	Description	Data points
Exercise	Triaxial accelerometer and associated fitness app by Fitbit	Tracks data on the frequency and timing of steps	Daily: steps, minutes sedentary, minutes active, distance traveled
Weight	Cellular-enabled Scale by BodyTrace	Tracks weight	Daily weight
Glucose	Food and Drug Association–approved wireless glucometer by iHealth	Tracks blood glucose readings	As prescribed by primary care physician
Medication adherence	Self-report via short message service text message [23]	Medication adherence over the last week	Baseline, biweekly up to 6 months
Hemoglobin A _{1c}	Electronic health record (EHR) laboratory results	Average level of blood sugar over the previous 3 months	Gathered from the EHR as available at baseline and 3 and 6 months post baseline

Six Months Post Baseline

After 6 months, participants were sent a link via email to complete a follow-up survey on their experiences in the study; this was administered again using REDCap. Participants who completed the study and the final survey were able to keep the mobile devices.

Study Phase 3: Data Visualizations and Interviews

Participant Interviews

We will complete semistructured telephone interviews with a subset of participants (n=20). To gain diverse perceptions, we will purposefully select participants for interviews based on frequency of data transmission (eg, consistent or inconsistent over the study period), management of diabetes (eg, controlled or not controlled), demographic characteristics (eg, age and race), and severity of diabetes (eg, A_{1c} level). All interviews will occur via telephone and will be conducted by 2 trained research assistants. The purpose of the interviews is to obtain participants' perceptions of the study, use of the mobile devices in diabetes self-management, and effectiveness of the data visualizations. The topic of questions for participants include those about the usefulness of the mobile devices and their data, and if they helped with diabetes self-management, challenges. Furthermore, we will provide participants with data visualizations of their own data, and we will discuss how they could be curated to be useful.

Data Visualizations

Before the interview, each participant will be sent a copy of their data visualizations via postal mail or email, depending on participant preference. These data visualizations will include graphic representations of the patient's weight, blood glucose, and exercise as obtained from the devices (Figure 3). They will be plotted as trajectories that will allow us to conduct analyses and identify missing data points and trends that lead to attrition. The research assistant will use these data visualizations to facilitate discussion about the challenges patients face in self-management and the personalized practices patients use to succeed. Details on how we will approach the development of these visualizations are published elsewhere [24]. All interviews

will be recorded, stored in an IRB-approved secure database, and transcribed verbatim.

Clinician Interviews

We will conduct interviews with health care clinicians following the completion of patient interviews. This will allow us to explore ways to address collaborative work in diabetes self-management using the device data that could be transmitted in near real time. We will obtain a convenience sample of up to 20 clinicians: 10 with prescribing privileges (eg, medical doctor, nurse practitioner, and physician assistant) and 10 case managers/nurses. This will provide us with diverse perspectives on how to use the device data in new care delivery models and in workflow integration. Questions will be similar to those asked of patients. All participants will provide written informed consent. Our team members will identify clinicians from primary care and endocrinology clinics who may be interested in participating. Study details and expectations will be discussed, questions about the study will be answered, and if interested, the study recruiter will schedule an appointment to participate.

We will present data trajectories from the patients [24] and interview themes from the patient participants. This will allow us to explore clinicians' perspectives and input on using the device data to develop algorithms for software that will facilitate patient self-monitoring and provide feedback to clinicians within existing and future care delivery models.

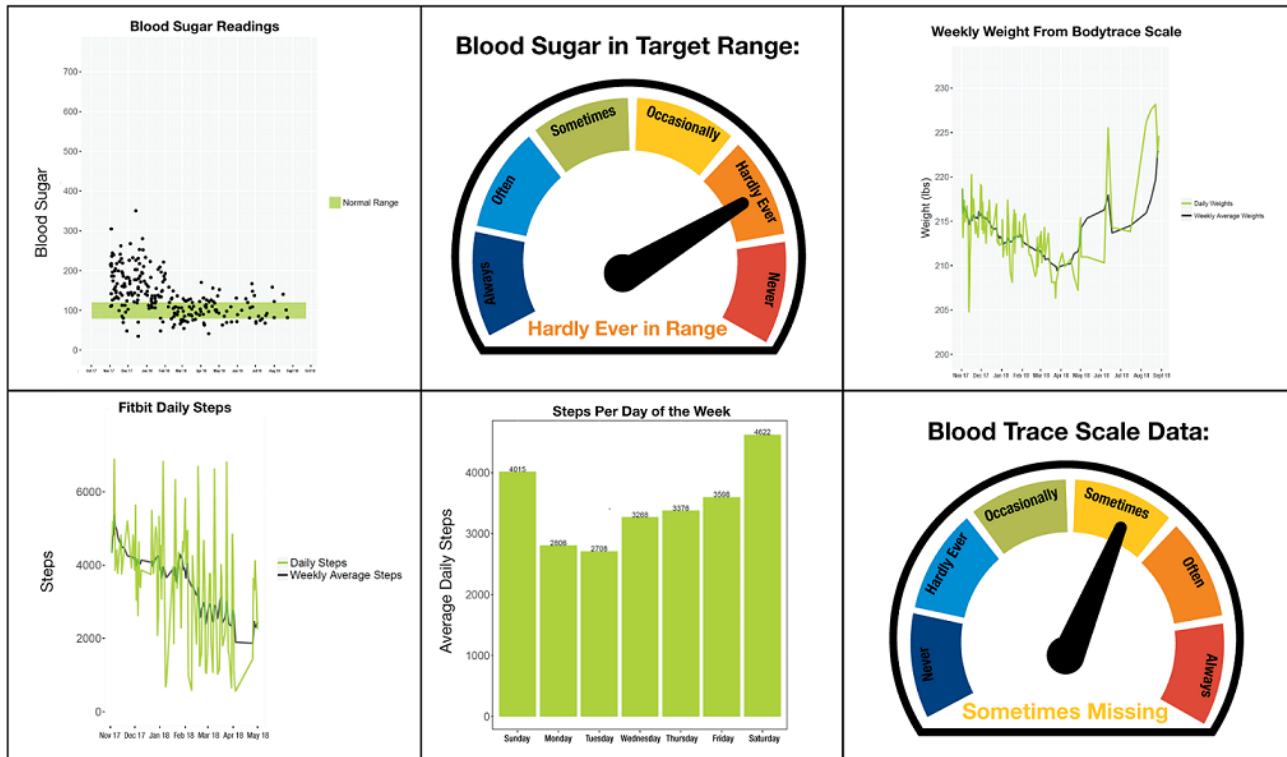
Changes to the Protocol

No changes to eligibility criteria or outcomes changes were made during the study. We did change clinician focus groups to interviews. Interviewing emerged as a better opportunity to discuss various data visualizations and to receive feedback about workflow integration among diverse clinicians

Data Analyses

All statistics will be calculated using SAS Version 9.3 (SAS Institute Inc.). Baseline demographic and clinical characteristics of enrolled participants are summarized by mean and SD for continuous variables and frequency and percentage for categorical variables. A significance level of 0.05 is considered as statistically significant for all tests.

Figure 3. Example data visualizations from multiple mobile health technologies.



Using the data collected in Prompt, we will create data visualizations using 2 different data visualization software packages (Tableau and R) and pilot their use with participants via a phone interview. We will use the interviews as an iterative process to discover how to present the visualizations back to patients and to refine the visualizations. We will start with plotting the actual data transmitted from each of the devices from individuals over the entire follow-up time to show patients overall trend in blood glucose, exercise level, and weight. For blood glucose data, we will add a band of ideal blood glucose range to help patients visualize if their measurements are within targeted range. For Fitbit data, we will plot both the average active steps daily and weekly over time and also plot the steps by weekday to explore if there are any cyclic and long-term drift trends in their exercise level. For weight data, similarly, we will plot both daily weight and weekly average to show overall trend. Further details on this approach are described elsewhere [24].

Patterns of Missing Data and Attrition

The primary analytical aim of this study is to estimate individuals' performance of all the tasks involved in the daily monitoring of weight, exercise, and glucose and responding to the SMS text message surveys for medication adherence. A proxy for this estimate will be the percentages of the 180 days of data points from the Fitbit, the wireless scale, and the glucometer that were transferred. We will calculate the percentage of 180 days on which each type of data was transferred for each participant. Patient's response to SMS text message surveys to medication adherence will be calculated by the number of surveys received out of 13 time points (baseline and every other week for 6 months). To examine if the performance of all tasks differ by important clinical groups, including age (<50 vs \geq 50 years), HbA_{1c} group, (<7 vs \geq 7,

respectively), and race (white vs black or other non-white race), we will then test whether this percentage differed by different group variable using independent samples *t* tests.

To further explore the trend in performance of all tasks (using devices for daily monitoring), we will compute proportions of missing data for each person over 2-week time periods for the entire 6-month follow up time for weight, Fitbit, and blood glucose. We will construct empirical summary plot of biweekly missingness. This consisted of plots of mean percentage missing at each biweekly period over 13 biweekly periods. At each time point, bars representing 1 SE below and above the mean are also included. To examine if the trends differ by important clinical group variables, these plots will also be produced by different age group, HbA_{1c} group, and race. We will fit a generalized linear model with this proportion as the dependent variable. Predictors included age and HbA_{1c} group, and race, with each predictor tested in separate models. Time will also be included to assess change in biweekly missingness over time, as well as interactions between time and each predictor, to assess differences in change in biweekly missingness over time by age and HbA_{1c} group and race. We will also test the change in perceived usefulness and ease of use of the devices by conducting a paired *t* test on these measures between baseline and 6-month follow-up survey.

We recognize that even though individuals may not provide data, they could still be compliant in weighing themselves, exercising, drawing blood glucose, and taking medication. The data may not transmit because (1) the device was not charged or (2) internet service was not available. Nevertheless, we will assess overall feasibility by examining data, which reflect both performing the measurement and being responsible for

transmitting the data. Since in practice, this will be required for real-time monitoring.

Patient Interviews

A coding team comprised 4 pre- and postdoctoral students trained in qualitative analysis will code these qualitative data. We will analyze the transcribed interview data using directed content analysis [25]. We will create a codebook that describes the creation of inductive and deductive codes and themes. Codes will be developed and analyzed in the context of diabetes self-management, the use of mobile technologies to support self-management, and the data visualizations. We will use Microsoft Excel in the initial first-level coding process and then upload data into Atlas.ti version 8 (Berlin, Germany) to support higher level coding and analyses [26]. First, the coding team will independently read and code transcripts and then meet to discuss coding and emerging themes and reconcile coding differences. This process will continue until first-level coding is complete. Following the completion of first-level coding, we will begin to develop more refined codes and to identify patterns of data across all transcripts. The coding team will ensure reliability and validity throughout the process by meeting regularly to discuss code and theme development, creating a codebook with agreed upon definitions, and recording an audit trail of our actions.

Clinician Interviews

We will use the same process to code the transcribed clinician interviews. The themes and codes from the interviews will be mapped onto visual data trajectories developed from the mobile devices. We will then examine the data at particular points in time over the 6-month period to identify trends. The data will be described in relation to time of the year, demographics, and clinical characteristics of patients.

We will conduct interviews in which we will present data trajectories and interview themes and explore ways to address collaborative work for self-monitoring and addressing challenges in diabetes self-management. The analysis team, in collaboration with the study recruiter, will conduct a preliminary analysis of field notes and transcribed interviews. Text data will be analyzed as described above.

Results

This study has received IRB approval. Enrollment of patients was completed in March 2018 with a sample size of 60 patients. At the patient level, data collection is complete, but data analysis is pending. At the clinician level, data collection is ongoing.

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Up to 20 health care providers will be enrolled for the clinician interviews.

Discussion

Overview

This study provides an overview of the methodology used in a study examining the feasibility of collecting near real-time data from mHealth technologies for patients with T2DM. Determining whether it is feasible for patients to use multiple mobile devices to self-manage their diabetes is an important first step in developing effective personalized care delivery strategies.

In addition to exploring the use of mobile technology to manage chronic illness, our approach has several strengths. First the use of mixed methods to address our aims is a strength of this study. The convergence of both quantitative and qualitative elements, data collection techniques, and analyses will facilitate a more in-depth and comprehensive approach to and understanding of diabetes self-management [27]. Another strength of our study is the use of data visualizations during participant interviews as an innovative approach to enhance discussion and gain insight into the challenges and successes participants experienced in diabetes self-management with mobile devices over the past 6 months. Presenting data this way could stimulate discussion and improve communication by graphically displaying patterns and trends [28-30].

We do acknowledge several limitations to this study. The first is the limited sample size, which does not allow us to draw statistical conclusions from the data. We are not testing the effect of any intervention, so cannot assess the impact on diabetes outcomes of using these technologies. Finally, we were not able to integrate these data into the EHR to assess pragmatic aspects of the use of the data at this time within the health system.

Conclusions

Our study is among the first to seek answers to the many questions related to integrating patient data from mobile devices into diabetes self-management care delivery models and EHRs. Questions such as how long patients will track multiple types of diabetes-related data, which strategies will best help patients self-manage their diabetes using self-generated data, and how clinicians might effectively guide patients to better manage their disease in near real time need to be addressed in the emerging era of digital health.

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Conflicts of Interest

DS is a consultant for Omada Health.

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Abbreviations

API: application programming interface
eHealth: electronic health
EHR: electronic health record
HbA_{1c}: hemoglobin A_{1c}
IRB: institutional review board
mHealth: mobile health
REDCap: Research Electronic Data Capture
SMS: short message service
T2DM: type 2 diabetes mellitus

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Protocol

An Affirmative Coping Skills Intervention to Improve the Mental and Sexual Health of Sexual and Gender Minority Youth (Project Youth AFFIRM): Protocol for an Implementation Study

Shelley L Craig^{1*}, PhD; Lauren B McInroy^{2*}, PhD; Andrew David Eaton^{1*}, MSW; Gio Iacono^{1*}, MSW; Vivian WY Leung^{1*}, MA; Ashley Austin^{3*}, PhD; Cheryl Dobinson^{4*}, MA

¹Factor-Inwentash Faculty of Social Work, University of Toronto, Toronto, ON, Canada

²College of Social Work, The Ohio State University, Columbus, OH, United States

³Ellen Whiteside McDonnell School of Social Work, Barry University, Miami Shores, FL, United States

⁴Planned Parenthood Toronto, Toronto, ON, Canada

* all authors contributed equally

Corresponding Author:

Shelley L Craig, PhD

Factor-Inwentash Faculty of Social Work

University of Toronto

246 Bloor St W

Toronto, ON, M5S 1V4

Canada

Phone: 1 4169788847

Email: shelley.craig@utoronto.ca

Abstract

Background: Sexual and gender minority youth (SGMY, aged 14-29 years) face increased risks to their well-being, including rejection by family, exclusion from society, depression, substance use, elevated suicidality, and harassment, when compared with their cisgender, heterosexual peers. These perils and a lack of targeted programs for SGMY exacerbate their risk for HIV and other sexually transmitted infections. Cognitive behavioral therapy (CBT) interventions support clients by generating alternative ways of interpreting their problems and beliefs about themselves. CBT, tailored to the experiences of SGMY, may help SGMY improve their mood and coping skills by teaching them how to identify, challenge, and change maladaptive thoughts, beliefs, and behaviors. Based on the promising results of a pilot study, a CBT-informed group intervention, AFFIRM, is being tested in a pragmatic trial to assess its implementation potential.

Objective: The aim of this study is to scale-up implementation and delivery of AFFIRM, an 8-session manualized group coping skills intervention focused on reducing sexual risk behaviors and psychosocial distress among SGMY. Our secondary aim is to decrease sexual risk taking, poor mental health, and internalized homophobia and to increase levels of sexual self-efficacy and proactive coping among SGMY.

Methods: SGMY are recruited via flyers at community agencies and organizations, as well as through Web-based advertising. Potential participants are assessed for suitability for the group intervention via Web-based screening and are allocated in a 2:1 fashion to the AFFIRM intervention or a wait-listed control in a stepped wedge wait-list crossover design. The intervention groups are hosted by collaborating community agency sites (CCASs; eg, community health centers and family health teams) across Ontario, Canada. Participants are assessed at prewait (if applicable), preintervention, postintervention, 6-month follow-up, and 12-month follow-up for sexual health self-efficacy and capacity, mental health indicators, internalized homophobia, stress appraisal, proactive and active coping, and hope. Web-based data collection occurs either independently or at CCASs using tablets. Participants in crisis are assessed using an established distress protocol.

Results: Data collection is ongoing; the target sample is 300 participants. It is anticipated that data analyses will use effect size estimates, paired sample *t* tests, and repeated measures linear mixed modeling in SPSS to test for differences pre- and postintervention. Descriptive analyses will summarize data and profile all variables, including internal consistency estimates. Distributional assumptions and univariate and multivariate normality of variables will be assessed.

Conclusions: AFFIRM is a potentially scalable intervention. Many existing community programs provide safe spaces for SGMY but do not provide skills-based training to deal with the increasingly complex lives of youth. This pragmatic trial could make a significant contribution to the field of intervention research by simultaneously moving AFFIRM into practice and evaluating its impact.

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KEYWORDS

sexual and gender minorities; youth; coping behavior; pragmatic clinical trial; cognitive behavioral therapy; implementation science

Introduction

Intersecting Vulnerabilities of Sexual and Gender Minority Youth

Compared with their cisgender, heterosexual peers [1-8], sexual and gender minority youth (SGMY, aged 14-29 years) face increased risks to their well-being, including rejection by family [9], exclusion from society [10], depression [10,11], substance use [12], elevated suicidality [13,14], and harassment [15-19]. In the pilot study that informed this protocol, participants attributed the stress of their SGM status as a significant contributor to their risks [20]. Yet, there remains a dearth of research and services for SGMY [21]. Existent risks and the lack of targeted programs [21-25] exacerbate their risk for HIV infection [12,26]. In 2013, nearly 25% of the 2090 Canadians diagnosed with HIV were aged between 15 and 29 years, and 43% of those youth contracted HIV through same-sex exposure (compared with only 26% in 2004) [12,26,27].

There is a particular lack of research with female-identified SGMY, who report higher rates of HIV-related risk behaviors than their male-SGMY and non-SGMY peers [28-37]. These risks include sex with multiple partners [28,29], unprotected vaginal intercourse [30], injection drug use [31], and pregnancy [32,33]. SGMY risk factors are further increased in female-identified SGMY, as they have higher rates of mental health concerns compared with male-identified SGMY, including depressive symptoms and suicidality at younger ages, suggesting earlier onset of co-occurring concerns [34-36].

Thus, multiple factors such as depression [10], sexual health-risk behaviors [31], discrimination [16] and perceptions that HIV is not a threat [28-30] may interact to exacerbate SGMYS' risk [3]. Female-identified SGMY—as well as transgender, gender diverse, and racialized SGMY—experience even greater vulnerabilities to mental health stressors, which in turn can exacerbate sexual health risk [38-40]. Holistic interventions that affirm SGMY identities and cultivate a sense of community, may mitigate these risks [41,42]. As nearly 70% of premature adult deaths are related to behaviors initiated in adolescence (eg, unsafe sex and substance abuse) [43], this age range is a critical period to implement interventions that help youth cope with the risks they experience.

Theoretical Approach

Syndemics, minority stress, and community-based research theories provide insight toward SGMY intervention

development. Syndemics theory highlights social inequities as root causes of synergistic interaction of 2 or more coexistent issues (eg, SGMY status and depression) or mutually reinforcing epidemics (eg, HIV) contributing to health disparities among marginalized populations [40,44-47]. Vulnerable individuals may encounter lifelong adversity, particularly from social marginalization and stigma [45], posing a greater risk for problems [44,46] that can lead to poorer sexual and health outcomes [47]. For SGMY, as the number of psychosocial health problems increases, the risk of major negative health outcomes also increases [47-49]. To comprehensively combat sexual health risks, overlapping vulnerabilities must be addressed concurrently [48,49].

Minority stress theory posits that marginalized populations experience a unique form of stress because of conflict between their identities and social expectations [50-53]. It partially explains why SGMY encounter disproportionate chronic stress, discrimination, and victimization [52], which subsequently increases likelihood of sexual risk taking, depressive anxiety, and substance abuse disorders [52,53]. An influential stressor, internalized homophobia (negative beliefs about one's own SGMY status) [54], is related to unprotected sex [54,55] and increased depression [10]. Minority stress may increase internalized homophobia and stress-related cortisol production associated with heightened depression, anxiety, and suicidal ideation [50,54]. SGMY may not learn to cope with stressors through traditional means (eg, family or community support) [55-58], resulting in vulnerability to health and mental health threats [48] and increasing likelihood of engaging in risky behaviors [49]. As traditional approaches do not address many of the co-occurring stressors for SGMY, interventions that enhance coping skills are critical [59-82].

Building on a rich history of community engagement in HIV/AIDS service delivery, community-based research is critical to intervention development with SGMY, particularly in diverse communities [83-88]. Community-based approaches build on shared values, belief systems, and social practices, allowing for discussions of HIV and sexual health-risk behaviors in a culturally sensitive manner [84-87]. Youth interventions developed in partnership with community also have a much higher rate of agency adoption than those with only academic stakeholders [88]. It is increasingly recognized that future youth interventions must include nimble design and flexible delivery [89-91]. Community feasibility studies improve an intervention's implementation potential while maintaining rigor in evaluation [92,93].

Affirmative Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) suggests that people's behaviors and emotions are influenced by their perceptions of life events [60-62] and how one interprets their situation will impact the way they feel or behave [63]. As an example, a person who is depressed may experience unhelpful interpretations or perceptions of themselves because of their problems and life events [61,62]. CBT interventions support clients by generating alternative ways of interpreting their problems and beliefs about themselves [59,63]. Generating alternative ways of thinking and beliefs may facilitate positive changes in one's behaviors and emotional states [64].

CBT tailored to the experiences of SGMY may help improve mood and increase coping by teaching youth how to identify, challenge and change maladaptive thoughts, beliefs, and behaviors [59,66,67]. Continuing to practice CBT skills after each session (ie, via an action plan) further strengthens adaptive and affirming beliefs and behaviors. This process may lead to changing deeply ingrained problematic ways of thinking and behaving [65-67]. The process of identifying and challenging unhelpful beliefs about sexual and gender identities in an affirming and supportive environment may facilitate a decrease in internalized homo-, bi-, and transphobic cognitions and emotions and lead to improvement in mood and coping [67-69]. Ultimately, CBT within an affirmative therapeutic context can support SGMY in challenging maladaptive coping skills (eg, negative beliefs, isolation, substance misuse, and self-harm) and learning adaptive coping skills (eg, balanced thinking, enhancing social supports, and goal-setting) through education, modeling, practicing skills, and positive reinforcement [15,69].

CBT has been effective at treating depression and sexual health-risk behaviors among minority status adolescents [70-72] and lesbian, gay, bisexual, transgender, and queer (LGBTQ) adults [66,72]. However, its effectiveness for SGMY is largely unknown [69]. While the majority of studies do not assess long-term treatment gains, some evidence suggests that such interventions have mental and sexual health benefits for minority populations [79]. Longitudinal research is needed to determine the sustained effectiveness of CBT interventions on adolescent and young adult SGM populations [80]. A few existing studies show promise with sustained reductions in depression found at 12 months [76,77] and 18 months [78], as well as sexual risk of young men who have sex with men at 6 months [72]. Despite the calls for resilience and coping-based research and interventions for SGMY [80], scholarship has maintained a focus on negative health and psychosocial outcomes [81]. To date, no studies have identified the utility of a large-scale implementation of CBT tailored for community-based, diverse groups of SGMY and drawing on an affirmative approach. This study is designed to fill that gap.

Methods

AFFIRM Structure

This pragmatic trial is designed to evaluate AFFIRM, a manualized group intervention for SGMY, which follows the structure described in [Textbox 1](#) and is described in more detail elsewhere [20].

Textbox 1. Description of AFFIRM intervention (session focus and session activities).

Session 1 focus

- Introduction to cognitive behavioral therapy (CBT), exploring lesbian, gay, bisexual, transgender, and queer (LGBTQ)+ identities, and understanding minority stress.

Session 1 activities

- Introductions
- Discussing the theory and purpose of CBT approaches
- Exploring stress and minority stress
- Understanding the causes of stress in our lives

Session 2 focus

- Understanding the impact of anti-LGBTQ attitudes and behaviors on stress.

Session 2 activities

- Check in and review
- Examining homophobia, heterosexism, and transphobia at the individual, institutional, and cultural level
- Identifying how these experiences impact thoughts, feelings, and behaviors
- Fostering strategies for both coping with and combating anti-LGBTQ discrimination at all levels

Session 3 focus

- Understanding how thoughts impact feelings.

Session 3 activities

- Check in and review
- Distinguishing between thoughts and feelings
- Exploring how thoughts influence feelings and behaviors
- Identifying counterproductive thinking patterns
- Recognizing negative self-talk and feelings of hopelessness
- Learning thought stopping

Session 4 focus

- Using thoughts to change feelings.

Session 4 activities

- Check in and review
- Increasing positive thinking and feelings of hope
- Changing negative thoughts to positive thoughts
- Challenging negative thinking and internalized homophobia/negative feelings through the ABCD (activating event, belief, consequence, and debate) method

Session 5 focus

- Exploring how activities impact feelings.

Session 5 activities

- Check in and review
- Examining the impact of various activities on feelings
- Identifying supportive and identity-affirming activities
- The impact of LGBTQ-affirming activities on feelings

Session 6 focus

- Planning to overcome counterproductive thoughts and negative feelings.

Session 6 activities

- Check in and review
- Distinguishing between clear and unclear goals
- Identifying short, mid-, and long-term goals
- Creating a sexual health plan
- Fostering hope for the future

Session 7 focus

- Understanding the impact of minority stress and anti-LGBTQ attitudes or behaviors on social relationships.

Session 7 activities

- Check in and review
- Anti-LGBTQ discrimination can lead to feelings of discomfort around others
- Responding to discrimination or harassment in social situations
- Learning to be assertive

Session 8 focus

- Putting it all together: developing safe, supportive, and identity-affirming social networks.

Session 8 activities

- Check in and review
- Maintaining a healthy social network: attending to thoughts, expectations, feelings, and behaviors within relationships
- Identifying a plan for building a supportive network

Research Questions, Hypotheses, and Objectives

This project is intended to scale-up implementation and delivery of AFFIRM, an 8-session manualized group coping skills intervention focused on reducing sexual risk behaviors and psychosocial distress among SGMY. This project aims to decrease sexual risk taking, depression, and internalized homophobia and increase levels of sexual self-efficacy and proactive coping among SGMY (ages 14-29 years). This project has the following research questions:

1. To what extent can AFFIRM be feasibly implemented in a range of practice settings, such as community health centers, family health teams, and community-based organizations?
2. What are the facilitative conditions and implementation barriers to effective delivery of AFFIRM?
3. How does participation in an affirmative coping skills intervention (AFFIRM) impact the psychosocial distress and sexual self-efficacy of SGMY?

Given these research questions, the study has the following hypotheses:

Hypothesis 1: AFFIRM can be feasibly implemented in a range of practice settings, and SGMY will have high rates of acceptability of the intervention.

Hypothesis 2: SGMY participating in AFFIRM will show significantly greater decreases in psychosocial distress (eg, internalized stigma and depression)

compared with wait-listed controls (ie, SGMY attending existing community programs).

Hypothesis 3: SGMY participating in AFFIRM will show significantly higher levels of sexual self-efficacy and coping compared with wait-listed controls.

Eligibility Criteria

Inclusion and Exclusion Criteria

Inclusion criteria are as follows:

- Aged 14 to 29 years at the time of screening
- Identifies as a sexual and/or gender minority
- Reads, writes, and speaks fluent English
- Is interested in participating in the 8-session AFFIRM Intervention.

Exclusion criteria are as follows:

- Assessed by the Facilitation Team to be in crisis (ie, high risk of suicidality)
- Warranting a more intensive intervention

Trial Design

This pragmatic quasi-experimental study uses a stepped wedge wait-list crossover design (SWWCD), whereby all participants receive the intervention in clusters [94-98]. SWWCD has been utilized in community-based research where traditional randomization with a no-treatment condition is unethical, unacceptable to community stakeholders, or not feasible [98].

This study will examine the effects of participating in an AFFIRM intervention group (each consisting of 6-10 participants) compared with wait-list for SGMY (ages 14-29 years).

Randomization

Randomization is not possible in this study because of participants' registration through various CCAS.

Blinding

Participants are not blinded as they know whether they are assigned to intervention or wait-listed control. Facilitators are blinded to outcome assessments as outcomes are administered via survey weblink.

Allocation

Participants are allocated in an approximate 2:1 fashion to intervention: wait-listed control. This ratio is based on the availability of practice sites to implement AFFIRM in their clinical practices [96,97]. Importantly, similar to community programming, the groups are constructed to be developmentally appropriate. Participants in a particular intervention group are typically within an age range of 3 to 5 years. For example, a 14 year old would generally not be placed in a group with anyone older than 18 years. Groups of people aged between 18 and 29 years may have a broader age range, as developmental stage is not as relevant for established adults. AFFIRM also consists of mixed identity groups (eg, sexual identities and gender identities), based on community feedback. This means that a single intervention group could comprise SGMY from a range of identities. Many community organizations do not focus on 1 particular SGM subpopulation but instead serve all SGMY.

Framework

This pragmatic trial is designed to assess AFFIRM's implementation potential in real-world practice conditions.

Study Setting

Collaborating community agency sites (CCASs) in a variety of urban, suburban, and rural communities across Ontario, Canada, are hosting a series of AFFIRM intervention groups, each consisting of 6 to 10 SGMY (aged 14-29 years). At present, there are 23 CCAS, of which 12 are urban, 8 are suburban, and 3 are rural, with more communities likely to be added in subsequent years of the study.

Justification

Age group of 14 to 29 years have been identified as a crucial time for SGMY as they start to come out, address family issues, and transition to postsecondary education and early employment [1-3]; as such, this age may be the ideal time for an affirmative CBT intervention. As SGMY face greater well-being risks than their cisgender, heterosexual peers, queerness is also an important qualifier for this study [4-8]. This study focuses on English-speaking CCASs in Ontario. Commitment to an 8-session intervention and exclusion because of crisis are criteria common to group intervention research [99].

Interventions

AFFIRM Intervention (Experimental)

AFFIRM aims to help SGMY develop coping skills through a combination of education (delivered by facilitators) and rehearsal (ie, simulation of real-life experiences) in a manner that affirms (ie, validates) participants' sexual and gender minority identities, as well as their experiences. Affirmations are explicated through (1) acknowledging and validating the unique struggles experienced by SGMY (eg, homophobia); (2) exploring how participants currently cope with SGM-specific stressors (eg, familial disapproval); (3) facilitating the development of realistic alternative ways of thinking and behaving that affirm youth identities and sexual health choices while integrating healthy ways of coping with internal/external stressors; and (4) enhancing social connection between participants. AFFIRM also includes an overview of sexually transmitted infections (STIs), HIV/AIDS and hepatitis C, and focuses on activities that promote harm reduction, such as a personalized sexual safety plan regardless of accumulated sexual experience. Each series of AFFIRM begins with an orientation session for introductions and discussion of the 8-session schedule. Each of the 8 group sessions of AFFIRM then consist of (1) warm-up/review; (2) discussion of session objectives; (3) behavioral activities; (4) practice and rehearsal; and (5) group reflection and summary.

Wait-List (Control)

If they choose, wait-listed participants will attend existing community programs, considered to be treatment as usual for community intervention studies. In a SWWCD study, sites offer iterations of the intervention in phases; individuals in this study will move from the wait-list to AFFIRM over time [94]. The wait-list time frame is minimized as much as possible to ensure an ethical research process. As it is increasingly acknowledged that evidence-based practice requires community and practice-based research [95], alternative intervention designs that are rigorous and work in *the real world* are needed. Such designs adapt to local needs and often have better intervention outcomes [96-100].

Discontinuation Criteria

Participants who are in crisis (eg, actively suicidal) at any point during their in-person participation in the AFFIRM intervention are immediately assessed, and appropriate steps are taken to address their individual situation—up to and including being taken to local support services or hospitals by AFFIRM facilitators. Participants who are in crisis are withdrawn from the intervention and the study. A distress protocol (Multimedia Appendix 1) and crisis response form (Multimedia Appendix 2) have been developed for AFFIRM facilitators and is systematically implemented throughout the intervention when participants indicate signs of distress. Importantly, to enhance participants' safety and well-being, as part of the Web-based data collection, participants are asked at various points if they need immediate help and are provided with immediate resources, including national crises organizations (such as Kids Help Phone Canada or the Trevor Project) with 24-hour counseling via

phone, chat, and/or SMS text messaging (short message service, SMS).

Protocol Adherence Strategy

The Core Facilitation Team (delivering the AFFIRM intervention) comprises social workers with a master's degree who are trained in AFFIRM, who meet weekly with the principal investigator to review study progress and ensure protocol adherence. All iterations of AFFIRM implemented in this study are cofacilitated by (1) one of the members of the Core Facilitation Team and (2) 1 representative of the CCAS (eg, a social worker, nurse, or community worker) where the intervention group is being held or another community-based professional, all of whom are trained in the AFFIRM intervention.

Concomitant Care and Interventions

There are no restrictions on participant involvement in other studies and/or interventions as a result of their participation in this project. While this prevents accounting for confounding factors (eg, combined effect of participating in another intervention), the geographic context of services in Ontario is such that it is unlikely that participants would have access to SGMY-specific affirmative interventions outside of this study.

Outcomes

Primary

The primary outcomes of this study are feasibility and acceptability. Feasibility will be measured by (1) number of sites that implement AFFIRM; (2) number of times each site runs the AFFIRM intervention; (3) availability of facilitators; and (4) number of participants that enroll, commence, and complete the intervention. Acceptability will be assessed through mixed-method participant and facilitator evaluations.

Secondary

This study's secondary outcome is implementation fidelity, that is, how closely AFFIRM facilitators adhere to the manualized intervention. This will be assessed through analysis of session audio recordings and facilitator process notes by analysts separate from the Core Facilitation Team.

Exploratory

Exploratory outcomes include changes in sexual health self-efficacy and capacity, mental health indicators, internalized homophobia, stress appraisal, proactive and active coping, and hope. These outcomes will be assessed through measures such as: the Sexual Health Capacity Scale [100], the Abstinence and Protection Self-Efficacy Scale [101], the Beck Depression

Inventory-II [102], the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) Self-Rated Level 1 Cross-Cutting Symptom Measure-Child [103], the Stress Appraisal Measure for Adolescents [104], the Brief COPE [105], the Proactive Coping Inventory for Adolescents-A [106], the Adult Hope Scale [107], the Internalized Homophobia Scale [108], the Current Mood Scale [109], the Everyday Discrimination Scale [110], and the LGBTQ Microaggression Scale [111] (see Table 1).

Data Collection

AFFIRM participant data are exclusively collected using Web-based surveys, *each of which takes approximately 20 min to complete*. However, data collection takes place in 2 different settings: (1) via tablets (eg, Android tablets) while at the intervention locations (ie, some Web-based screenings, some pre- and posttests); and (2) independently Web-based (eg, some Web-based screenings, some pretests, or follow-ups). Secure collection of data is facilitated by the use of software with secure servers (Qualtrics). Instead of a unique identifier, which participants could forget over the course of the year, participants report their name, age, date of birth, 2 email addresses, gender identity, and sexual orientation at each time point.

Measures

All measures are completed at all time points, including demographics, as identities and circumstances are generally very flexible for SGMY because of their developmental stage, marginalized sexual and/or gender identities, and contextual circumstances. Measures include the following: (1) *demographics* (eg, age, sexual identity, gender identity, ethno-racial identity, and socioeconomic-status); (2) *sexual health self-efficacy and capacity*, including sexual health capacity [100] and abstinence and protection self-efficacies [101]; (3) *mental health*, including current mood [109], depression [102], and DSM-V cross-cutting symptoms [103]; (4) *coping*, including proactive coping [105] and coping strategies such as active coping, denial, and humor [106]; (5) *stress appraisal*, including perceiving stress as challenge or threat, and seeking out resources to overcome stress [104]; (6) *hope*, including agency and planning to meet goals [107]; (7) experiences with everyday discrimination [110]; (8) *internalized homophobia* [108]; (9) microaggressions, including interpersonal and environmental microaggressions [111]; (10) *AFFIRM Satisfaction Survey*, a 20-item questionnaire developed for AFFIRM completed after intervention delivery, which includes questions regarding (1) satisfaction, (2) overall experience, and (3) suggestions for improvement. For details of adaptation of existing survey measures, please see Table 1.

Table 1. Survey instruments.

Construct	Scale, study	Items	Modification
Sexual health self-efficacy and capacity	Sexual Health Capacity Scale [100]	5	Change scale from 5-point (1-5) to 4-point (1-4); Excluded 2 items; Added 1 item: "I understand how my mental and sexual health are connected."
	Abstinence Self-efficacy Scale [101]	4	Excluded 6 items; Wordings modified
	Protection Self-efficacy Scale [89]	8	Added 4 items: "I can ask for/get a test for HIV and STIs from a doctor, Planned Parenthood, or a clinic."; "I can read or think about my sexual health plan before having sex."; "I can access/get information about my sexual health (websites, agencies, trusted adults, professionals, or friends)."; "I can manage my own sexual health."; Wordings modified
Mental health	Beck Depression Inventory-II [102]	20	No modifications
	DSM-5 ^a Self-Rated Level 1 Cross-Cutting Symptom Measure—Child [103]	20	Excluded 5 items from section 9 (Psychosis) and 10 (Repetitive Thoughts and Behaviors); Slightly modified 1 item
	Current Mode Scale [109]	6	Wordings simplified
Coping	Brief COPE [105]	28	2 items slightly modified
	Proactive Coping Inventory for Adolescents-A—Reflective Coping subscale [106]	11	4 items slightly modified
Stress appraisal	Stress Appraisal Measure for Adolescents [104]	13	1 item excluded; 1 item slightly modified
Hope	Adult Hope Scale [107]	12	No modifications
Internalized homophobia	Internalized homophobia [108]	10	Separated into 2 sections for microaggressions toward sexual orientation and gender identity minorities
Discrimination and microaggressions	Everyday Discrimination Scale [110]	7	2 items excluded; 1 item slightly modified
	LGBTQ ^b Microaggressions Scale—Interpersonal subscale [111]	10	Excluded 10 items; Separated into 2 sections for microaggressions toward sexual orientation and gender identity minorities
	LGBTQ Microaggressions Scale—Environmental subscale [111]	5	Excluded 2 items; Added 2 items: "In my online environment it was OK to make jokes about LGBTQ+ people." and "I heard or read someone making fun of chosen pronouns."

^aDSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition.

^bLGBTQ: lesbian, gay, bisexual, transgender, and queer.

Participant Timeline

Table 2 shows the schedule of events. Participants complete a Web-based screening questionnaire, which includes their preferred site to participate in AFFIRM. For every 2 participants allocated to the intervention-only group, 1 participant is allocated to the wait-list group. The intervention-only group completes 4 data collection time points (pretest, posttest, 6-month follow-up, and 12-month follow-up). The wait-list group completes 5 data collection time points (prewait, pretest, posttest, 6-month follow-up, and 12-month follow-up). The prewait survey is completed immediately following their wait-listed control allocation, so that the pretest for the wait-list group serves as the follow-up on outcomes for the control group. Participants complete the pretests and posttests before the first week and at the last week of the intervention, respectively. The

Web-based pretest is completed independently shortly before the first group session. The posttest is completed on tablets (eg, Android tablets) at the intervention location following the final group session. Participants complete the prewait (if applicable), the 6-month follow-up, and the 12-month Web-based independent follow-up. Participants are reminded to participate via email and provided the link to the survey. If participants do not participate following the initial email, up to 2 follow-up emails are sent as reminders for each time point. The follow-up emails are sent at 2 weeks and 4 weeks after the initial email (ie, every 2 weeks for 1 month). If participants indicated in their Web-based screening that SMS text message or phone call is their preferred form of communication, they also receive follow-up SMS text messages at 2 to 4 weeks after the initial email.

Table 2. Schedule of events.

Visit details	Screening period			Study period (facilitator meeting; 8 weekly, 1-hour sessions)			Follow-up period	
Visit name	Screening survey	Prewait	Pretest	Orientation	Sessions 1-8	Posttest	6-month follow-up	12-month follow-up
Visit number.	-3	-2	-1	0	1,2,3,4,6,7,8	8	9	10
Week number	-8 to 0	-8 to 0	-8 to 0	0	1-8	8	32	56
Day number	-56 to 0	-56 to 0	-56 to 0	1-56	1-56	1-56	+224 to +238	+392 to +406
Visit window	±56	±14	±0	±0	±0	±0	±14	±14
Procedures								
Written informed consent	X ^a	— ^b	—	—	—	—	—	—
Entry criteria assessment	X	—	—	—	—	—	—	—
Participant demographics	X	—	—	—	—	—	—	—
Group session (intervention or wait-listed control)	X	—	—	—	—	—	—	—
Facilitator process notes	—	—	—	X	X	—	—	—
Sexual health self-efficacy and capacity	—	X	X	—	—	X	X	X
Mental health	—	X	X	—	—	X	X	X
Internalized queerness	—	X	X	—	—	X	X	X
Coping	—	X	X	—	—	X	X	X
Hope	—	X	X	—	—	X	X	X

^aProcedure conducted.

^bNot applicable.

Sample Size

Approximately 300 participants will participate in AFFIRM. Each CCAS has agreed to complete a minimum of 1 AFFIRM iteration, comprising 1 intervention group and 1 wait-list group. This sample was primarily determined to assess the implementation-based outcomes. In addition, this sample would be sufficient for analysis of exploratory objectives, as described below.

Recruitment

Potential participants are recruited in multiple ways (1) via CCASs and other local community organizations (which are provided with flyers and cards directing potential participants to the independent Web-based screening); (2) via emails to local organizations and community groups serving SGMY (which are provided e-versions of the flyers and cards); and (3) Web-based postings on Facebook and Instagram. The Web-based postings involve geographically and demographically targeted *paid boosts* using Facebook's Ad Manager.

Data Management and Monitoring

Data are downloaded from Qualtrics, cleaned, and saved as password-protected files on an encrypted research drive. After data collection and cleaning for the entire study is completed, the data will then be deleted from Qualtrics servers. A data

monitoring committee is not required at this stage, as the current phase is primarily focused on implementation acceptability in community sites; however, one will be formed before instigation of a larger trial.

Harms

As a psychosocial study, risks for adverse effects are negligible or nonexistent. The study's distress plan, discussed above, will be used if participants present in crisis.

Ethics and Dissemination

This study has been approved by the University of Toronto's HIV/AIDS Research Ethics Board (protocol ID#35229). As an uncontrolled, nonrandomized trial, registration at this stage was not completed. If this implementation stage proves promising and the study proceeds to a full-scale multicenter trial, a new protocol will be registered and submitted for publication before participant enrollment.

Results

It is anticipated that data analyses will use effect size estimates, paired sample *t* tests, and repeated measures linear mixed modeling (LMM) using SPSS to test for differences pre- and postintervention [112-114]. Descriptive analyses will summarize data and profile all variables, including internal consistency estimates. Distributional assumptions, univariate, and

multivariate normality of all variables will be assessed. Data determined to be missing at random will be imputed with the expectation-maximization method with importance re-sampling [113].

Clinically significant change estimates and repeated measures LMM will be used to compare the influence of participation in AFFIRM to wait-list on sexual health self-efficacy and capacity, internalized queerness, hope, and depression of SGMY [114]. To test the influence of intervention on multiple outcomes, LMM using both time and interaction terms will be fit using SPSS [115,116]. Repeated measures LMM is considered an improvement over classical repeated measures analyses (eg, repeated measures analysis of variance) because of frequent correlated errors and nonindependence of observations that are forbidden by the assumptions of standard general linear approaches [114-116]. LMM also allows for the exploration of time effects, which is a potential source of confounding because of the partially randomized nature of the design and assumption of no interaction between intervention effects and time [117]. A total of 2 mixed models will be constructed to test the relationship between the intervention condition (AFFIRM group or the treatment as usual or wait-list [TAU/WL] group) and change in outcome variables from pre- to postintervention. Model 1 will include time and condition and will indicate whether there is a significant change in outcome variables over time and if significant cross-sectional associations between treatment condition and outcome variables exist. In model 2, interaction terms will be added to assess the longitudinal associations between treatment condition and the change (slope) of outcome variable scores from pre- to postintervention. The interaction of multiple intersecting identities as well as site, group, and individual-level covariates will be included in this analysis. The impact of behavioral interventions also can be

identified through effect size [114]. The potential clinical significance of AFFIRM will be assessed by calculating Cohen *d* effect sizes, comparing percentages of participants at 2 time points. It is expected that compared with the TAU/WL group, the AFFIRM group will show statistically significant change in hypothesized outcomes. The use of similar sample sizes with multiple time points and measures is considered appropriate [112] and allows for analysis of change effects using data points. The qualitative data collected through the acceptability measures will be analyzed using content analysis with ATLAS.ti software by a minimum of 3 coders [118].

Discussion

AFFIRM is a potentially scalable intervention for SGMY as (1) AFFIRM fosters positive health behaviors by identifying and modifying less healthy behaviors; (2) participants learn how to better cope with minority stressors by rehearsing and having facilitators validate these emerging coping skills; and (3) AFFIRM's pilot showed positive results on mental and sexual health outcomes [20]. Other CBT-informed group interventions have been effective in reducing adolescent depression and sexual risk, improving mood and behavior, increasing HIV and STI knowledge, and improving self-efficacy [58-60]. This study's exploratory measures will assess if AFFIRM results in similar outcomes. Group interventions offer SGMY opportunities to learn, observe, and practice skills [79,89], as well as obtain support from peers experiencing similar difficulties [76,77]. Many existing community programs provide safe spaces for SGMY but do not provide skills-based training to deal with the increasingly complex lives of adolescents and young adults. This pragmatic trial could make a significant contribution to the field of intervention research by simultaneously moving AFFIRM into practice and evaluating its impact.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Distress protocol for AFFIRM intervention.

[[DOCX File, 15KB - resprot_v8i6e13462_app1.docx](#)]

Multimedia Appendix 2

AFFIRM crisis response form.

[[DOCX File, 18KB - resprot_v8i6e13462_app2.docx](#)]

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Abbreviations

CBT: cognitive behavioral therapy
CCAS: collaborating community agency site
DSM: Diagnostic and Statistical Manual of Mental Disorders
LGBTQ: lesbian, gay, bisexual, transgender, and queer
LMM: linear mixed modeling
SGMY: sexual and gender minority youth
STI: sexually transmitted infections
SWWCD: stepped wedge wait-list crossover design
TAU/WL: treatment as usual or wait-list

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Protocol

Stimulation of Nucleotide Oligomerization Domain and Toll-Like Receptors 2 to Enhance the Effect of Bacillus Calmette Guerin Immunization for Prevention of Mycobacterium Tuberculosis Infection: Protocol for a Series of Preclinical Randomized Controlled Trials

Michael Eisenhut¹, MD, FRCP, FRCPC, DTM&H

Luton&Dunstable University Hospital NHS Foundation Trust, Luton, United Kingdom

Corresponding Author:

Michael Eisenhut, MD, FRCP, FRCPC, DTM&H

Luton&Dunstable University Hospital NHS Foundation Trust

Lewsey Road

Luton,

United Kingdom

Phone: 44 01582491166

Email: michael_eisenhut@yahoo.com

Abstract

Background: Bacillus calmette guerin (BCG) immunization has been associated with a reduction in *Mycobacterium tuberculosis* (MTB) infection. BCG immunization has been shown to enhance innate immunity. This effect of BCG can be explained by an enhancing effect on innate immunity.

Objective: This study aimed to test the following hypotheses: (1) BCG immunization can prevent infection with MTB, (2) prevention of infection occurs via stimulation of NOD2 (nucleotide oligomerization domain) and toll-like receptors 2 (TLR2), and (3) the effect of BCG immunization on prevention of infection with MTB can be enhanced by giving stimulators of NOD2 and TLR2.

Methods: To detect the influence of immunization on infection rates, the ultralow dose (ULD) infection model is used. The infection rate of mice vaccinated with BCG and exposed after 6 weeks to ULD of MTB and unvaccinated mice are compared via cultures of lung homogenates and interferon (IFN) gamma release assay. If a reduced infection rate by BCG immunization is confirmed, the experiment is repeated by giving BCG combined simultaneously or in time sequence with the enhancers of innate immunity murabutide or beta-glycan. The influence of murabutide or beta-glycan alone on infection rates is investigated. To quantify the contribution of innate immunity levels of tumor necrosis factor, IFN gamma expression, histone H3 K4me3 trimethylation, and concentrations of monocytes with features of activation of innate immunity as defined by the Ly6Chigh as well as CD11b positive phenotype in immunized versus unimmunized infected and uninfected mice in the various immunization protocols is compared. The experiments will be repeated with prior application of the inhibitors of epigenetic programming of innate immunity histone methyltransferase inhibitor 5'-deoxy-5'-methylthio-adenosine and histone acetyl transferase inhibitor epigallocatechin-3-gallate. The influence of BCG on innate immunity is further corroborated by a prospective observational study in human infants.

Results: Investigations of derivatives of muramyl dipeptide (MDP) to enhance early immunity in the C57BL/6 mouse strain (mice aged 7 weeks) by another group used 300 micrograms per mouse of oil-associated 6-0-mycoloyl-N-acetylmuramyl-L-alanyl-D-isoglutamine (mycol-MDP) 50/50 mixed with Freund's incomplete adjuvant. Comparison of colony-forming unit (CFU) count in the lungs 3 weeks after aerosol challenge with *Mycobacterium bovis* of groups (n=5) between groups receiving mycol-MDP in oil emulsion (see above) versus controls (n=5) showed a significantly lower CFU count of 94.5 x10⁶ (SD 22.0) in cases versus controls with 204.0 X 10⁶ (SD 77.6). It is important to note that after elimination of T-cells in this model, a reduction of CFU in lungs of mice treated with mycol-MDP persisted albeit without statistical significance, which was possibly related to the small number of animals used.

Conclusions: Demonstration of a reduction of MTB infection by enhancement of innate immunity could show a new approach to improving vaccine efficacy against this pathogen.

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KEYWORDS

innate immunity; BCG; bacillus calmette guerin vaccine; Mycobacterium tuberculosis infection; toll-like receptors

Introduction

Background

Bacillus calmette guerin (BCG) immunization has been associated with a reduced reactivity of interferon (IFN) gamma release assays for Mycobacterium tuberculosis (MTB) infection in exposed children [1]. This finding is compatible with a reduction of infection because of an abortion of infection before engagement of T-effector cells induced by an enhancement of innate immunity by BCG immunization [2,3]. Previous vaccination studies used mouse models with infection of all mice and vaccine efficacy identified by reduced organ colony forming units. To demonstrate that BCG immunization can reduce MTB infection experimentally, one needs to reduce the aerosol inoculation dose to an amount that does not overwhelm first line innate immunity and which enables detection of a lack of engagement of adaptive immunity in form of T-effector cells. In the ultralow dose (ULD) model, infection rate is measurable, and the ULD model can be used to identify host or bacterial factors that modulate the initial infection event and may be used to assess the effects of vaccination on the infection event by comparing infection rates in control and vaccinated groups exposed to the same aerosol [4]. Should a reduction of MTB infection in BCG immunized mice be confirmed with the above experiment, further experiments can be conducted investigating both the underlying mechanisms as well as ways to enhance the effect of BCG by identification of compounds able to reduce MTB infection by enhancing innate immunity with and without concomitant BCG immunization. Components of innate immunity potentially modifiable are pattern recognition receptor signaling including toll-like receptor 2 (TLR2) signaling by action of muramyl dipeptide (MDP) derivatives with a single octanoyl or stearoyl fatty acid chain, nucleotide oligomerization domain (NOD) 1 by H-Ala-D-γ-Glu-diaminopimelic acid, and NOD 2 signaling also by use of MDP, which is a stimulator of NOD expression and possibly murabutide (see rationale and protocol in [3]), a nontoxic derivative of MDP [5-10]. Simultaneous stimulation of TLR 2 and NOD 2 has hereby been shown to be associated with a synergistic effect on antimycobacterial cytokine production [6]. The most powerful stimulator of innate immunity may be yeast-derived beta glucan through stimulation of the intramembranous C-type lectin receptor dectin-1 [11,12]. Essential effector mechanism of innate immunity coupled to pattern recognition receptor stimulation is the induction of tumor necrosis factor (TNF) and IFN gamma production in monocytes through action of nuclear factor kappa B. TNF and IFN gamma enhance autophagy and production of nitric oxide metabolites toxic to mycobacteria [3,13].

NOD 2 stimulation has previously been shown to lead to recruitment of Ly6C^{high} and CD11b positive monocytes, which were found to be associated with NOD2 stimulation, and which

can, therefore, be used as a marker for stimulation of innate immunity [14].

Hypotheses

The hypotheses of this research are as follows:

- BCG immunization can prevent infection with MTB
- Prevention of infection occurs via stimulation of NOD 2 and TLR2
- The effect of BCG immunization on prevention of infection with MTB can be enhanced by giving stimulators of NOD 2 and TLR2

Explanation of the Hypothesis

The reduction of MTB infection found in BCG immunized children exposed to MTB can be explained by stimulation of innate immunity, which is mediated among other pathways through stimulation of NOD2 and TLR2. Stimulation of receptors mediating innate immunity in addition to stimulation by BCG could, therefore, enhance the effect of BCG on reduction of MTB infection.

Testing the Hypothesis

Objectives

The objectives of this research are as follows:

1. To confirm the validity of a mouse model of a partial infection with MTB.
2. To investigate whether BCG immunization can reduce infection with MTB.
3. To investigate whether stimulators of NOD2, TLR2, or dectin-1 receptors can enhance an effect of BCG on reduction of infection with MTB.
4. To investigate the influence of T-suppressor cells on a reduced reactivity in the gamma IFN release assay results in MTB exposed BCG vaccinated mice.
5. To investigate whether a reduction of infection with MTB in BCG-immunized mice and in mice injected with enhancers of innate immunity is associated with a significant increase in markers of enhancement of innate immunity such as H3K4 trimethylation of monocyte deoxyribonucleic acid (DNA) and increase in Ly6C^{high} and CD11b positive monocytes in uninfected mice.
6. To investigate whether a reduction of infection with MTB is associated with an increased intracellular expression of TNF and IFN gamma messenger ribonucleic acid (mRNA) levels in monocytes in uninfected mice.
7. To establish whether inhibition of epigenetic programming can reduce the effect of BCG immunization and stimulators of innate immunity on MTB infection and markers of activation of innate immunity.

Methods

Definitions

MTB infection in the mouse model is defined as MTB positive culture of lung homogenates or positive IFN gamma release assay performed in mice with culture negative lungs after sacrificing at 18 weeks after exposure to an aerosol of MTB.

The Infection Model

To detect the influence of immunization on infection rates, the ULD infection model is used [4]: Groups of female adult C57BL/6 mice are exposed to ULD MTB aerosol for 20 min. An adult mouse model is used because the effect of BCG immunization on MTB has also been detected in adult humans [15,16], and tissue (spleen) required for IFN gamma release assay in adult mice will be big enough to detect specific reactive T-effector cells and provide the cell populations for subsequent experiments. Before using large numbers of mice (a total of 222 initially) for the first experiment, the reproducibility of the ULD model is tested by initially exposing 28 mice (the number is identical to the number of the first reported ULD experiment in mice in Saini et al (2012) [4] with at least 10 mice expected to have detectable evidence of infection. The number of mice with a detectable infection is expected to be at least as large because the definition of infection in our study, unlike Saini et al [4] who only used lung cultures to confirm infection, includes enzyme-linked immunospot (ELISpot) positivity in culture negative mice.

Sample Size Calculation

With an ULD MTB aerosol model, it is expected that with a starting inoculum of $OD\ 2.5 \times 10^{-4}$ with a prenebulizer bacterial count of 3.05×10^4 colony-forming unit (CFU)/ml, the result is 1.1 CFU presented/ per mouse with a predicted infection rate of 36% (36/100) [4]. BCG immunization was found to be associated with a reduction of the infection rate from 67/143 (47%) to 16/56 (29%) in children in an outbreak investigation in the United Kingdom [17]. This study was chosen for the sample size calculation because the geographical setting of the United Kingdom is more applicable to the laboratory setting with its reduced likelihood of infection with nontuberculous mycobacteria, absence of malnutrition, and lack of concomitant helminth infections, which can all influence both effectiveness of BCG immunization as well as the results of IFN gamma release assays by induction of bias away from a Th-1 response essential for antimycobacterial immunity. For the comparison of the BCG immunized and nonimmunized groups of mice using the ULD model to detect a difference of 18% in prevalence of infection between groups with 80% power at a significance level of 5%, 111 mice need to be used in each group.

The Composition of Experimental Groups

The composition of the experimental groups is as follows:

1. Control group: Mice exposed to ULD of MTB and not vaccinated.
2. Intervention group: Mice vaccinated with BCG at a dose of 5×10^4 CFU per mouse and exposed after 6 weeks to ULD of MTB.

Randomization and Blinding Procedures

The mice are randomized into each group after labeling with a number (attached to the tail) using computer randomization [18]. The numbers in each group are registered and allocation concealed from members processing mice and analyzing data. The persons processing the mice for mycobacterial culture and IFN gamma release assay as well as involved in culture and assay procedure are blinded to the allocation of the numbers to groups. The persons analyzing the data are blinded to which group received the immunization.

Care and Use of Laboratory Animals and Ethics

All animal work was carried out in accordance with the UK Animal (Scientific Procedures) Act 1986, under appropriate Personal and Project licenses. The study will only go ahead after approval by the Institutional Animal Use Ethics Committee. Animals will be housed in appropriate biological containment facilities according to the code of practice for the housing and care of animals bred, supplied, or used for scientific purposes as outlined in [19].

Outcomes

The outcomes are as follows:

1. Proportion of exposed mice found not to be infected with MTB: This is taken as confirmation of the validity of the model of partial infection with MTB in mice.
2. Reduction of the infection rate in BCG immunized mice compared with controls. This is taken as confirmation that BCG immunization can reduce the infection event itself.
3. Infection rate with MTB after application of enhancers of innate immunity.

Detection of *Mycobacterium tuberculosis* on Culture in Infected Mice

Lungs of mice succumbing before 18 weeks after exposure to aerosol and lungs of mice sacrificed at 18 weeks because alive at that time after exposure to aerosol are put in 0.9% sodium chloride and sent to a collaborating microbiological laboratory for culture.

Detection of *Mycobacterium tuberculosis* Infection by Interferon Gamma Release Assay

IFN gamma release assays are conducted in all mice surviving to 18 weeks in the form of an ELISpot assay using spleen cells.

Enzyme-Linked Immunospot

The procedure below was taken in modified form from a published protocol [20]:

1. Preparation of ELISpot 96-well plate by coating with capture anti-IFN-gamma antibody:
 - Pretreatment of plates with 200 microl/well of 70% ethanol for 10 min.
 - Rinsing the wells with 200 microlitres/well of tissue culture medium in PBS 3 times (5 min each wash).
 - Coating of plates with 100 microl/well of 10 microl/ml solution of capture, rat antimouse IFN-gamma antibody (clone R4-6A2) in 1 X PBS, and incubation overnight at 4 degrees Celsius.

2. The spleen of mice sacrificed after survival at 18 weeks is removed and put in RPMI-1640 medium supplemented with 100 IU ml⁻¹ penicillin, 50 µg ml⁻¹ streptomycin, 1 mM l-glutamine, 25 mM HEPES, 1 mM sodium pyruvate, 5 × 10⁻⁵ M β-mercaptoethanol, vitamins and nonessential amino acids (Gibco-Invitrogen), and 10% endotoxin-tested heat-inactivated fetal bovine serum (Atlas Biologicals) as described previously [21].
3. The spleen is digested with an enzyme mixture containing 1 mg ml⁻¹ collagenase type IV (Sigma-Aldrich) and 25 U ml⁻¹ DNase (Roche) in supplemented RPMI-1640 at 37 °C for 1 h. The digested spleen is pressed through a 70-µm pore size cell strainer (BD Falcon) to obtain a single cell suspension. The erythrocytes are lysed with RBC lysis buffer (eBioscience) at 22°C, and cells are washed extensively (×4), resuspended in supplemented RPMI-1640, and counted using an automated cell counter (Countess, Invitrogen) employing the trypan blue dye exclusion method. Cell concentration is adjusted to 10⁶ cells ml⁻¹ in supplemented RPMI-1640 before addition to appropriate wells.
4. All reagents are brought to room temperature, except the detection antibody concentrate and dilution buffer, which should remain at 2 to 8°C. All samples and controls are assayed in duplicate. An assay record template is used to record controls and samples assayed. All wells in the microplate are filled with 200 µL of sterile culture media and incubated for approximately 20 min at room temperature. When cells are ready to be plated, the culture media is aspirated from the wells.
5. 100 µL of the appropriate cells are added to each well. The cells are plated in duplicate with 10⁵ cells per well, incubated (37 degrees, 5% CO₂) 24 hours with media, 4 micrograms/ml Con A, 2.5 micrograms/ml anti-CD3 (clone 145-2C11), 2 micrograms/ml MTB Erdman CFP, and 10 micromol of an ESAT-6 MHC class II-restricted epitope peptide (MTEQQWNFAGIEAAA. Cells are incubated in a humidified 37 °C CO₂ incubator. The controls are:
 - Positive control 1 to check T-effector cells for ability to release IFN gamma controls: Cells stimulated with phytohaemagglutinin are added to 2 wells.
 - Positive control 2 to check binding capacity of coating antimouse IFN gamma antibodies: recombinant mouse IFN-γ is added to 2 wells.
 - Negative control 1: Unstimulated Control cells—using the same number of unstimulated cells as stimulated cells.
 - Negative control 2: Instead of cells only sterile culture media is used.
 - Negative control 3: Detection antibody control: Phosphate buffered saline is substituted for the detection antibody.
6. Each well is aspirated and washed and the process repeated 3 times for a total of 4 washes. Wash is performed by filling each well with wash buffer (250-300 µL) using a squirt bottle, manifold dispenser, or auto-washer. Complete removal of liquid at each step is essential to good

- performance. After the last washing step, any remaining wash buffer is removed by aspirating or decanting. The plate is inverted and blotted against clean paper towels.
7. 100 µL of diluted detection antibody mixture is added into each well and incubated overnight at 2 to 8°C.
8. The washing procedure is repeated as described in step 7.
9. 100 µL of diluted Streptavidin-AP is added into each well and incubated for 2 hours at room temperature.
10. The wash procedure is repeated as described in step 7.
11. 100 µL of BCIP/NBT Chromogen is added into each well and incubated for 1 hour at room temperature. The plates are protected from light.
12. The chromogen solution is discarded from the microplate, and the microplate rinsed with deionized or distilled water. The microplate is inverted and tapped to remove excess water. The flexible plastic under drain is removed from the bottom of the microplate, the bottom of the plate wiped thoroughly with paper towels, and dried completely either at room temperature (60-90 min) or 37°C (15-30 min).
13. Spot forming is counted manually with a dissecting microscope. More than 6 spots constitute a positive result indicating previous infection with MTB.

Data Analysis

Percentage of infected mice between groups is compared by chi-square or Fisher exact testing as appropriate. Statistical significance set to be indicated by a *P* value of <.05.

Experiments to Identify Compounds Associated with an Increased Protection Against *Mycobacterium tuberculosis* Infection and Identification of Mechanisms Related to Protection Against Infection

Sample Size Calculation

A sample size calculation in the experiments below is guided by the outcome of the experiments conducted above.

Randomization and Blinding Procedures

See above.

The Composition of Experimental Groups

The composition of the experimental groups is as follows:

1. Negative control group: Mice exposed to ULD of MTB and not vaccinated.
2. Positive control: Mice vaccinated with BCG a dose of 5×10⁴ CFU per mouse and exposed after 6 weeks to ULD of MTB.
3. Mice vaccinated with BCG followed by inoculation with murabutide at a dose of 0.1mg/kg 2 months later followed after 6 weeks by exposure to ULD of MTB aerosol.
4. Mice vaccinated with BCG followed by inoculation with beta-glucan at a dose of 0.1mg/kg 2 months later followed after 6 weeks by exposure to ULD of MTB aerosol.
5. Mice vaccinated with BCG and simultaneously with murabutide mixed in the same syringe at a dose of 0.1mg/kg and exposed after 6 weeks to ULD of MTB.
6. Mice vaccinated with BCG and simultaneously with beta-glucan mixed in the same syringe at a dose of 0.1mg/kg and exposed after 6 weeks to ULD of MTB.

7. Mice vaccinated with murabutide at a dose of 0.1mg/kg and exposed after 6 weeks to ULD of MTB.
8. Mice vaccinated with beta-glucan at a dose of 0.1mg/kg and exposed after 6 weeks to ULD of MTB.

Detection of Mycobacterium tuberculosis on Culture in Infected Mice

Lungs of mice succumbing before 18 weeks after exposure to aerosol and lungs of mice sacrificed at 18 weeks because alive at that time after exposure to aerosol are put in 0.9% sodium chloride and sent to a collaborating microbiological laboratory for culture.

Detection of Mycobacterium tuberculosis Infection by Interferon Gamma Release Assay

IFN gamma release assays are conducted in all mice surviving to 18 weeks in the form of an ELISpot assay using spleen cells.

Data Analysis

Percentage of infected mice between groups is compared by chi-square or Fisher exact testing as appropriate. Statistical significance set to be indicated by a *P* value of <.05.

Investigation of the Role of Epigenetic Programming of Innate Immunity in Protection Against Mycobacterium tuberculosis Infection

The following two courses of investigation will be undertaken:

- To assess whether clearance of infection in BCG-immunized mice is related to activation of innate immunity, the influence of inhibition of epigenetic programming on MTB infection is examined
- To investigate whether protection from infection is related to activation of innate immunity H3K4 trimethylation of monocyte DNA and numbers of activated monocytes and degree of intracellular TNF and IFN gamma, mRNA expression is measured and degree of methylation and numbers of activated monocytes and degree of TNF and IFN gamma expression compared between infected and uninfected mice

Experimental Procedure

Above experiment is conducted with the modification that mice receiving BCG, murabutide or beta glucan alone, or murabutide or beta glucan and BCG are at the time of the first injection of these agents intraperitoneally injected with inhibitors of training of innate immunity the histone methyltransferase inhibitor 5'-deoxy-5'-methylthio-adenosine, and the histone acetyl transferase inhibitor epigallocatechin-3-gallate [5,11] to abolish the training effect on innate immunity and infection rates compared with controls receiving these agents without prior injection with inhibitors of epigenetic programming.

In mice in all groups at death or at sacrifice at 18 weeks after aerosol exposure with MTB, spleen cells are used for measurement of H3K4 trimethylation, enumeration of activated monocytes by flow cytometry, and measurement of intracellular TNF and IFN gamma expression.

Details of Methods

Determination of Epigenetic Programming in Form of Histone Modification by Chromatin Immunoprecipitation

Chromatin immunoprecipitation (ChIP) is a technique allowing the analysis of the histone modifications associated with specific genomic regions in the context of intact cells. ChIP is then used to connect epigenetic marks to intergenic regions, active coding regions, and/or silenced coding regions.

The main steps of the ChIP technique are cell fixation, chromatin shearing, immunoselection, immunoprecipitation (IP), and analysis of the immune-precipitated (IP'd) DNA.

In short, cells are briefly fixed with a reversible cross-linking agent. Next, the cross-linked chromatin (DNA-protein) is sheared, and the DNA fragments associated with the protein of interest are immunoprecipitated using specific antibodies. Finally, the IP'd DNA is examined for the presence of particular sequences by quantitative polymerase chain reaction (qPCR). Enrichment of specific sequences in the precipitate indicates that the sequences are associated with the protein of interest in vivo.

Protocol for Chromatin Immunoprecipitation

The following protocol is taken from the Instruction Manual Version 2 01.14 available from a source quoted below [22]:

1. Cell fixation and collection of 10x10⁶ cells splenic cells obtained for the ELISpot procedure.
2. Cell lysis and chromatin shearing.
3. Immuno-selection and precipitation using antibody antihistone H3 K4me3.
4. DNA purification.
5. qPCR of TNF and IFN gamma genes.
6. Determination of occupancy of the 2 promoters by the modified histones is evident based on fluorescent qPCR analysis of immunoprecipitated DNA.

Quantification of intracellular cytokine mRNA expression:

1. Cells are harvested by trypsinization, and total RNA extracted using TRIzol reagent (Gibco BRL, Gaithersburg, MD). A total of 5 µg of total RNA is reverse-transcribed according to the manufacturer's protocol (Superscript II Preamplification System, Gibco BRL) using oligo (dT) as primer.
2. cDNA prepared from 0.5 µg RNA is subjected to PCR using murine gene-specific primers for TNF and IFN gamma. All of the primer pairs span at least 1 intron in the corresponding genomic DNA. Positive RNA controls are performed previously to confirm specificity of primer pairs. Negative controls are performed by omitting the RT step or the cDNA template from PCR amplification.
3. For semiquantitative PCR, target sequences for TNF alpha and IFN gamma are amplified at 56°C between 22 and 32 cycles to yield visible products within the linear amplification range.
4. PCR products are separated by electrophoresis on a 2% agarose gel and stained with ethidium bromide.

5. All reverse transcription PCR bands at the expected size are also directly sequenced to confirm their identity.
6. Glyceraldehyde-3-phosphate dehydrogenase or acidic ribosomal phosphoprotein are used as internal controls.

Investigation of the Change in the Monocyte Phenotype as a Marker of Nucleotide Oligomerization Domain 2 and Beta Glucan-Induced Activation

As a correlate of NOD2 activation by MDP derivatives flow cytometry on spleen cells to detect Ly6C^{high} as well as CD11b positive monocytes is performed, and numbers of these monocyte populations is compared between immunized and not immunized mice in each group.

Outcomes

The outcomes are as follows:

- MTB infection defined as positive culture of lung homogenates in mice with active tuberculosis or positive IFN gamma release assay performed in spleen cells of mice with culture negative lungs after sacrificing at 18 weeks after aerosol challenge
- Level of TNF and IFN gamma and histone H3 K4me3 trimethylation in infected versus uninfected mice
- Concentrations of monocytes with features of activation of innate immunity as defined by Ly6C^{high} as well as CD11b positive phenotype
- Change in TNF and IFN gamma mRNA expression in infected versus uninfected mice
- Correlation of TNF and IFN gamma mRNA expression with monocyte phenotype and levels of histone H3 K4me3 trimethylation

Testing the Role of T-Suppressor Cells in Apparent Reduction of Infection Rate as Measured by Interferon Gamma Release Assay

The experiment is repeated with all groups of mice except 1 control group undergoing depletion of T-suppressor cells by injection of the monoclonal antibody 2.43, which reacts against an antigen present on T suppressor/cytotoxic (CD8) cells before injection of murabutide, BCG or murabutide and BCG as described previously [23].

For data analysis, the rate of infection as measured by ELISpot assay is compared between BCG immunized and/or murabutide injected groups.

Results

Evidence Supporting the Hypothesis

The first experiments using derivatives of MDP to enhance early immunity in the C57BL/6 mouse strain (mice aged 7 weeks) used 300 micrograms per mouse of oil-associated 6-0-mycoloyl-N-acetylmuramyl-L-alanyl-D-isoglutamine (mycol-MDP) 50/50 mixed with Freund's incomplete adjuvant suspended with 0.9% sodium chloride solution with 0.2% Tween aiming at a final oil concentration of 3% and given intravenously. Comparison of CFU count in the lungs 3 weeks after aerosol challenge with *Mycobacterium bovis* of groups (n=5) between groups receiving mycol-MDP in oil emulsion

(see above) versus controls (n=5) receiving only oil emulsion showed a significantly lower CFU count of 94.5×10^6 (SD 22.0) in cases versus controls with 204.0×10^6 (SD 77.6) [24]. It is important to note that after elimination of T-cells in this model (by irradiation and thymectomy), a reduction of CFU in lungs of mice treated with mycol-MDP persisted albeit without statistical significance, which was possibly related to the small number of animals used. This result confirmed the findings of a previous study of the same group in the mouse strain C3H/He [25].

The BCG primed increased TNF release by monocytes has been shown to be related to effects of epigenetic programming in form of stimulation of trimethylation of histone H3 at lysine 4 (H3K4). Establishment of innate immunity in monocytes could hereby be inhibited by use of inhibitors of epigenetic programming [8].

Evidence Against the Hypothesis

The most important alternative hypothesis, which could be advanced to explain the apparently reduced infection rate on gamma IFN release assay testing in BCG immunized humans or mice, is clonal imprinting (previously termed *original antigenic sin* phenomenon) where previous exposure to an antigen (in this case BCG) leads to reinforcement of the immune reaction to this antigen on exposure of the immune system to a similar antigen (MTB) containing this previous antigen (in this case BCG) rather than a reaction to the new antigen (MTB-specific epitopes) not contained in the antigen mixture of the previous exposure. This process has been found to be dependent on the action of the cytokine IL-10 [26]. IL-10 is hereby produced by nonantigen specific T-suppressor cells [27], thus postulated to reduce IFN gamma release in MTB exposed individuals in the gamma IFN release assays if there was a previous exposure to BCG. This alternative hypothesis can be tested by elimination of T-suppressor cells.

The protective effect of BCG immunization against infection with MTB is reduced in low income countries [1], but its effect against other infections, which is more consistent with enhancement of innate immunity, is considerable [28]. This is more supportive of the hypothesis that the reduction of infection with MTB is also because of T-effector cells, which can be influenced by malnutrition and helminth infection triggered regulatory T-cell activation and not because of effects of BCG on innate immunity. The conclusion would, therefore, be that innate immunity can actually not be enhanced by antigens similar to BCG derived substances, which can stimulate NOD2 or TLR2.

Discussion

Impact of Confirmation of Reduction of *Mycobacterium tuberculosis* Infection by Enhancement of Innate Immunity

Should above experiments confirm that a reduction in MTB infection by BCG immunization can be confirmed in the mouse model and enhanced by amplifiers of innate immunity, this approach would have to be then tested in nonhuman primates

and if again successful would lead to an enhanced BCG immunization schedule in humans. The potential of enhancing innate immunity extends far beyond immunization against MTB infection, and one may want to investigate the impact of such an approach on infections with all other pathogens.

Testing Bacillus Calmette Guerin Enhancement of Innate Immunity in Humans

The Influence of Neonatal Bacillus Calmette Guerin Immunization on Neutrophil-Mediated Innate Immunity in Infants at Risk of HIV Infection

BCG immunization is known to influence innate immunity against MTB infection [8] associated with its effect on cells of the monocyte/macrophage lineage. Neutrophil leucocytes may be an important contributor to innate immunity against MTB infection in collaboration with macrophages [29]. Infants of mothers with human immunodeficiency virus (HIV) infection and undetectable HIV viral load at 36 weeks gestation have routinely blood samples taken at birth and at 6 weeks of age to check for evidence of HIV infection, and a BCG immunization is given after birth. In infants born to mothers with detectable viral load at 36 weeks gestation, BCG immunization is withheld until after HIV DNA PCR is negative at 3 months of age. From this information one can formulate the following hypothesis: BCG immunization increases neutrophil-mediated innate immunity.

Outcomes suitable for investigation of an effect of BCG immunisation on neutrophil innate immunity are: change in neutrophil associated antimycobacterial activity in whole blood

associated with BCG immunization as measured using MTB luciferase assay adapted to small sample sizes [30].

Neutrophil leucocyte attributable innate immunity to MTB could be compared in infants with and without BCG immunization born to mothers with HIV infection.

To assess neutrophil leucocyte attributable innate immunity, 1 ml of blood is taken in addition to the routine bloods taken: 0.5 ml subjected to MTB luciferase assay (30) and 0.5 to MTB luciferase assay after neutrophil depletion. The same is repeated at 6 weeks of age (after the BCG immunization in the immunized group). Groups with and without BCG immunization are compared with control for general changes of innate immune response in the postnatal period.

Impact

In vitro studies could determine the component of BCG, which enhances neutrophil antimycobacterial activity by exposure of neutrophils in vitro to components of BCG and measuring antimycobacterial activity by MTB luciferase assay before and after exposure to each component; starting with muramyl dipeptide, a compound produced by BCG previously associated with enhancement of antimycobacterial activity in monocytes [1].

Should an increase of neutrophil dependent innate immunity by BCG immunization be confirmed, a change in neutrophil-mediated immunity could serve as an outcome measure in future trials of BCG immunization and correlated with negative IFN gamma release assay results in exposed people in future vaccine trials.

Authors' Contributions

ME conceived the hypotheses and ways to test the hypotheses and wrote the entire manuscript. ME gave the final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

None declared.

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Abbreviations

BCG: bacillus calmette guerin
CFU: colony-forming unit
ChIP: chromatin immunoprecipitation
DNA: deoxyribonucleic acid
ELISpot: enzyme-linked immunospot
IFN: interferon
IP: immunoprecipitation
MDP: muramyl dipeptide
mRNA: messenger ribonucleic acid
MTB: *Mycobacterium tuberculosis*
NOD: nucleotide oligomerization domain
qPCR: quantitative polymerase chain reaction
TLR2: toll-like receptors 2
TNF: tumor necrosis factor
ULD: ultralow dose

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Original Paper

Aims, Study Design, and Enrollment Results From the Assessing Predictors of Infant Respiratory Syncytial Virus Effects and Severity Study

Edward E Walsh^{1*}, MD; Thomas J Mariani^{1*}, DPhil; ChinYi Chu^{1*}, MA; Alex Grier^{1*}, MA; Steven R Gill^{1*}, DPhil; Xing Qiu^{1*}, DPhil; Lu Wang^{1*}, MA; Jeanne Holden-Wiltse^{1*}, DPhil; Anthony Corbett^{1*}, MA; Juilee Thakar^{1*}, DPhil; Lauren Benoodt¹, MA; Matthew N McCall^{1*}, DPhil; David J Topham^{1*}, PhD; Ann R Falsey^{1*}, MD; Mary T Caserta^{1*}, MD

University of Rochester School of Medicine and Dentistry, Rochester, NY, United States

*these authors contributed equally

Corresponding Author:

Edward E Walsh, MD

University of Rochester School of Medicine and Dentistry

1425 Portland Avenue

Rochester, NY, 14621

United States

Phone: 1 585 922 4331

Fax: 1 585 922 5168

Email: edward.walsh@rochesterregional.org

Abstract

Background: The majority of infants hospitalized with primary respiratory syncytial virus (RSV) infection have no obvious risk factors for severe disease.

Objective: The aim of this study (Assessing Predictors of Infant RSV Effects and Severity, AsPIRES) was to identify factors associated with severe disease in full-term healthy infants younger than 10 months with primary RSV infection.

Methods: RSV infected infants were enrolled from 3 cohorts during consecutive winters from August 2012 to April 2016 in Rochester, New York. A birth cohort was prospectively enrolled and followed through their first winter for development of RSV infection. An outpatient supplemental cohort was enrolled in the emergency department or pediatric offices, and a hospital cohort was enrolled on admission with RSV infection. RSV was diagnosed by reverse transcriptase-polymerase chain reaction. Demographic and clinical data were recorded and samples collected for assays: buccal swab (cytomegalovirus polymerase chain reaction, PCR), nasal swab (RSV qualitative PCR, complete viral gene sequence, 16S ribosomal ribonucleic acid [RNA] amplicon microbiota analysis), nasal wash (chemokine and cytokine assays), nasal brush (nasal respiratory epithelial cell gene expression using RNA sequencing [RNAseq]), and 2 to 3 ml of heparinized blood (flow cytometry, RNAseq analysis of purified cluster of differentiation [CD]4+, CD8+, B cells and natural killer cells, and RSV-specific antibody). Cord blood (RSV-specific antibody) was also collected for the birth cohort. Univariate and multivariate logistic regression will be used for analysis of data using a continuous Global Respiratory Severity Score (GRSS) as the outcome variable. Novel statistical methods will be developed for integration of the large complex datasets.

Results: A total of 453 infants were enrolled into the 3 cohorts; 226 in the birth cohort, 60 in the supplemental cohort, and 78 in the hospital cohort. A total of 126 birth cohort infants remained in the study and were evaluated for 150 respiratory illnesses. Of the 60 RSV positive infants in the supplemental cohort, 42 completed the study, whereas all 78 of the RSV positive hospital cohort infants completed the study. A GRSS was calculated for each RSV-infected infant and is being used to analyze each of the complex datasets by correlation with disease severity in univariate and multivariate methods.

Conclusions: The AsPIRES study will provide insights into the complex pathogenesis of RSV infection in healthy full-term infants with primary RSV infection. The analysis will allow assessment of multiple factors potentially influencing the severity of RSV infection including the level of RSV specific antibodies, the innate immune response of nasal epithelial cells, the adaptive response by various lymphocyte subsets, the resident airway microbiota, and viral factors. Results of this study will inform disease interventions such as vaccines and antiviral therapies.

KEYWORDS

respiratory syncytial virus; innate immunity; T-lymphocytes; immunoglobulins; gene expression; transcriptome; microbiota

Introduction

Background

Respiratory syncytial virus (RSV), a negative strand ribonucleic acid (RNA) virus in the *pneumoviridae* family, is the most important cause of respiratory tract infection during infancy, causing annual winter outbreaks lasting 18 to 24 weeks in the United States [1-5]. In the United States, 50 to 70% of the 4 million newborns each year are infected during their first winter, and 1 to 3% are hospitalized, 4 to 7% are seen in emergency departments, and 10 to 16% require physician office visits because of RSV [6]. Although mortality is low in the United States (approximately 50 deaths annually), in developing countries RSV is estimated to cause as many as 118,000 deaths, 6 million cases of severe acute lower respiratory illness, and 3 million hospitalizations annually in children younger than 5 years [7,8]. In addition, severe RSV infection has been linked to development of asthma and implicated recently in development of chronic obstructive lung disease [9-12].

Major risk factors for severe illness include prematurity, cyanotic congenital heart disease, severe neuromuscular disease, immune compromise, and bronchopulmonary dysplasia [13,14]. However, approximately 70% of hospitalized infants have no overt risk factors for severe illness, although young age at infection, environmental factors (secondhand tobacco smoke, lack of breast feeding, household crowding, and low socioeconomic status), and viral, host genetic, and immune factors have been associated with severe disease [14,15]. In addition, high RSV viral load has also been associated with more severe disease in several but not all studies [16], and although group A RSV strains are more common than group B strains among hospitalized infants, the relationship of viral genetic differences to disease severity has not been demonstrated conclusively [17-22].

RSV is not considered highly cytopathic in airway epithelium, whereas host immune responses are thought to be a major contributor to disease pathogenesis [23,24]. Single nucleotide polymorphisms in a number of cytokine and chemokine genes (IL-1, IL-4, IL-8, IL-13, IL-18, RANTES, CCR5), Toll-like

receptor 4, and vitamin D receptor have been associated with increased risk of severe disease [25-28]. In contrast, high levels of cord blood neutralizing antibody are associated with delayed onset of hospitalization with RSV and diminished illness severity [29-31]. High levels of maternally derived RSV-specific antibody at infection have also been associated with diminished illness severity in 2 recent reports [31,32]. The most compelling evidence of the beneficial effect of antibody comes from studies of prophylactic administration of immunoglobulin with high titers of RSV neutralizing antibodies or monoclonal antibody to high-risk infants that demonstrate approximately 50% reductions in hospitalization from RSV [33,34]. Some studies suggest that a type 2 helper (Th2)-biased response during primary infection may also be a contributing factor to disease severity [35-37]. Finally, more severe RSV disease has been associated with greater abundance of *haemophilus influenzae* and *streptococcus pneumoniae* in the nasal microbiota during RSV infection [38-40].

Objectives

The Assessing Predictors of Infant RSV Effects and Severity study was designed to simultaneously measure a number of host demographic, environmental, and innate and adaptive immune parameters in conjunction with viral factors and the respiratory microbiota in relation to disease severity in full-term healthy infants younger than 10 months undergoing primary RSV infection. We hypothesize that assessment of the interplay of these factors will provide insight into the pathophysiology of RSV disease in this population.

Methods

Study Design and Setting

The study was performed in Rochester, New York, encompassing 3 winter RSV seasons spanning from 2012 to 2016. To capture the full spectrum of RSV severity from very mild outpatients to hospitalized infants, 3 cohorts of infants were recruited. Inclusion and exclusion criteria are shown in [Textboxes 1](#) and [2](#). The investigational review boards of the University of Rochester, Highland Hospital, and Rochester General Hospital (RGH) approved the study.

Textbox 1. Inclusion criteria for all cohorts.

Inclusion criteria for all infants in the 3 cohorts:

- Gestational age ≥ 37 weeks
- Parent/guardian can provide informed consent
- Infant will be available for duration of the study for birth cohort. For the supplemental and hospital cohorts, infants unable to participate in the full study because of logistic problems such as long travel times from home may be enrolled as long as they agree to complete requirements for visit 1.
- Born after the previous May 1.

Additional criteria for hospital cohort only

- Acute illness documented to be because of respiratory syncytial virus infection on admission to hospital.

Textbox 2. Exclusion criteria for all cohorts.

Exclusion criteria for all infants in the 3 cohorts:

- Any infant eligible to receive respiratory syncytial virus (RSV) prophylaxis with Palvizumab.
- Presence of underlying neuromuscular disorder (ie, Down syndrome, cerebral palsy).
- Immunosuppressive condition (ie, HIV infection in mother) or use of immunosuppressive medications before RSV infection.
- Presence of malignancy (ie, Wilms tumor).
- Inability to contact for the duration of the study.
- Any other condition deemed to place infant at higher risk for severe RSV infection (ie, neonatal intensive care unit transfer at birth, recurrent aspiration).

Additional criteria for hospital cohort only

- Infants hospitalized for apnea only.

Cohort Enrollment

Birth cohort: Infants were enrolled at birth in the late summer through midwinter (approximately August 15 to February 1). Infants were enrolled at 3 hospitals: the University of Rochester Medical Center's (URMC's) Strong Memorial Hospital and Highland Hospital, and RGH.

Supplemental cohort: A second cohort, designated the supplemental cohort, was recruited from infants seen with acute respiratory illness not requiring hospitalization at URMC's Golisano Children's Hospital and RGH emergency departments or at pediatric clinics at URMC's Golisano Children's Hospital and RGH, and the Elmwood Pediatric Practice, a private pediatric office affiliated with URMC.

Hospital cohort: Infants were enrolled on admission to URMC's Golisano Children's Hospital and RGH with documented RSV infection.

Surveillance for Respiratory Syncytial Virus

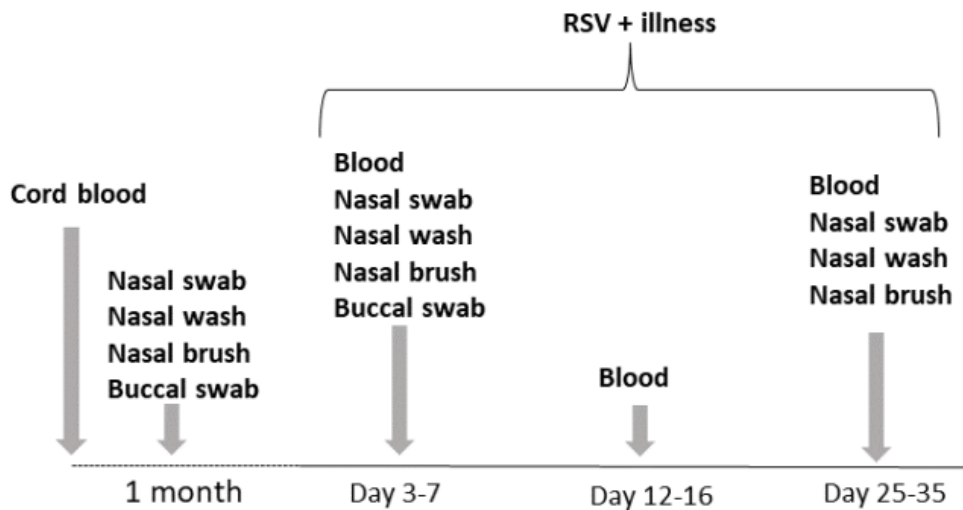
Illness surveillance and surveillance visits: Infants enrolled in the birth cohort were followed by passive and active surveillance for development of respiratory symptoms throughout their first winter (mid-November until April 15). Parents were asked to call when their infant developed any of the following symptoms: nasal congestion, nasal discharge, cough, wheezing, sustained rapid breathing, or fever. A study nurse evaluated the infant in

the research clinic or at a home visit, and a nasal swab was collected for RSV diagnosis. Supplemental cohort infants had nasal swabs collected at the time of evaluation in the emergency department or physician's office. Nasal swabs were tested for the presence of RSV RNA using an RSV-specific reverse-transcriptase polymerase chain reaction (RT-PCR) assay or by rapid antigen testing (Quidel) and confirmed by RT-PCR, as described [41]. The hospital cohort infants were identified as RSV-infected by the clinical virology laboratory using either of 2 commercial RT-PCR assays (Focus Simplexa RSV/influenza duplex PCR or the Pasteur Merrieux Biofire multiplex PCR assay).

Study Visits

The chronology of study visits for the birth cohort (cord blood and 1-month visit) and illness visits for all RSV infected infants in each of the cohorts are exemplified in [Figure 1](#). Enrollment visit: At enrollment a study nurse and 1 of the physician investigators (MTC, EEW, ARF) explained study objectives and procedures to the parents and obtained written informed consent. Demographic data were collected including gestational age, birth weight, household size including number and age of siblings or other children, tobacco use by mother/household members, and breastfeeding frequency. For infants in the birth cohort, a cord blood sample and a buccal swab were obtained ([Figure 1](#)).

Figure 1. Schematic of chronological procedures for Assessing Predictors of Infant respiratory syncytial virus (RSV) Effects and Severity study. Dotted line represents time course for birth cohort before identification of RSV illness. Solid line represents time course of samples and procedures for RSV positive infants in all 3 cohorts. RSV: respiratory syncytial virus.



One-month visit: The birth cohort was seen at the age of 1 month at a time when asymptomatic and a nasal swab, nasal wash, nasal brush, and buccal swab was collected.

Acute respiratory Illness visits: When infants in the birth cohort and supplemental cohort were seen for respiratory illness, a nasal swab was obtained for same day RSV diagnosis. If RSV was identified, the infant was scheduled for an RSV positive illness visit within 24 hours at the research clinic or during a second home visit.

RSV positive illness visits: RSV-infected Infants were evaluated at 3 time points: acute visit when RSV was first identified, at 12 to 16 days, and approximately 28 days after illness onset. At the acute illness visit, clinical information was collected (date of illness onset, presence of nasal congestion/discharge, cough, wheezing, rapid breathing, apnea, cyanosis, fever, lethargy, poor feeding). A physical examination was performed noting weight, pulse, respiratory rate, temperature, room air oxygen saturation (SaO₂), presence of cyanosis, nasal discharge, rales or rhonchi, wheezes, and chest retractions. Biological samples were collected in the following sequence: buccal swab, nasal swab from 1 nostril, nasal wash followed by nasal brush from the contralateral nostril, and 2 to 3 ml venous blood sample. Parents were given an illness diary card to record signs of illness for a 10-day period beginning retrospectively from illness onset. Medical records of hospitalized infants and those seen in the emergency department or physicians' offices were reviewed and clinical information recorded. For hospitalized infants the following information was also collected: amount and duration of supplemental oxygen, respiratory support and intensive care requirements, fluid and antibiotic administration, and worst values for each of the respiratory (respiratory rate, pulse, wheezing, rales/rhonchi, retractions, and SaO₂) and systemic signs (fever, lethargy, difficulty feeding). Length of

hospitalization and results of complete blood count, blood cultures, and chest radiographic findings, if available, were recorded. Interim history and findings on physical examination and room air SaO₂ were recorded; a 2 to 3 ml venous blood sample obtained at the second visit; and a nasal swab, nasal wash, nasal brush, and 2 to 3 cc venous blood sample was obtained at the third visit.

Clinical Study Procedures

Multiple study procedures were performed on enrolled subjects (Table 1).

Cord Blood

Cord blood was collected on all birth cohort subjects and the plasma fraction stored at -80°C .

Buccal Swab

A buccal swab was collected using a cotton tipped swab at enrollment, the 1-month visit for the birth cohort, and the first RSV-positive illness visit in all cohorts.

Diagnostic Nasal Swab

For infants in birth and supplemental cohorts, a viral diagnostic swab was collected at an illness visit using a medium-sized pediatric flocked swab (cat. no. 518CS01, Copan Diagnostics, Murrieta, CA). The swab was placed in 3 ml of UTM viral transport media (Copan Diagnostics) for RT-PCR as described [41].

Respiratory Syncytial Virus Illness Visit Nasal Swab

A nasal swab was collected from 1 nostril and placed in 2 ml of ultraviolet-inactivated sterile water. The swab was agitated and removed and the sample split into 2 equal portions and frozen at -80°C . The swab sample was used for quantitative RT-PCR and microbiota assays.

Table 1. Time and events table for Assessing Predictors of Infant Respiratory Syncytial Virus Effects and Severity study.

Samples/data	Birth cohort visits			RSV ^a positive illness		
	Birth	1 month	Illness surveillance	Acute (day 2-7)	Day 12-16	Day 25-35
Demographic	X ^b	X	— ^c	X	X	X
Clinical	X	X	—	X	X	X
Cord blood for antibody	X	—	—	—	—	—
Buccal swab for <i>cytomegalovirus</i> polymerase chain reaction	X	X	—	X	—	—
Nasal swab RSV RT-PCR ^d	—	—	X	—	—	—
Nasal swab for:						
Quantitative RSV RT-PCR	—	—	—	X	—	X
Viral coinfection	—	—	—	X	—	X
RSV gene sequencing	—	—	—	X	—	X
Microbiome	—	X	—	X	—	X
Nasal wash	—	X	—	X	—	X
Nasal brush for epithelial cell RNAseq ^e	—	X	—	X	—	X
Blood for:						
Peripheral blood mononuclear cells flow cytometry	—	—	—	X	X	X
CD ^f 4, CD8, B, natural killer RNAseq	—	—	—	X	X	—
Antibody assays	—	—	—	X	X	X

^aRSV: respiratory syncytial virus.

^bX indicates samples at this time point.

^cIndicates no samples collected at time point.

^dRT-PCR: reverse-transcriptase polymerase chain reaction.

^eRNAseq: ribonucleic acid sequencing.

^fCD: cluster of differentiation.

Nasal Wash And Nasal Brush

A nasal wash was performed using the opposite nostril as the nasal swab by rapidly instilling and retrieving 5 ml of preservative-free sterile phosphate buffered saline using a small sterile nasal suction bulb, as described [42]. The nasal wash fluid was frozen at -80°C . Immediately following the nasal wash, the same nostril was brushed with a medium-sized pediatric flocked swab by rubbing the swab back and forth and rotating it against the middle turbinate mucosa for 5 seconds. The swab was immediately placed in RNA stabilizer (RNAprotect, Qiagen, Germantown, MD) and held at 4°C until cells were recovered by filtering through a $0.45\ \mu\text{m}$ membrane filter. Cells were lysed and homogenized by passing through a 28 g needle, and total RNA was recovered (AbsolutelyRNA Miniprep kit, Agilent, Santa Clara, CA) according to manufacturer's instructions and stored at -80°C .

Venipuncture

A total of 2 to 3 mL of blood was collected from an antecubital or hand vein into heparin coated syringes and transferred to a heparinized vacutainer vial. Blood was transported at room temperature to the laboratory within 2 hours for processing.

Laboratory Procedures, Assays, and Data to Be Generated

RSV RT-PCR: Diagnosis of RSV infection and designation as group A or B RSV was made by RT-PCR using nasal swab samples as previously published [41].

Quantitative RSV RT-PCR

Viral load in nasal swab and nasal wash samples was determined using an RSV group-specific quantitative RT-PCR and reported as plaque forming units (pfu)/ml equivalents [43].

Respiratory Syncytial Virus Gene Sequences

RNA was extracted from 250 ul of nasal wash or nasal swab specimens as previously described [41]. Full genome sequence of RSV was produced by reverse transcription and PCR amplification of 4 overlapping genome regions in a method similar to Schobel et al and Bose et al [44,45]. The 4 genome amplicons were paired-end sequenced using Nextera XT and Illumina V3 chemistry on a MiSeq (Illumina, San Diego, California). The sequencing reads were assembled into genome contigs using the viral-ngs package (version V1.15.3, Broad Institute Viral Genomics), aligned to a curated set of complete RSV genome isolate sequence from Genbank using MUMmer

(SourceForge.net) and annotated using VIGOR (SourceForge.net) [46-48].

Non-Respiratory Syncytial Virus Reverse-Transcriptase Polymerase Chain Reaction/Polymerase Chain Reaction/

The presence of other respiratory viruses (parainfluenza viruses 1-3, influenza A and B, coronaviruses, human metapneumovirus, rhino/enteroviruses, adenoviruses, bocavirus) in nasal swab or wash samples was determined using a TaqMan Array Card (Applied Biosystems, Waltham, MA), as described [49].

Blood

Whole blood was centrifuged at 300 x g for 10 min at 4°C and the plasma removed and stored at -80°C. Peripheral blood mononuclear cells (PBMCs) were separated by Ficoll-hypaque gradient and approximately 4 million cells set aside for T and B cell lymphocyte subset sorting (below) and the remainder frozen in liquid nitrogen in 90% fetal calf sera/10% deoxymethylsulfoxide (DMSO) and frozen in liquid nitrogen for flow cytometry.

Peripheral Blood Mononuclear Cell Sorting

PBMC were flow-sorted into 4 subsets (cluster of differentiation [CD]4⁺, CD8⁺, B cells, and natural killer [NK] cells) using published methods [50]. Cells were immediately lysed in RNA protect and stored at -80°C.

Flow cytometry: PBMCs were thawed, rested overnight, and assayed for cytokine and surface markers by flow cytometry following stimulation with cell culture grown RSV, overlapping 18-mer peptide pools representing the RSV fusion, attachment, nucleocapsid and matrix proteins dissolved in DMSO, and controls (DMSO alone, uninfected cell culture supernatant, staphylococcal endotoxin B), as described [51].

Ribonucleic Acid Purification

RNA was recovered from nasal brushes stabilized in RNAprotect, fresh sorted PBMC, or thawed and restimulated PBMC using the AbsolutelyRNA Miniprep kit (Agilent, Santa Clara, CA), as previously described [37,52].

Plasma Immunoglobulin G Titers to Respiratory Syncytial Virus Proteins

IgG titers to purified RSV F, G_a, G_b proteins were determined in by enzyme immunoassay (EIA) as described [41]. IgG titers to the conserved central CX3C containing region of G_a and G_b proteins were determined by competition EIA with a Fab fragment of a murine mab (L9) specific for the conserved central region of the RSV G proteins [31].

Neutralization titers to RSV A and B strains

Serum neutralization titers to RSV group A virus (A2 strain) and B virus (B1 virus) were performed using a modification of previous methods [31]. Plasma was first converted to serum by enzymatic digestion of heparin by heparinase, followed by inactivation of both the enzyme and complement at 56°C for 30 min.

Host transcriptomics: RNA sequencing of nasal brush samples and flow-sorted T and B cells (CD4⁺, CD8⁺, and CD19⁺ cells)

was performed as previously described [37,52]. Starting with 1 ng of RNA and using the SMARTer Ultra Low amplification kit (Clontech, Mountain View, CA), libraries were constructed using the NexteraXT library kit (Illumina, San Diego, California) and sequenced on the Illumina HiSeq2500 to generate approximately 20 million 100 bp single end reads per sample. Preanalysis data processing was as described [52].

Host Gene Expression Validation

Quantitative RT-PCR (qPCR) validation of RNAseq-based gene expression estimates were performed as described [37,52]. Nasal washings were used for quantitative EIA analysis of various cytokines and chemokines.

Nasal Microbiota Analysis

Total genomic deoxyribonucleic acid (DNA) was extracted by mechanical lysis and 16S ribosomal RNA was amplified with high-fidelity DNA polymerase and dual indexed primers specific to the V3-V4 hypervariable regions as previously described [52]. Amplicons were pooled and paired-end sequenced (2 X 300 nt) on an Illumina MiSeq. Each sequencing run included: (1) positive controls consisting of standardized bacterial genomic DNAs and (2) negative controls consisting of sterile saline. Sequence processing and initial microbial composition analysis were performed with the Quantitative Insights into Microbial Ecology (QIIME) software package, version 1.9.1 [53]. Operational taxonomic units (OTUs) were picked using the reference-based USEARCH (version 5.2) pipeline in QIIME using the May 2013 release of the GreenGenes 99% OTU database as a closed reference [54-56]. Representative OTU sequences used to make taxonomic assignments for each cluster were selected on the basis of abundance. The RDP Naïve Bayesian Classifier was used for taxonomic classification with the GreenGenes reference database, using a minimum confidence threshold of .85 and otherwise default parameters [57].

Planned Statistical Analyses

Demographic and clinical data will be assessed by descriptive analysis using means and SE, medians and inter-quartile ranges for continuous variables, and proportions for categorical variables. We will use graphical methods such as histograms, Q-Q plots, and box-plots to visualize the data and identify potential data problems such as outliers, missingness, and skewness. For continuous variables, we will test their normality by Shapiro-Wilk test and Kolmogorov-Smirnov test. If problems are detected, appropriate data preparation steps such as outlier removing, data imputation, and log-transformations will be considered. For those variables that pass the normality test, we will perform 1-way analysis of variance (ANOVA) *F* test followed by Bonferroni *post hoc* testing for pairwise group comparisons. When groups exhibit unequal variances, Welch ANOVA method will be used instead. For non-normal variables, nonparametric Kruskal-Wallis test with Dunn *post hoc* test will be used instead. Extended Fisher exact test will be used to compare the proportions of categorical variables such as gender and race between cohort groups. Pearson and Spearman correlation analysis will be used to assess associations between 2 continuous variables such as severity and gene expression

levels. Multivariate linear regression will be used to model the associations between covariates and continuous outcome variables, controlling for possible confounding effects such as age and sex. ANOVA F test and regression t test will be used to assess the significance of the overall and specific linear association between the covariates and the outcome variables. Multivariate logistic regression will be used to model associations between covariates and categorical outcome variables such as hospitalization, controlling for possible confounding effects. The Wald test will be used to assess significance of the association between covariates of interest and the outcome variables. P values $<.05$ will be considered statistically significant for standard statistical analyses. Some research aims involve analyzing high-throughput data such as RNAseq-based transcriptomic data and 16S-based microbiome data, and we will apply suitable multiple testing procedures, such as the Benjamini-Hochberg procedure, to control false discovery rate at a prespecified level (0.05) [58]. These high-throughput data may have high-level of between-sample variations, in part because of technical issues such as technical noise and batch effects. These undesirable variations can be reduced by a combination of stringent quality assurance analysis and specialized data transformation techniques. Specifically, samples with insufficient quality metrics (low read number, mapping rate or poor sample-wide correlation) will be excluded from analysis. Before statistical analysis, we will explore the dataset by principle component analysis (PCA), principal coordinates analysis, and hierarchical clustering to identify any unwarranted structure or association. If necessary, batch correction methods such as ComBat [59] and surrogate variable analysis [60] may be applied. Due to the non-normal nature of these data, specialized normalization methods and analytical pipelines will be used whenever appropriate [53,60-69]. All statistical analyses will be performed in R 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.3 (SAS Institute).

Primary hypothesis: Our primary hypothesis is that we will be able to identify a number of factors associated with disease severity during primary RSV infection in full-term healthy infants. The first step toward this goal was to develop a Global Respiratory Severity Score (GRSS) reflecting the severity of the entire illness as the main outcome variable in most of our analyses [70]. PCA and multivariate logistic regression was used to determine the 9 optimal clinical parameters and their relative weights that comprise the GRSS (available as a Web-based algorithm [71]). We will assess each of the following datasets for their association with disease severity: (1) $CD4^+$, $CD8^+$ T cell, B cell, and NK cell gene expression during RSV infection; (2) nasal epithelial cell gene expression before, during, and after RSV infection; (3) $CD4^+$ and $CD8^+$ cytokine synthesis as measured by flow cytometry during and after RSV infection; (4) serum antibody to RSV F and G proteins and the conserved central CX3C G protein region; (5) serum neutralizing titers to RSV A2 and B1 viruses during and after infection; (6) nasal microbiota composition before, during, and after RSV infection; (7) viral load; and (8) complete RSV genomic sequences. Each analysis will be adjusted for confounding demographic variables

such as sex, gestational age, breast feeding history, age at infection, history of exposure to tobacco smoke, coinfection with other respiratory viruses, and the presence of pathogenic bacteria such as *streptococcus pneumoniae*, *haemophilus influenzae*, and *moraxella catarrhalis* as determined by direct PCR. Most importantly, we will seek to integrate several datasets in complex analyses to assess various interactions between virus, nasal epithelial cell and T cell gene expression, nasal microbiota, and adaptive immune responses as they relate to disease severity. Due to the inclusion of multiple high-dimensional datasets, we plan to assemble novel data integration pipelines that use state-of-the-art dimension reduction methods such as multi-omics factor analysis [72] and multi-set canonical correlation analysis [73] to extract the most informative features from individual high-throughput datasets, and afterwards, use statistical learning techniques such as penalized regression [74-76] and support vector machine classification [77] to predict disease severity. Strict cross-validation criterion will be used to evaluate the performance of the proposed methods. Recently, we developed FUNNEL, which is a time-course gene set enrichment method that has the capability to incorporate both between-gene correlation and weights [78]. We propose to design a new weighting method based on supervised principal component analysis [79] and extend FUNNEL for cross-sectional data and use this new method to study the biological functions of key genes with the largest absolute loadings in the extracted principle components/canonical vectors.

Results

Recruitment and Enrollment

During the 3 seasons, 226 infants were enrolled in the birth cohort. Of these, 126 (55.8%) attended the scheduled 1-month visit, indicating a relatively high early attrition rate. Following the 1-month visit, 150 respiratory illnesses were reported in 81 infants (64% of active subjects) during their first winter season, each of which was evaluated during a home visit or clinic visit. A total of 36 infants had a single illness, 29 had 2 illnesses, 11 had 3, and 5 had 4 or more illnesses. A total of 19 of the 81 (23.5%) evaluated infants were shown to be RSV positive, and the overall incidence of RSV infection in the active birth cohort was 15% (19/126). Among the 19, 4 were hospitalized during the RSV infection, 1 of whom was admitted to the pediatric intensive care unit (PICU) for noninvasive respiratory support.

The supplemental cohort was recruited during the second and third winter seasons when it was apparent that the early withdrawal rate in the birth cohort was higher than anticipated. A total of 149 infants with respiratory illness met inclusion/exclusion criteria for the supplemental cohort. Of these, 60 (41%) were documented to have RSV infection, and 42 (70%) were enrolled in the full study. A total of 24 (57%) infants were enrolled from physician offices, whereas 18 (43%) were enrolled from the emergency departments. A total of 2 infants were subsequently hospitalized, 1 of who was admitted to the PICU and intubated.

Table 2. Demographic characteristics of 3 cohorts comprising final study populations.

Characteristic	Birth cohort enrolled (n=226)	Birth cohort RSV ^a + (n=19)	Hospital cohort RSV+ (n=78)	Supplemental cohort RSV+ (n=42)
Male sex, n (%)	119 (53)	9 (47)	36 (46)	20 (48)
Race, n (%)				
White	128 (57)	12 (63)	52 (67)	21 (50)
Hispanic	39 (17)	3 (16)	9 (12)	8 (19)
Gestational age (weeks), mean (SD)	39.3 (1.1)	38.8 (1.1)	38.8 (1.3)	39.1 (1.4)
Birth weight (kg), mean (SD)	3.3 (0.5)	3.3 (0.7)	3.4 (0.6)	3.3 (0.6)
C-section, n (%)	69 (31)	9 (47)	25 (32)	6 (14)
Mother's age (years), mean (SD)	28.4 (6.7)	31.3 (5.3)	28.1 (6.0)	29.0 (4.9)
Household members, mean (SD)				
Siblings	1.1 (1.2)	1.4 (1.2)	1.5 (1.2)	1.4 (1.3)
Adults	2.1 (0.7)	2.0 (0.6)	2.4 (1.2)	2.6 (2.4)
Other children	0.2 (0.8)	0.1 (0.5)	0.3 (0.7)	0.4 (1.0)
Total household size	3.4 (1.5)	3.5 (1.3)	4.1 (1.7)	4.1 (1.7)
Smoking in home, n (%)				
Mother	11 (5)	0 (0)	15 (19)	8 (19)
Others	52 (23)	0 (0)	30 (39)	12 (29)
Residence, n (%)				
House	165 (73)	16 (84)	55 (71)	35 (83)
Apartment	61 (27)	3 (16)	23 (30)	7 (17)
Mother's education				
College degree	100 (44)	12 (63)	34 (44)	15 (36)
High school degree	77 (39)	5 (26)	30 (39)	10 (24)
History of asthma in siblings; no. (%)	29 (21) ^b	2 (14)	20 (32) ^b	14 (47) ^b
Age at RSV infection, mean (SD)	— ^c	2.3 (1.0)	2.9 (2.2)	4.7 (2.0)

^aRSV: respiratory syncytial virus.

^bPercentage calculated only for those with siblings in household.

^cNot applicable.

During 3 seasons, 78 RSV-infected infants meeting inclusion/exclusion criteria were enrolled at the time of hospitalization. A total of 9 were cared for in the PICU and 4 intubated. The average length of stay for all hospitalized infants, including those from the birth and supplemental cohorts, was 4.2 (SD 0.6) days, with a median of 2.3 days. None of the infants died. The demographic characteristics of the RSV-positive subjects in the 3 cohorts are shown in [Table 2](#).

Although for most factors the differences between cohorts were relatively minor (ie, gestational age, mother's age, household size, number of siblings in the home), there were several significant differences. Birth by cesarean section was significantly lower in the supplemental cohort (6/42) compared with the birth cohort (9/19) and the hospital cohort (25/78; $P=.001$ and $P=.05$, respectively). Maternal smoking was more common in both the supplemental (8/42) and hospital cohorts

(15/78) compared with the RSV-infected birth cohort (0/19), both significant ($P=.05$ and $P=.04$, respectively).

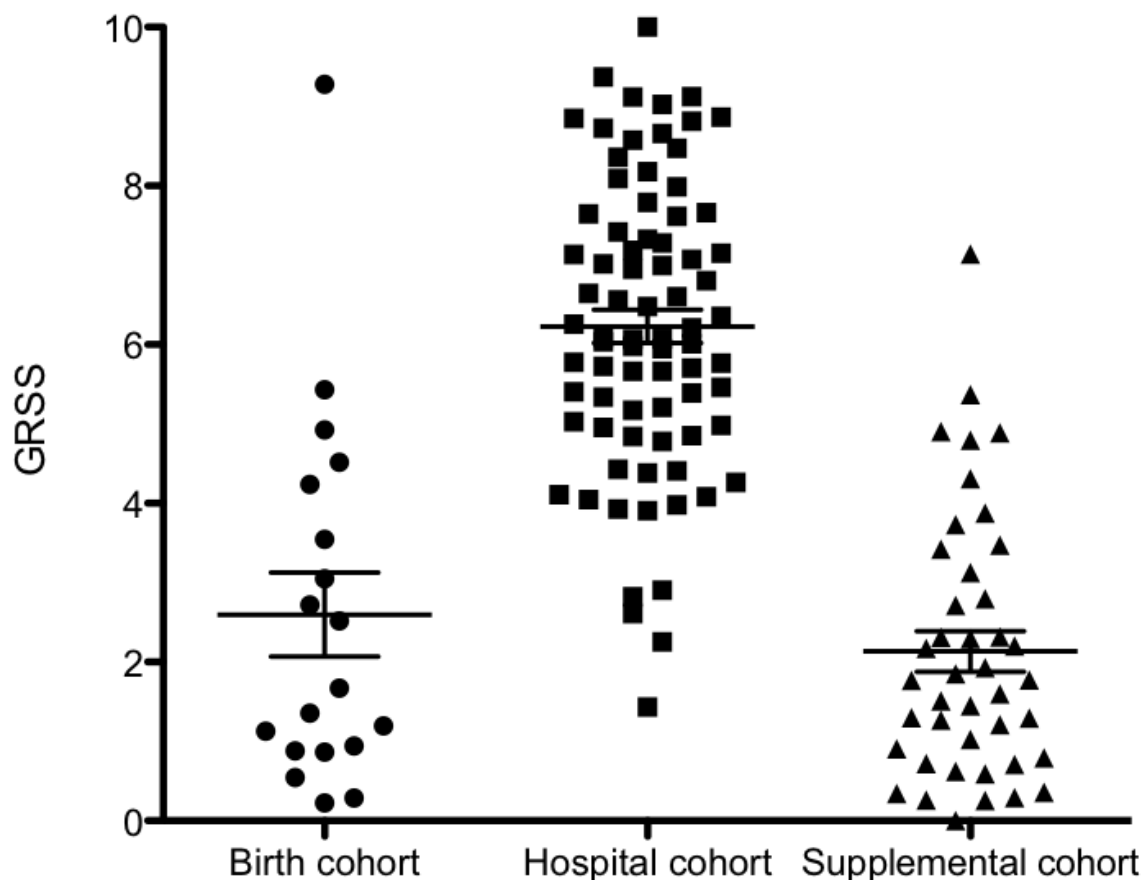
A large number of biological samples were collected from the enrolled subjects, including 217 cord blood samples (birth cohort only), 533 buccal swabs, 322 illness blood samples, 661 nasal swabs, 356 nasal wash samples, and 366 nasal brush samples.

Severity Score Outcome

As noted, we first completed development of the GRSS [70]. The GRSS distribution of the enrolled infants varied by cohort as expected, with lower severity scores in the birth and supplemental cohorts and higher severity score in the hospital cohort ([Figure 2](#)).

The mean (SE) GRSS for the birth and supplemental cohorts (both including hospitalized infants from these cohorts) were 2.6 (0.5) and 2.1 (0.3), respectively, and was 6.2 (0.2) for the hospital cohort.

Figure 2. Distribution of the Global Respiratory Severity Score for respiratory syncytial virus–infected infants enrolled in the 3 cohorts. GRSS: Global Respiratory Severity Score.



Discussion

Although conditions such as extreme prematurity, cyanotic heart disease, and immunosuppression have been clearly identified as risk factors for severe RSV infection, the majority of hospitalized infants are normal full-term infants. The pathogenesis of RSV in this population is not completely understood, although a number of additional factors have been suggested as potentially relevant, such as a Th2 bias following birth, genetic variations in regulation of cytokine and chemokine genes, levels of RSV-specific antibodies, variations in nasal microbiota, and viral factors. Our study was designed to simultaneously measure and analyze many of these factors as they relate to severe RSV disease in full-term infants during primary infection. In addition to more severely ill infants hospitalized with RSV infection, we sought to enroll RSV-infected infants spanning the entire spectrum of disease severity by prospectively following a large birth cohort with the expectation that the majority of infections would represent very mild illness.

Limitations

A comprehensive study of this type, one that requires a large number of simultaneously collected samples at several time points before, during, and after RSV infection, offered several obstacles in recruitment and retention of subjects. We believe

the relatively intensive commitment required on the part of young parents, often with the stress of caring for their first infant, resulted in a higher than anticipated attrition rate among the birth cohort. To adjust for loss of subjects in the birth cohort, we modified the enrollment strategy to include infants seen in the outpatient setting for acute respiratory illness or during routine visits for immunization when they were noted to have very mild respiratory signs. This modification of the enrollment strategy resulted in enrollment of mildly ill RSV-infected infants, thus, allowing development of a GRSS with a scale of 0 to 10 that spans the entire severity spectrum. This tool will allow us to utilize the severity endpoint as either a dichotomous or continuous variable in our analyses of the various parameters measured. As these datasets are completed, they will be made available in public repositories for use by other investigators.

Strengths

We chose to assay host gene expression responses as a primary indicator of health status of subjects. The methods we have developed to interrogate nasal gene expression, which appears to be a reasonable surrogate of the airway and is capable of being recovered from infants of varying age and health status, is highly novel. This approach is clearly capable of providing significant new opportunities to define the molecular status of the airway in ill infants, a major impediment to prior research of infant lung diseases [80]. We also chose to separate peripheral

blood cells into major subtypes before interrogation of their gene expression. Although this raised some significant technical challenges, they have been overcome [37,50]. Furthermore, this approach allows us to better achieve our primary objectives of defining the biology of the system and how it is affected by disease state.

Future Plans

Ultimately, we plan to integrate each of the datasets using disease severity (GRSS) as the clinical outcome, allowing us to identify and account for interactions among the various data types during the infant's response to RSV infection. These analyses should provide important insights into the complexity of RSV disease pathogenesis and potentially to novel interventions to alter RSV severity.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

ANOVA: analysis of variance

AsPIRES: Assessing Predictors of Infant RSV Effects and Severity

CD: cluster of differentiation

DMSO: deoxymethylsulfoxide

GRSS: Global Respiratory Severity Score
IgG: immunoglobulin G
NK: natural killer
OTU: Operational taxonomic unit
PBMC: peripheral blood mononuclear cell
PCA: principle component analysis
PCR: polymerase chain reaction
PICU: pediatric intensive care unit
qPCR: quantitative polymerase chain reaction
RGH: Rochester General Hospital
RNA: ribonucleic acid
RNAseq: ribonucleic acid sequencing
RSV: respiratory syncytial virus
RT-PCR: reverse-transcriptase polymerase chain reaction
SaO₂: room air oxygen saturation
Th2: type 2 helper
URMC: University of Rochester Medical Center

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Protocol

Diet-Induced Alteration of Microbiota and Development of Obesity, Nonalcoholic Fatty Liver Disease, and Diabetes: Study Protocol of a Prospective Study

Martine Uittenbogaart¹, MD; Wouter KG Leclercq¹, MD; Danielle Bonouvrie¹, MD; Marleen M Romeijn¹, MD; Arijan APM Luijten¹, MD; Steven WM Olde Damink^{2,3}, MD; Francois MH van Dielen¹, MD, PhD; Sander S Rensen³, PhD

¹Department of Bariatric Surgery, Máxima Medical Center, Veldhoven, Netherlands

²Department of Surgery, Maastricht University Medical Centre, Maastricht University, Maastricht, Netherlands

³School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, Netherlands

Corresponding Author:

Martine Uittenbogaart, MD

Department of Bariatric Surgery

Máxima Medical Center

De Run 4600

Veldhoven, 5504 DB

Netherlands

Phone: 31 0642283558

Email: m.uittenbogaart@mmc.nl

Abstract

Background: Development of obesity and obesity-related diseases, such as type 2 diabetes mellitus and nonalcoholic fatty liver disease (NAFLD), is associated with altered gut microbiota composition. The aim of this study is to investigate associations among dietary compounds, intestinal cell function, and gut microbiota composition. We hypothesize that dietary lipid intake is associated with Paneth cell and goblet cell properties that affect gut microbiota composition.

Objective: The primary objective of this study is to determine whether a difference in dietary intake is associated with a difference in intestinal mucin-2 expression and gut microbiota composition.

Methods: This is a single-center prospective study, including 1 obese group undergoing laparoscopic Roux-en-y gastric bypass and 2 lean control groups undergoing either laparoscopic cholecystectomy or upper gastrointestinal endoscopy (n=228). During laparoscopy, biopsies will be taken of visceral fat (omentum majus), liver, muscle tissue of the abdominal wall, and subcutaneous fat. In the obese group, a small segment of the jejunum will be collected for analysis, which will be compared with an endoscopically derived jejunal biopsy from the upper gastrointestinal endoscopy control group. Stool samples for microbiota profiling will be collected at baseline and 1 year after surgery. Primary outcomes are fecal microbiota composition and mucus characteristics. Secondary outcomes include Paneth cell phenotype, body weight, diet composition, glucose tolerance, resolution of comorbidities, and weight loss 1 year after surgery.

Results: This trial is currently open for recruitment. The anticipated completion date is December 2019.

Conclusions: The Diet-Induced Alteration of Microbiota and Development of Obesity, NAFLD, and Diabetes study will improve insight into the pathophysiology of obesity and its associated metabolic disorders. Better understanding of weight loss failure and weight regain following bariatric surgery might also behold new therapeutic opportunities for obesity and obesity-related comorbidities.

Trial Registration: Netherlands Trial Register NTR5660; <https://www.trialregister.nl/trial/5540> (Archived by WebCite at <http://www.webcitation.org/7817jOZre>)

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KEYWORDS

microbiota; type 2 diabetes; obesity; NAFLD; gastric bypass

Introduction

Obesity-associated diseases, such as type 2 diabetes mellitus (T2DM) and nonalcoholic fatty liver disease (NAFLD), are major public health issues worldwide, affecting more than 6% and 25% of the world population, respectively [1,2]. The influence of gut bacteria on the development of obesity and metabolic syndrome is not entirely understood.

Numerous experimental studies show that gut bacteria are influential in the development of obesity. For example, transplantation of gut microbiota from obese into germ-free mice has been shown to cause a higher fat mass increase than transplantation of lean microbiota. [3] Thus, altering gut bacterial composition can have a direct effect on body weight. In addition, gut microbiota might play a potential role in the treatment of T2DM. Indeed, targeting gut microbiota by antibiotic treatment has been shown to improve body weight and glucose tolerance of high-fat fed mice [4,5]. Prebiotic, as well as probiotic, treatment also improves glucose metabolism in high-fat diet-induced diabetes [6,7]. Moreover, infusion of gut microbiota from lean human donors into subjects with metabolic syndrome has been reported to result in increased insulin sensitivity [8], demonstrating the feasibility of gut microbiota modulation for improving glucose homeostasis in a clinical setting. NAFLD is the hepatic manifestation of the metabolic syndrome, characterized by ectopic fat accumulation in the liver. Previous animal studies have indicated a link between development of NAFLD and gut microbiota. For example, gut microbiota transplantation from mice with NAFLD to wild-type recipients led to replication of the NAFLD phenotype, showing that NAFLD is transmissible through gut bacteria [9]. The factors that underlie the microbiota alterations in obesity, T2DM, and NAFLD are unclear, although the genetic makeup of the host is considered to play a significant role. Gut microbiota composition and function are strongly affected by endogenous antimicrobial proteins secreted by Paneth cells in the small intestine [10], as well as by mucus components made by intestinal goblet cells [11]. Next to these host factors, dietary macronutrient composition has a strong impact on gut microbiota [12]. In particular, high-fat diets decrease abundance of *Akkermansia muciniphila*, a mucus associated bacterium that has been found to be inversely correlated with body mass in mice [13]. Besides this specific bacterium, diet also has an effect on the ratio of 2 major intestinal bacterial phyla: high-fat diets induce Firmicutes while reducing Bacteroidetes [3,14,15].

The data on changes in gut microbiota composition after bariatric surgery are relatively limited. Within 3 months after Roux-en-Y gastric bypass (RYGB), gut microbiota has been found to be more diverse with an increased relative abundance of *Akkermansia muciniphila* [16]. However, most of the available clinical studies have small sample sizes and only analyze fecal samples collected at 12 months postoperatively or less. The possible impact of gut microbiota on failure to maintain weight loss after bariatric surgery is still unknown. This phenomenon, better known as secondary nonresponse, can occur in up to 25% of all patients who undergo RYGB surgery, and it can become apparent at 12 to 24 months postoperatively [17,18]. A recent study showed no difference in microbiota

composition between a group of patients following RYGB surgery who obtained more than 50% excess weight loss after 2 years and a group of patients who did not reach that weight goal [19]. Unfortunately, that study lacked baseline samples, and that study had a very small sample size. The overall aim of the proposed study is to investigate associations among intake of dietary compounds, intestinal cell function, and gut microbiota composition. The primary objective is to determine the relationship between diet and intestinal mucin-2 expression in obesity. Secondary objectives are assessment of the relationships among diet, intestinal goblet cell and Paneth cell function, and gut microbiota composition, as well as changes in these parameters in association with secondary nonresponse, presence of T2DM, and NAFLD. We hypothesize that dietary lipid intake is associated with Paneth cell and goblet cell properties that affect gut microbiota composition.

Methods

Study Design

This study will be conducted as a single-center prospective study, and it comprises a cross-sectional and a longitudinal part. In the cross-sectional part, differences at baseline between severely obese patients and lean subjects will be studied, focusing on the presence and severity of NAFLD, insulin resistance, T2DM and intestinal microbiota composition, Paneth cell products, and mucus composition. The longitudinal part will focus on changes in microbiota composition, Paneth cell products, and mucus in the severely obese group between baseline measurement and 1 year after RYGB.

Ethical Approval and Recruitment

The Diet-Induced Alteration of Microbiota and Development of Obesity, Nonalcoholic Fatty Liver Disease, and Diabetes (DIAMOND) study is registered within the Netherlands National Trial Register (NTR560). The protocol was ethically approved by the official Independent Ethics Review Board of Máxima Medical Centre (reference 15.053) in November 2015. Written informed consent will be obtained from all participants. The study will be performed in accordance with the principles of the Declaration of Helsinki, as well as the guidelines of Good Clinical Practice. Recruitment started in the first quarter of 2016, and recruitment is currently ongoing. Patients deemed eligible for enrollment in either the obese group or the lean control (cholecystectomy) group are initially recruited by their surgeon or a specialized gastroenterology nurse at the time of approval for surgery or endoscopy. If interested in participation, the patient is contacted by the researcher and given detailed information about the study, in both oral and written form. After a 2-week period, the subjects are contacted to obtain informed consent, and then they will be officially enrolled in the study.

Setting

Recruitment of patients and subsequent sampling are performed in a large teaching hospital in the Netherlands, which is awarded as a Center of Excellence in Metabolic and Bariatric Surgery.

Study Population

The study population will comprise 3 groups: the obese group and 2 lean control groups. For the obese group, patients are screened by a multidisciplinary team, and they are approved for surgery according to the International Federation for the Surgery of Obesity and Metabolic Disorders guidelines. All patients with severe obesity and undergoing laparoscopic RYGB are considered eligible for inclusion. The surgical procedure is performed according to the circular stapling technique described by Dillemans et al [20].

Further inclusion criteria are a body mass index (BMI) between 35 and 45 kg/m² and willingness to sign the informed consent form. Patients are excluded on the basis of the following criteria: (1) age <18 or >65, (2) presence of type 1 diabetes, substance abuse, inflammatory diseases, or neoplasms, (3) chronic use of corticosteroids prescribed by a physician, and (4) use of antibiotics in the 3 months preceding surgery.

For the 2 lean control groups, all patients with a BMI between 20 and 25 kg/m² undergoing either upper gastrointestinal endoscopy or a laparoscopic cholecystectomy are eligible for inclusion. Patients are excluded on the basis of the following criteria: (1) age <18 or >65, (2) presence of type 1 or T2DM, substance abuse, inflammatory diseases, or neoplasms, (3) chronic use of corticosteroids prescribed by a physician, (4) use of antibiotics in the 3 months preceding surgery or endoscopy, and (5) presence of cachexia, defined as unintended weight loss (>5% in 1 month or >10% in 6 months). A flowchart for each of the groups is provided in Figure 1.

Data Collection

Characteristics

Phenotyping of obesity will be based on measurement of body weight and calculation of BMI. Presence and severity of T2DM

will be assessed by analysis of hemoglobin A1_c in blood, as well as analysis of plasma glucose and insulin levels, both fasting and during an oral glucose tolerance test. Presence of NAFLD will be determined on the basis of the liver biopsy, according to the validated Kleiner score [21]. Plasma levels of aspartate transaminase and alanine transaminase will be measured as markers of liver damage. Furthermore, plasma lipid spectrum, total leukocyte count, and differentiation count, as well as C-reactive protein, will be measured.

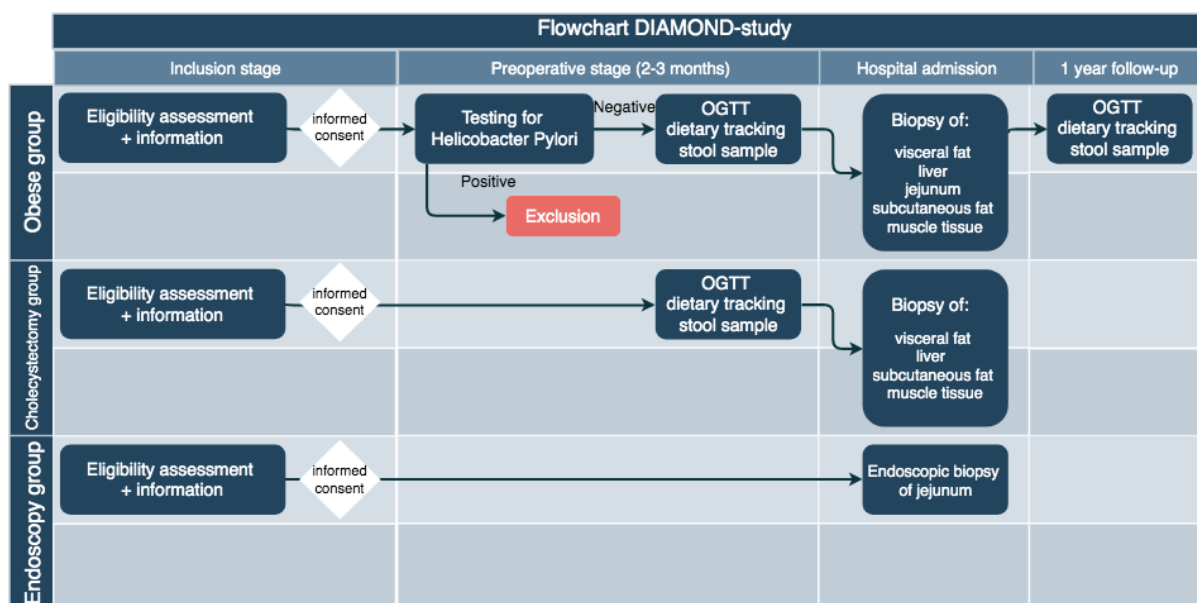
Dietary Habits

Dietary habits will be recorded using a Dutch food tracker [22], which can either be used as a Web-based program or as a smartphone app. All participants will be asked to record their diet for the duration of 7 consecutive days at baseline. The obese group will repeat this at 1-year follow-up.

Intestinal Microbiota Composition

Participants will be provided a stool sample collection kit and will be asked to sample their stool before surgery. The samples will be stored in the home freezer (−20°C) and transported to the hospital on the day of admission, where they will be stored in the laboratory freezer (−80°C) until analysis. Participants in the obese group will be asked to provide a second stool sample at 1-year follow-up. Stool samples will be analyzed according to the shotgun metagenomics approach. By sequencing the whole genome, we will be able to compare this with a reference genome and evaluate abundance of DNA fragments. This will include detecting the 2 primary intestinal phyla—Firmicutes and Bacteroidetes—as well as *Akkermansia muciniphila* abundance. Furthermore, we will analyze the fecal samples for presence of short-chain fatty acids, that is, acetate, propionate, and butyrate.

Figure 1. Flow chart. DIAMOND: Diet-Induced Alteration of Microbiota and Development of Obesity, Nonalcoholic Fatty Liver Disease, and Diabetes; OGTT: Oral Glucose Tolerance Test.



Biopsies

In both the obese group and the lean control group, the following biopsies will be performed during laparoscopic surgery: visceral fat (omentum majus), liver, muscle tissue of the abdominal wall, and subcutaneous fat. In the obese group, a small segment of the jejunum will be collected during laparoscopic RYGB, a standard element of the procedure, and it will be used for analysis. In the control group, the jejunal full-thickness biopsy will be substituted by the endoscopically derived jejunal biopsy in the endoscopy group.

Directly after sampling, all tissues will be flash frozen and stored in the laboratory freezer (-80°C) until analysis. According to standard operating procedure protocol, the sampling in the obese group and lean cholecystectomy group will be performed by 3 surgeons involved in this study. The sampling in the lean endoscopy group will be performed by 1 gastroenterologist. The researcher will be present at the operating room and at the endoscopy suite at each procedure to flash freeze the samples directly after the biopsy. Stored data and materials will be only identifiable to the person by an assigned subject number. As such, patient privacy is guaranteed according to the Dutch Personal Data Protection Act.

The jejunal samples will be analyzed by means of quantitative PCR, specifically investigating HD5/DEFA5 lysozyme, mucin-1, and mucin-2, as well as Kruppel like factor 4 messenger RNA expression. Furthermore, a hematoxylin and eosin staining will be performed to allow for Paneth cell quantification. Liver samples will be taken to assess the presence and severity of NAFLD and nonalcoholic steatohepatitis, the use of the Kleiner score [21] will be done by a dedicated pathologist. Muscle tissue, visceral fat, and subcutaneous fat will be stored for future purposes to enable more detailed interorgan investigations of peripheral tissues involved in glucose and lipid homeostasis.

Statistical Analysis

Power

Sample size is calculated on the basis of the smallest expected difference in the main outcome parameter, that is, intestinal mucin-2 expression, using G*power 3 (Erdfelder, Faul, and Buchner, 1996). A pilot study with lean nondiabetic and obese diabetic rats revealed a difference in expression of 1.00 ± 0.71 versus 0.65 ± 0.78 . Taking this into account and using a significance level of 0.05 and a power of 80%, each group will require 73 patients. Considering an expected loss to follow-up

of 5%, 76 patients need to be included in each group, amounting to 228 patients in total.

Analysis of Primary and Secondary Outcome Parameters

SPSS will be used for statistical analysis (IBM Corp, Released 2013, IBM SPSS Statistics for Macintosh, Version 22.0.). A 2-tailed P value $< .05$ will be considered statistically significant. To allow comparisons among groups, data will be tested for normal distribution, and appropriate statistical tests will be applied, potentially including Students t test, Mann-Whitney U test, analysis of variance, Kruskal-Wallis test, Chi-square test, or Fisher exact test.

Ethics Approval

Ethics approval was granted by the Máxima Medical Centre Ethics Committee (reference 15.053) in November 2015.

Results

This trial is currently open for recruitment. The anticipated completion date is December 2019.

Discussion

The field of microbiota research is rapidly expanding and a plethora of links among diseases like obesity, T2DM or NAFLD, and gut microbiota composition are currently unraveled. However, a majority of novel findings in this context are based on animal models and remain to be substantiated in humans. The DIAMOND study aims to identify associations among dietary compounds, gut microbiota composition, and Paneth cell function, as well as intestinal mucus characteristics in man.

A limitation of the DIAMOND study design is the inability to prove causality. Cancelling out potential direct effects of dietary compounds on microbiota and metabolism, such as fermentation of dietary fibers to produce short-chain fatty acids [23], is unattainable. In addition, obtaining new biopsies after 1 year of weight loss to identify the impact of weight loss on primary and secondary outcomes is not implemented in this study, as it is considered too invasive.

In conclusion, the DIAMOND study will explore whether Paneth cell function and mucus composition are associated with diet and alterations in gut microbiota composition, and the study will investigate the impact of RYGB-induced weight loss on these parameters. This will not only benefit our understanding of weight loss failure and weight regain following bariatric surgery, but it might also behold new therapeutic opportunities for obesity and obesity-related comorbidities.

Authors' Contributions

This is an investigator-initiated study. MU, WL, FvD, SR, and SOD designed the study. MU, WL, MR, DB, FvD, and SR drafted the manuscript. All authors read, edited, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BMI: body mass index

DIAMOND: Diet-Induced Alteration of Microbiota and Development of Obesity, Nonalcoholic Fatty Liver Disease, and Diabetes

NAFLD: nonalcoholic fatty liver disease

RYGB: Roux-en-Y gastric bypass

T2DM: type 2 diabetes mellitus

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Protocol

Preliminary Effectiveness and Safety of High Frequency Oscillation in Addition to Mechanical Insufflation and Exsufflation for Intratracheal Mucus Removal in Patients With Neuromuscular Disease: Protocol for a Prospective Study

Hiroyuki Awano¹, MD, PhD; Masashi Nagai¹, MD; Ryosuke Bo¹, MD, PhD; Mariko Murao¹, MD; Yusuke Ishida¹, MD; Tsukasa Tanaka¹, MD, PhD; Kazumi Tomioka¹, MD, PhD; Masahiro Nishiyama¹, MD, PhD; Hiroaki Nagase¹, MD, PhD; Kazumoto Iijima¹, MD, PhD

Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan

Corresponding Author:

Hiroyuki Awano, MD, PhD

Department of Pediatrics

Kobe University Graduate School of Medicine

7-5-1

Chuo-ku, Kusunoki-cho

Kobe, 6500017

Japan

Phone: 81 78 382 6090

Fax: 81 78 382 6099

Email: awahiro@med.kobe-u.ac.jp

Abstract

Background: Mechanical insufflation-exsufflation (MI-E) is necessary for noninvasive management of respiratory clearance in patients with neuromuscular disorders (NMDs). Its utility has been proven, and the technique is recommended in a number of international guidelines for the management of patients with NMDs. However, the clearance of thick secretions adhering to the tracheobronchial walls could be problematic when these patients suffer from respiratory tract infections. To improve the effectiveness of the noninvasive technique, a novel device combining MI-E with high frequency oscillation (HFO) has been developed. However, the efficacy of HFO therapy in NMDs has not been well studied.

Objective: The aim of this study was to elucidate the effect of MI-E combined with HFO for mucus removal in NMD patients. To evaluate its efficacy, changes in transcutaneous oxygen saturation (SpO₂), which may predict intratracheal mucus removal, will be measured before and after use of MI-E.

Methods: This is a single-center, nonblinded, nonrandomized prospective study that will enroll 5 subjects hospitalized in Kobe University Hospital owing to respiratory tract infection. All subjects will receive MI-E therapy a few times daily and will receive HFO every other day, for 6 days. Before and after MI-E use, SpO₂ will be obtained and the change in SpO₂ (Δ SpO₂) between MI-E with and without HFO will be calculated. For every subject, the average of Δ SpO₂ with or without HFO will be obtained and the null hypothesis that there is a mean change of 0 in the SpO₂ between MI-E with and without HFO will be tested using the paired *t* test. If the treatment with HFO is found to be statistically significantly superior to the treatment without HFO, the study will conclude that HFO addition is more efficacious than no HFO addition.

Results: A total of 2 subjects have already been recruited and enrolled in this study as of August 2018.

Conclusions: This unique protocol will assess the efficacy of adding HFO to MI-E during the acute phase of respiratory tract infection in patients with NMDs.

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KEYWORDS

neuromuscular diseases; airway management

Introduction

Background

Patients with neuromuscular disorders (NMDs) often have weak breathing muscles. As the disease progresses, vital capacity declines and the inability to expand and empty the chest fully results in reduced chest wall compliance [1-3]. As peak cough flow correlates with disease progression and lung capacity in patients with NMDs [4,5], insufficient coughing is problematic in patients with severe and advanced NMDs. Cough efficacy is related to clearance of secretions in the lung. Retention of intratracheal mucus leads to airway obstruction, causing increased work of breathing, decreased oxygenation, and ultimately respiratory failure [6]. Weak cough is thus a critical factor contributing to respiratory morbidity in NMD patients [7].

Therefore, coughing aids are necessary for patients with NMDs, and the use of assisted coughing techniques has been an important advance in the respiratory care of such patients, allowing intratracheal mucus to be controlled without the need for invasive methods, such as tracheostomy. Coughing aids include manually assisted and mechanically assisted aids [8]. Mechanical insufflation-exsufflation (MI-E) is performed using a device that generates positive pressure, provoking insufflation of the lung, and negative pressure, inducing exsufflation. A rapid change from positive to negative pressure generates air flow during exsufflation and facilitates the removal of intratracheal secretions [3,9].

It has been proven that MI-E helps to increase the peak cough flow, reduce the chance of hospitalization, permit a paradigm shift from invasive tubes to noninvasive management, and facilitate discharge to home [9-12]. Therefore, the use of MI-E is recommended in a number of international guidelines for the management of patients with NMDs [13-17].

Even if proper respiratory care is given, an inability to cough effectively and clear secretions puts patients with NMDs at risk of ventilatory failure during respiratory infection [18]. To improve the effectiveness of noninvasive techniques especially in cases of acute respiratory failure, a novel device that combines MI-E with high frequency oscillation (HFO) has been developed. During insufflation, exsufflation, or both phases, the device generates high-frequency oscillatory vibrations.

The application of HFO to the airway in patients with chronic obstructive pulmonary disease has been shown to change the viscoelastic properties of the secretions, making them more mobile [19]. Therefore, the addition of HFO to MI-E is expected to remove tenacious secretions in a noninvasive manner.

Objectives

The aim of this study is to elucidate the effect of MI-E with HFO in terms of mucus removal in patients with NMDs. To evaluate the efficacy of the approach, changes in transcutaneous oxygen saturation (SpO₂) and heart rate, and the subjective amount of mucus removed, are to be measured before and after use of MI-E, with and without HFO. The safety of the approach

will also be evaluated by noting the frequency of adverse events and complications.

Methods

Study Design and Setting

This is a single-center, nonblinded, nonrandomized prospective study. As the use of oscillation is obvious, this study cannot be performed blindly. The study will be performed in the Department of Pediatrics, Kobe University Hospital, in Kobe, Japan. The study implementation period is from March 27, 2018, to January 31, 2022 (enrollment period: 3 years; follow-up period: 4 months from enrollment of the last subject).

Eligibility Criteria

This study is conducted in patients who fulfill the following inclusion criteria and who do not meet any of the following exclusion criteria.

The inclusion criteria are as follows: patients with NMDs hospitalized in Kobe University Hospital owing to respiratory tract infection, who have already used MI-E without HFO or have started MI-E use in this study in addition to noninvasive ventilation, tracheostomy ventilation, and home oxygen therapy, and who provide written voluntary consent (or whose parents provide written voluntary consent) to participate in this study.

The exclusion criteria are as follows: patients with severe acute respiratory failure who have a very low SpO₂ level (<90%) for more than 1 hour, albeit adequate ventilation or oxygen therapy; those who do not have tracheostomy and require intubation; those who refuse to participate in the study; and those for whom it is deemed inappropriate to participate in this study in the opinion of the investigator. These exclusion criteria are set to target patients with NMDs who have mild-to-moderate respiratory infection and to secure the safety of the subjects.

Interventions

Description of Material

The Cough Assist E70 (Philips Respironics) is employed in this study. The device is used according to the manufacturer's recommendation. The Cough Assist E70 is applied via an oronasal mask or the tracheostomy opening by trained parents, nurses, or doctors. It is used at least 3 times a day, as well as whenever SpO₂ decreases, heart rate increases, or the patients have an increase in dyspnea or sense of retained secretions, in addition to the standard treatment, including oxygen supplementation and increased oxygen. It is set at 20 to 40 cm H₂O for insufflation and -20 to -40 cm H₂O for exsufflation pressure, with an insufflation and exsufflation time ratio of 1.5 to 2.5 and 0.8 to 1.5 seconds, respectively, and a pause of 0.5 to 2.0 seconds between each cycle. A total of 3 to 5 cycles are applied in every session. The frequency setting of oscillation is 15 Hz and the amplitude setting is 5 cm H₂O. This oscillation frequency was derived from a similar previous study [20]. As a >5 cm H₂O amplitude in the beginning of HFO use is not tolerated in child patients based on our clinical experience, 5 cm H₂O is employed.

Description of the Processes and Interventions

The principal subinvestigator will obtain written informed assent or consent from patients or from their parents. After informed consent is obtained, the principal investigator or subinvestigator will determine the subject's eligibility for enrollment. Enrollment should be done within 2 days after obtaining written consent, and protocol treatment should be started within 1 day after enrollment.

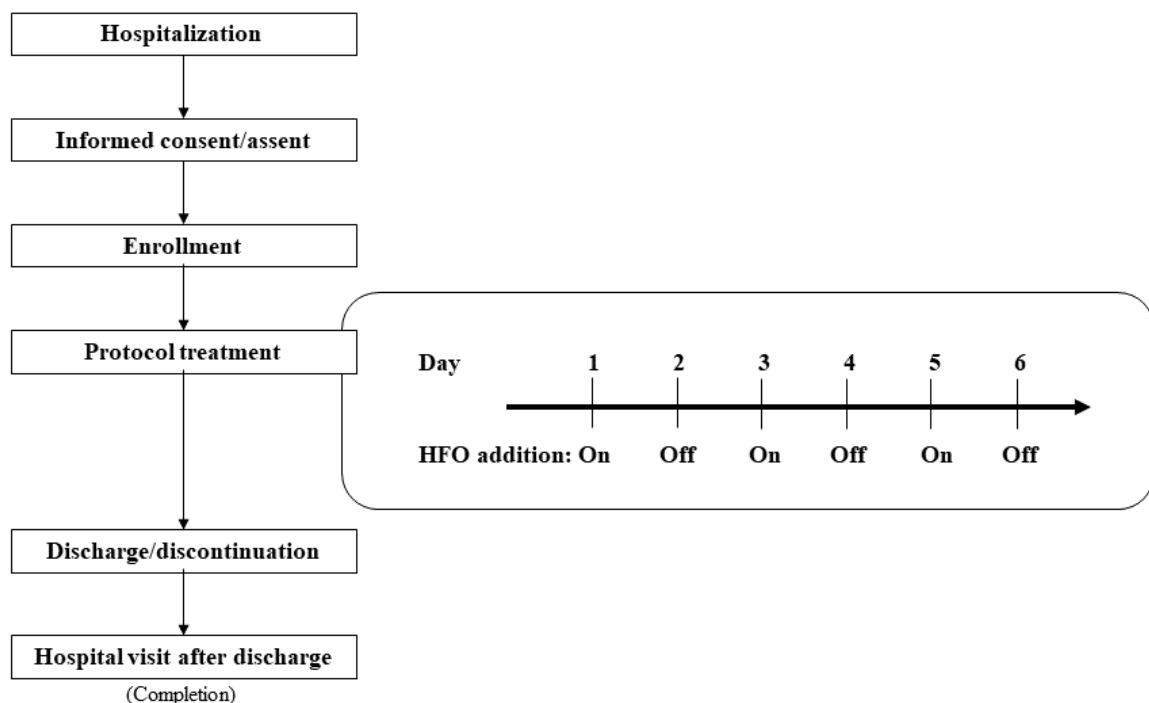
For the patients currently using MI-E, they will continue to use it with their existing settings. For new MI-E users, the setting described above will be used.

The following subject information will be recorded in the case report form (CRF) at the time of obtaining informed consent:

date of informed consent; subject identification code; and subject's baseline characteristics, including sex, birth date, height, body weight, medical history, concurrent diseases, and original setting of MI-E.

HFO will be added to MI-E in every subject on every other day, for 6 days. The addition of HFO on day 1 or day 2 will be determined in a random manner. When the subject is randomly selected to start the protocol with HFO on, the subject will receive MI-E with HFO treatment on days 1, 3, and 5 (Figure 1). If the subject is randomly selected to start the protocol with HFO off, they will receive MI-E with HFO on days 2, 4, and 6. The subject will thus be treated using MI-E with HFO for 3 days and without HFO for 3 days. During protocol treatment, the time for switching to HFO on and off has been set as 9 am.

Figure 1. Outline of the study. Subjects will receive high frequency oscillation (HFO) every other day for 6 days. This shows the study schedule when the subject is randomized to start the protocol with HFO-on.



Criteria for Discontinuation

When continuation with the study is judged to be impossible for any of the following reasons, the principal investigator or subinvestigator will terminate the subject's participation in the study and specify the date and time of discontinuation or dropout, reason for discontinuation, and clinical course in the medical records and CRF. The reasons for discontinuation include the following: when the subject or their parents request to withdraw from the study; when the subject's respiratory status worsens and continuation of the study treatment is judged to be undesirable; when an adverse event, including pneumothorax, occurs and further continuation with the study is difficult; when the subject is discharged from the hospital; and when discontinuation from the study is appropriate for other reasons in the opinion of the principal investigator or subinvestigator.

When subjects who have already used MI-E have completed the protocol, MI-E will be set at the original setting. For subjects who commence use of MI-E for the first time in this study, MI-E will be set at a clinically favorable setting. HFO will be added if requested by the subject. For each subject, the observation period will end on the day when the subject visits the outpatient clinic of Kobe University Hospital for follow-up at 2 to 4 weeks after discharge.

Outcomes

Primary Outcomes

Oxygenation change (SpO₂) is the primary outcome in this study. Data will be obtained at every MI-E use during the study protocol. SpO₂ values will be recorded at any point within 15 min before MI-E treatment and at 3 min after treatment.

Secondary Outcomes

To evaluate the efficacy of the treatment, changes in heart rate will be obtained at the same time point used for SpO₂. Additionally, the amount of mucus removed will be assessed subjectively, according to 3 grades (little, moderate, and abundant). As it was recommended by an external reviewer, peak cough flow was added to the secondary outcomes at the midpoint of the study. As safety end points, adverse events and the incidence of complications during the observation period will be obtained. The worst grade of the event will be considered the severity grade of each observed adverse event.

Data Analysis Methods

Target Sample Size and Rationale

The primary endpoint of this study is the change in SpO₂ (Δ SpO₂) between MI-E with and without HFO. As no previous study has elucidated HFO efficacy in patients with NMDs, it is difficult to estimate how much change will be achieved. We assumed that the ratio of the average Δ SpO₂ difference between HFO-on and HFO-off to the standard deviation would be about 1.1 to 1.2. To test the null hypothesis that there would be a mean change of 0 in the SpO₂ between MI-E with and without HFO, using a paired *t* test with a 2-sided significance level of 5% and 80% power for the analysis of the primary endpoint, the required number of subjects was calculated to be 5. MI-E is applied more than 3 times a day, at least 45 data points are expected to be obtained from HFO-on or HFO-off. As the number of subjects enrolled per year can be assumed to be 1 to 2, the enrollment period has been set to 3 years.

Statistical Analysis

This study will evaluate whether MI-E with HFO is significantly superior to MI-E without HFO in terms of the change in SpO₂ as the primary endpoint of this study. If the protocol treatment with HFO is found to be statistically significantly superior to the treatment without HFO, the study will conclude that the addition of HFO to MI-E is more efficacious than not adding HFO.

The Δ SpO₂ is calculated by subtracting the SpO₂ value of pre-MI-E from the SpO₂ value of post-MI-E. For every subject, the average of Δ SpO₂ with or without HFO will be obtained. Then, a statistical analysis will be performed using a paired *t* test for the average Δ SpO₂ values. The hypothesis testing will use a 2-sided significance level of 5%, with a calculation of the 2-sided 95% CI. The change in heart rate (Δ HR) as the secondary efficacy endpoint will be examined in the same way.

The safety endpoint of this study is the frequency of adverse events and complications. A summary table will be prepared for this endpoint. For estimation of the proportion, the exact 2-sided 95% CI for binomial distribution will be calculated by group. As necessary, Fisher exact test will be used for intergroup comparison. The final analysis will be performed after data from the subjects have been obtained and locked after the end of the follow-up period. The full analysis dataset and safety analysis dataset will consist of all subjects enrolled in this study, who

performed at least one protocol treatment and for whom efficacy data are available.

The statistical analysis will be performed using GraphPad PRISM 7.02 (GraphPad Software).

Ethics

The study protocol was approved by the ethics committee of the Graduate School of Medicine, Kobe University (approval #290090).

Results

A total of 2 subjects have already been recruited and enrolled in this study as of August 2018.

Discussion

Overview

This study will describe the efficacy of the addition of HFO to MI-E for the treatment of NMD patients with mild-to-moderate respiratory disease. A further goal is to provide the best selection of an airway clearance technique to prevent respiratory failure, especially when the patients have respiratory tract infection. The efficacy of HFO therapy in patients with NMDs has not been well studied to date. The efficacy of combined therapy including MI-E and HFO has been studied in patients with amyotrophic lateral sclerosis [20], but that study did not demonstrate an effect of increasing the peak cough flow. The peak cough flow is considered a key marker of the effect of airway clearance techniques. However, it is not recognized as a standard measurement, as the process, including device specification, instructions, and normal ranges, is not yet well-established [18]. In addition, it is difficult to test the peak cough flow on uncooperative pediatric patients or patients with advanced disease who only have a faint cough. In this study, we have set Δ SpO₂ as the primary outcome for evaluating the effect of mucus removal by MI-E and HFO combination therapy. Continuous SpO₂ monitoring is a simple noninvasive method of establishing the percentage of hemoglobin that is saturated with oxygen. It has been used for monitoring both the acute and chronic respiratory status of NMDs [14,21-23]. SpO₂ has also been used as a measure of secretion clearance [24].

We recognized some limitations in this study. First, there is no previous report similar to this study. Therefore, it is difficult to estimate how much change will be obtained between HFO-on and HFO-off conditions and how many target samples will be sufficient to observe a statistically significant difference. Second, this is a single-center study, which limits the generalization of the findings. Third, the included subject group will be heterogeneous, and the subjects are expected to demonstrate considerable variability in severity. Finally, as the optimal HFO setting in patients with NMDs has not been established [25], it is unclear if our appointed setting applied in this study will be appropriate for effective secretion removal.

Conclusions

This is a unique protocol to assess the efficacy of adding HFO to MI-E during the acute phase of respiratory tract infection in

patients with NMDs. This is a preliminary study in an area that requires further investigation; the findings of this study may provide a basis for developing the best way to use MI-E.

Conflicts of Interest

None declared.

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Abbreviations

CRF: case report form

HFO: high frequency oscillation

MI-E: mechanical insufflation-exsufflation

NMD: neuromuscular disorders

SpO₂: transcutaneous oxygen saturation

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Protocol

A Pragmatic Cluster Randomized Trial of an Electronic Clinical Decision Support System to Improve Chronic Kidney Disease Management in Primary Care: Design, Rationale, and Implementation Experience

Elaine C Khoong¹, MD, MS; Leah Karliner^{2,3}, MD, MAS; Lowell Lo⁴, MD; Marilyn Stebbins⁵, PharmD; Andrew Robinson⁶, BS; Sarita Pathak^{2,3}, MPH; Jasmine Santoyo-Olsson², MSc; Rebecca Scherzer⁷, PhD; Carmen A Peralta^{4,7,8}, MD, MAS

¹Division of General Internal Medicine at Zuckerberg San Francisco General Hospital, Department of Medicine, University of California San Francisco, San Francisco, CA, United States

²Division of General Internal Medicine, Department of Medicine, University of California San Francisco, San Francisco, CA, United States

³Multietnic Health Equity Research Center, University of California San Francisco, San Francisco, CA, United States

⁴Division of Nephrology, Department of Medicine, University of California San Francisco, San Francisco, CA, United States

⁵School of Pharmacy, University of California San Francisco, San Francisco, CA, United States

⁶University of California San Francisco, San Francisco, CA, United States

⁷Kidney Health Research Collaborative, San Francisco Veterans Affairs Medical Center, University of California San Francisco, San Francisco, CA, United States

⁸Cricket Health, San Francisco, CA, United States

Corresponding Author:

Elaine C Khoong, MD, MS

Division of General Internal Medicine at Zuckerberg San Francisco General Hospital

Department of Medicine

University of California San Francisco

Ward 13, Building 10, Floor 3

1001 Potrero Avenue

San Francisco, CA, 94110

United States

Phone: 1 4152063188

Email: elaine.khoong@ucsf.edu

Abstract

Background: The diagnosis of chronic kidney disease (CKD) is based on laboratory results easily extracted from electronic health records; therefore, CKD identification and management is an ideal area for targeted electronic decision support efforts. Early CKD management frequently occurs in primary care settings where primary care providers (PCPs) may not implement all the best practices to prevent CKD-related complications. Few previous studies have employed randomized trials to assess a CKD electronic clinical decision support system (eCDSS) that provided recommendations to PCPs tailored to each patient based on laboratory results.

Objective: The aim of this study was to report the trial design and implementation experience of a CKD eCDSS in primary care.

Methods: This was a 3-arm pragmatic cluster-randomized trial at an academic general internal medicine practice. Eligible patients had 2 previous estimated-glomerular-filtration-rates by serum creatinine ($eGFR_{Cr}$) <60 mL/min/1.73m² at least 90 days apart. Randomization occurred at the PCP level. For patients of PCPs in either of the 2 intervention arms, the research team ordered triple-marker testing (serum creatinine, serum cystatin-c, and urine albumin-creatinine-ratio) at the beginning of the study period, to be completed when acquiring labs for regular clinical care. The eCDSS launched for PCPs and patients in the intervention arms during a regular PCP visit subsequent to completing the triple-marker testing. The eCDSS delivered individualized guidance on cardiovascular risk-reduction, potassium and proteinuria management, and patient education. Patients in the eCDSS+ arm also received a pharmacist phone call to reinforce CKD-related education. The primary clinical outcome is blood pressure change

from baseline at 6 months after the end of the trial, and the main secondary outcome is provider awareness of CKD diagnosis. We also collected process, patient-centered, and implementation outcomes.

Results: A multidisciplinary team (primary care internist, nephrologists, pharmacist, and informaticist) designed the eCDSS to integrate into the current clinical workflow. All 81 PCPs contacted agreed to participate and were randomized. Of 995 patients initially eligible by eGFR_{Cr}, 413 were excluded per protocol and 58 opted out or withdrew, resulting in 524 patient participants (188 usual care; 165 eCDSS; and 171 eCDSS+). During the 12-month intervention period, 53.0% (178/336) of intervention patient participants completed triple-marker labs. Among these, 138/178 (77.5%) had a PCP appointment after the triple-marker labs resulted; the eCDSS was opened for 73.9% (102/138), with orders or education signed for 81.4% (83/102).

Conclusions: Successful integration of an eCDSS into primary care workflows and high eCDSS utilization rates at eligible visits suggest this tailored electronic approach is feasible and has the potential to improve guideline-concordant CKD care.

Trial Registration: ClinicalTrials.gov NCT02925962; <https://clinicaltrials.gov/ct2/show/NCT02925962> (Archived by WebCite at <http://www.webcitation.org/78qpx1mjR>)

International Registered Report Identifier (IRRID): DERR1-10.2196/14022

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KEYWORDS

chronic kidney disease; clinical decision support systems; pragmatic clinical trial; electronic health records

Introduction

Management of Early Chronic Kidney Disease

Chronic kidney disease (CKD) is common in adults; in the United States, 14% of all adults and nearly half of individuals aged ≥ 70 years have CKD [1]. CKD is an important predictor of morbidity and cardiovascular mortality [2]. Although most patients with early CKD are seen by primary care providers (PCPs), studies have consistently shown that patients and PCPs remain largely unaware of the patient's CKD diagnosis until the disease is more advanced [3,4]. Even when early CKD is recognized, PCPs frequently are unaware of the best practices for risk stratification and prevention of CKD-related complications [3]. In particular, both CKD staging and complication risk stratification are greatly improved using a triple marker strategy: urine albumin-creatinine ratio (ACR), estimated glomerular filtration rate (eGFR) based on both serum creatinine levels (eGFR_{Cr}) and cystatin-c levels (eGFR_{Cys}) [5-9]. Early detection of CKD and risk stratification enable clinicians and patients to take individualized actions that improve outcomes and have the potential to attenuate progression, such as blood pressure management and renin-angiotensin blockade [10-13], statin therapy [13-16], avoidance of nephrotoxic medications [17,18], and glucose management in individuals with diabetes [19-21].

Approaches to Increase Guideline-Concordant Early Chronic Kidney Disease Management

With the adoption of electronic health records (EHRs), there have been opportunities to implement low-cost interventions to improve patient care. Given that CKD diagnosis is based on laboratory results easily extracted from EHRs, CKD identification and management is an ideal area for targeted electronic efforts [22,23]. Previous studies have shown the feasibility of electronic clinical decision support systems (eCDSS) to improve guideline-concordant care for patients with CKD [24-29]. However, most studies have not been randomized nor have they provided individualized recommendations for

patients based on laboratory results. Instead, they have utilized standard reminders or checklists. In addition, concerns about the eCDSS being burdensome or disruptive to workflow have hindered the development and testing of more complex, individualized eCDSS [23,30,31].

Team-based approaches for providing chronic disease management in primary care practice have also been shown to improve patient outcomes [32,33]. For example, blood pressure (BP) control is improved when managed by nonphysician members of the team, including nurses and pharmacists [34-37]. Initial studies have suggested that CKD, like other chronic diseases, may also benefit from a team-based approach [38,39].

Trial Aims

Given the promise of both eCDSS and team-based care to improve guideline-concordant CKD care in primary care practice, we designed a pragmatic cluster randomized 3-arm trial (usual care; eCDSS; and eCDSS plus pharmacist follow-up). This trial aimed to assess the feasibility and impact of a CKD eCDSS with individualized recommendations and any additional benefit of pharmacist outreach to follow-up compared with usual care. In this paper, we have reported the study design and initial implementation outcomes of this trial.

Methods

Overall Design

This was a 3-arm cluster randomized controlled trial with randomization at the provider level. There was 1 usual care control arm and 2 intervention arms. For patients of PCPs in the intervention arms, the research team ordered triple-marker testing (serum creatinine, serum cystatin-c, and urine ACR) at the beginning of the study period, to be completed when the patient visited the lab for regular clinical care. The eCDSS launched for PCPs and patients in the intervention arms during a regular PCP visit subsequent to completing the triple-marker testing. Patients in the eCDSS+ arm also received a pharmacist phone call to reinforce CKD-related education after a PCP visit in which the eCDSS was utilized. We planned for an 18-month

trial beginning October 4, 2017, that included a 12-month intervention period and subsequent 6-month follow-up period. This trial was registered on ClinicalTrials.gov (NCT02925962). The University of California San Francisco Human Research Protection Program approved the protocol for this study.

Setting

This study was conducted at a general internal medicine practice (with 2 locations) at the University of California San Francisco that cares for a diverse population of more than 24,000 adult patients. The PCPs in this practice include faculty attending physicians, resident physicians, and nurse practitioners (NPs). This practice is a certified primary care medical home (PCMH) that follows a team-based approach to care; each of the 10 teams includes 10 to 14 part-time PCPs, 2 medical assistants, a licensed vocational nurse, and administrative staff. Additional personnel of the PCMH include 5 registered nurses, 2 pharmacy technicians, and a clinical pharmacist available 1 day a week. The EHR used within this practice is Epic (EpicCare, Epic Systems).

Pilot Activities

To optimize the chance of a successful intervention, we worked with a multidisciplinary team (general internist, informatics specialist, and nephrologists) to develop the eCDSS logic. The team focused on areas with the strongest evidence base for CKD management in primary care and developed the logic to apply guideline recommendations in real-time for individual patients. In the first step, patients were classified as either at high risk ($eGFR_{Cys} < 60$ mL/min and/or $ACR > 30$ mcg/mg) or low risk ($eGFR_{Cys} > 60$ mL/min and $ACR < 30$ mcg/mg) for experiencing CKD-related complications [5,17]. After risk stratification, the eCDSS logic focused on 5 domains of CKD care for high-risk patients: (1) cardiovascular risk reduction; (2) potassium management; (3) proteinuria management; (4) appropriateness for nephrology referral; and (5) patient education. For low-risk

patients, the logic defaulted to a recommendation for repeat triple-marker testing in 6 months.

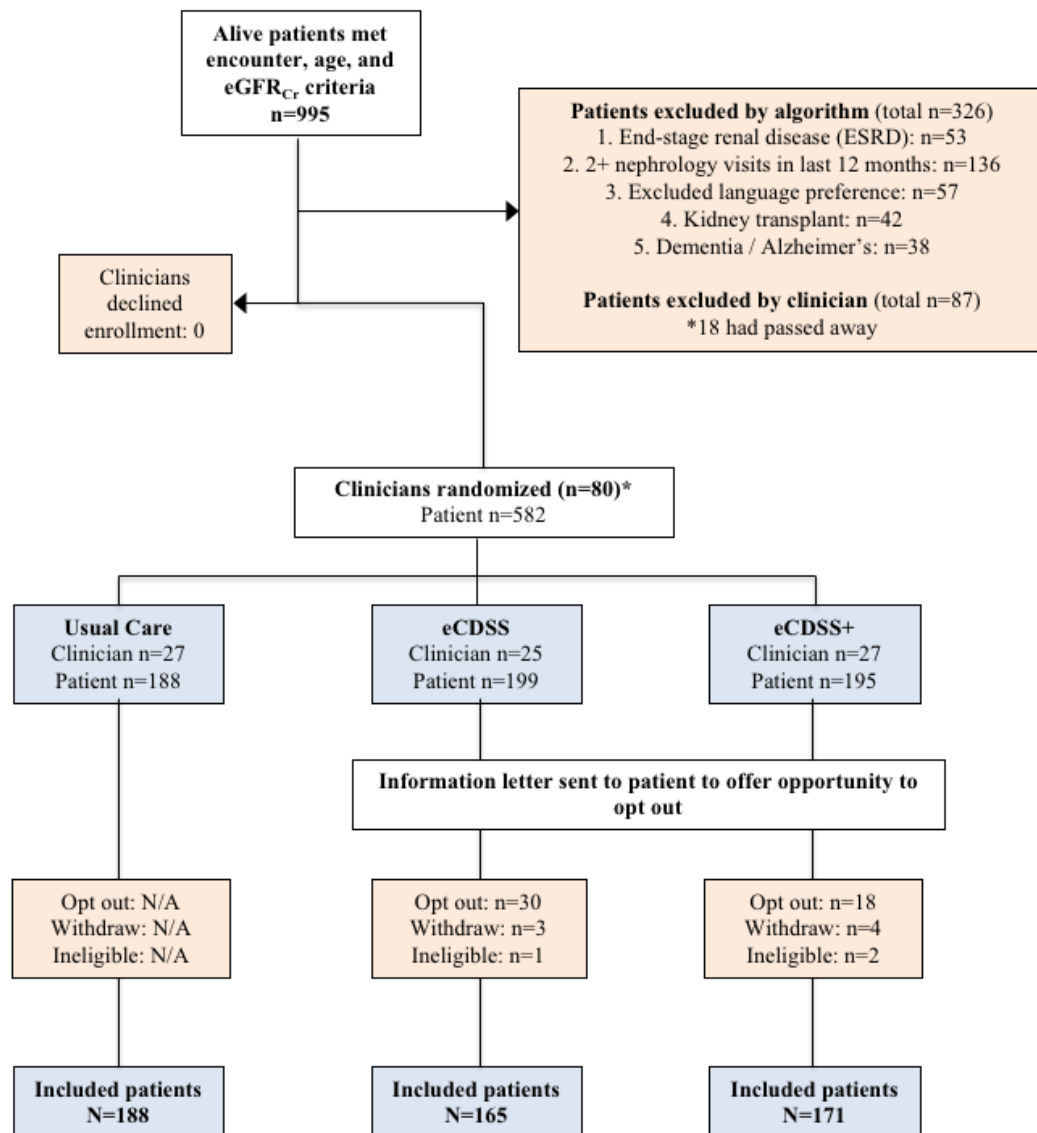
We elicited feedback from PCPs in focus group settings during development of the eCDSS and during implementation planning, which is a recommended practice to increase adoption and uptake of eCDSS [23]. Focus group discussions centered on eCDSS messaging and orders, as well as ways to facilitate integration into the usual clinical workflow.

Eligibility and Selection of Participants

All providers practicing at the general internal medicine practice with a primary care panel were eligible for inclusion and randomization.

Eligible patients were identified using a previously described and validated algorithm [40]. (Patients were considered eligible for inclusion if they were aged 18 to 80 years; had a preferred language of English, Spanish, or Chinese; had at least 2 outpatient $eGFR_{Cr} = 30$ to 59 milliliters/minute (mL/min) at least 90 days apart, one of which was within the 12 months before August 14, 2017 (when providers were first contacted for study recruitment); and had a primary care visit in the past 18 months. (see Figure 1 for the Consolidated Standards of Reporting Trial diagram) Participants were automatically excluded (based on EHR data) if they were deceased; diagnosed with end-stage renal disease; engaged with a nephrology clinic with 2 or more visits in the past 12 months; kidney transplant recipients; or diagnosed with dementia. PCPs were then sent a list of potential participants for inclusion and asked to exclude participants for additional criteria that were unreliably captured when extracted from the EHR: current pregnancy, life expectancy <6 months, limited communication ability owing to impaired cognition or severe mental illness, New York Heart Association Class III/IV heart failure, or known ejection fraction <25%. PCPs could also exclude any other participants they felt would be inappropriate for study staff to contact.

Figure 1. Flow diagram of participant selection. Note that 1 clinician who was randomized did not ultimately participate because their only eligible patient opted out. eGFR_{Cr}: estimated glomerular filtration rate by serum creatinine; eCDSS: electronic clinical decision support system trial arm; eCDSS+: electronic clinical decision support system and pharmacist follow-up trial arm; N/A: not applicable.



Recruitment and Consent Process

We recruited PCPs with eligible patients by eGFR_{Cr} by email between August 14, 2017 and September 8, 2017. PCPs were given 2 weeks to either opt-out entirely or exclude individual patients. We then randomized participating PCPs as described below. Participation letters were mailed to eligible intervention arm patients between September 1, 2017 and September 27, 2017, and patients were given 2 weeks to either return an opt-out card or call the study coordinator to opt out. Patients opting out after the study start date of October 4, 2017, were considered withdrawn from the study.

The usual care group PCPs received no additional contact beyond recruitment from the study team, and the usual care patients were never contacted directly by the study team. Usual care PCPs did have access to the same labs and medications to use at their clinical discretion without any recommendations or direction from the study team.

Randomization and Blinding

We utilized block randomization at the PCP level based on panel size. The study statistician randomized PCP participants to each of the 3 study arms using an automated procedure that accounted for cluster size, to assure balance both in terms of number of patients and number of providers per arm. Eligible patient participants were assigned to study arms based on their PCP's assignment. The study statistician was blinded to the identification of the PCPs and patients and will be similarly blinded for the analyses.

Intervention

Before the eCDSS rollout but after randomization, all participating PCPs randomized to an intervention arm were asked to watch an educational video that provided background on guideline-based CKD care, as well as information on what to expect when an enrolled patient participant came in for a visit. PCPs were given an incentive of US \$10 and a chocolate

bar upon watching the video. Overall, 69.8% (72.0% eCDSS and 67.9% eCDSS+) viewed the video.

Before the eCDSS rollout, between October 5, 2017 and October 12, 2017, one of the study investigators (LK) ordered triple-marker testing for each patient participant from the eCDSS arm (n=169) and each patient participant from the eCDSS+ arm (n=177). We excluded 48 patients who opted out. In total, 10 patients withdrew later.

After the triple-marker testing was ordered, the next time the patient participant visited the lab for their regular clinical care, the triple-marker labs were also collected. We programmed the eCDSS to trigger the first time that the patient participant visited their PCP after all 3 lab results were available. (see Figure 2 for the study workflow) The eCDSS best practice advisory (BPA) appeared above the current medications in the electronic chart

(Figures 3 and 4). PCPs could choose to open the BPA by clicking an “accept” button. We also allowed PCPs to view the recommendations by hovering over the BPA before accepting it. For patient participants categorized as low risk, when the PCP accepted the BPA, triple-marker labs with an expected completion date 6 months hence prepopulated were automatically pending for the PCP to sign. For patient participants categorized as high risk, when the PCP accepted the BPA, a SmartSet (EpicCare, Epic Systems) of tailored orders and recommendations appeared (Figure 5). If the PCP did not open the BPA and sign the orders in the SmartSet during the first PCP visit after the triple-marker labs were available, the BPA would trigger at up to 2 additional PCP visits during the study period. The eCDSS did not trigger if the patient participant saw a provider who was not their PCP.

Figure 2. Flow diagram of study workflow for intervention arms. BPA: best practice advisory; PCP: primary care provider.

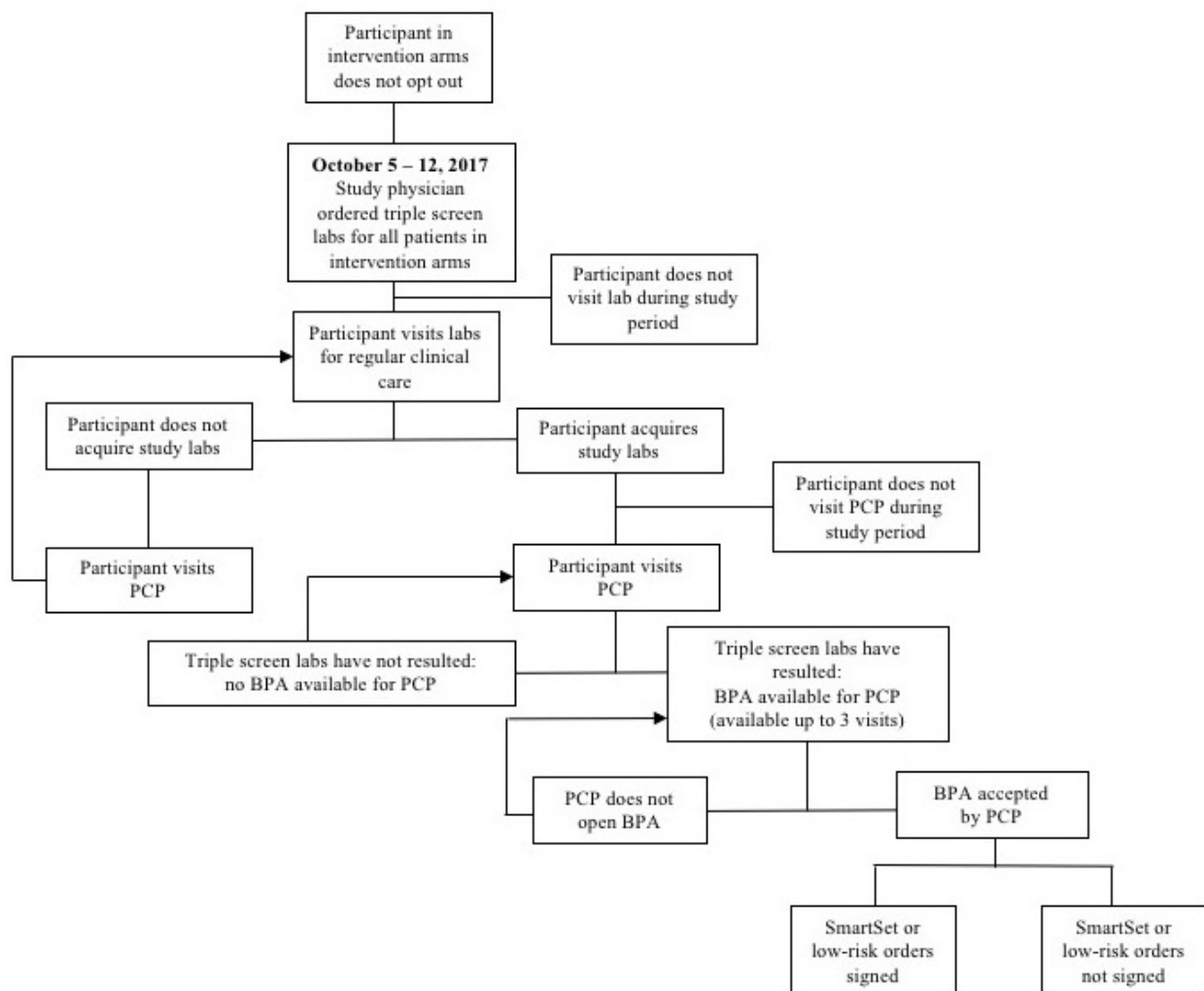


Figure 3. Electronic clinical decision support system trial arm low-risk best practice advisory. CKD: chronic kidney disease; Cr: serum creatinine; eGFR: estimated glomerular filtration rate.

CKD Action Required (1) ⤴

CKD is not confirmed in this patient by recent Cr, cystatin C, or albuminuria.

⚠ Your patient can be considered as having no CKD per international guidelines. Repeat creatinine, cystatin C, and albuminuria in 6 months. If results are stable repeat annually. ✔ Accept (3) ⤴

Order	Do Not Order	🏠 Cystatin C with eGFR
Order	Do Not Order	🏠 Creatinine, Serum / Plasma
Order	Do Not Order	🏠 Albumin (Microalbumin), spot urine

✔ Accept (3)

Figure 4. Electronic clinical decision support system trial arm high-risk best practice advisory. BP: blood pressure; CKD: chronic kidney disease; mg/g: milligrams per grams.

CKD Recommendations 🔄

CKD Action Required (1) ⤴

Your patient has CKD and they are at high risk for progression and/or complications.

⚠ **Blood Pressure Control** ✔ Accept (1) ⤴

Patients with CKD should have sustained BP <140/90. Consider lower targets in persons with albumin to creatinine ratio ≥ 300 mg/g.

Open SmartSet Do Not Open **Personalized CKD Recommendations** Preview

✔ Accept (1)

Figure 5. Electronic clinical decision support system trial arm example SmartSet. ACEi/ARB: angiotensin converting enzyme inhibitor / angiotensin II receptor blocker; AVS: after visit summary; CKD: chronic kidney disease; eCDSS: electronic clinical decision support system; CDSS+: electronic clinical decision support system and pharmacist follow-up trial arm; K+: potassium; mg/g: milligrams per grams; NSAID: nonsteroidal anti-inflammatory drug; OTC: over-the-counter;.

Personalized CKD Recommendations ^

✓ From BestPractice

Your patient has CKD and they are at high risk for progression and/or complications.

Blood Pressure Control
Patients with CKD should have sustained BP <140/90. Consider lower targets in persons with albumin to creatinine ratio >=300 mg/g.

▼ Recommendations

Review prescription and OTC NSAID use and counsel patient on NSAID minimization

▼ Albuminuria / Potassium Management

This patient has albuminuria

- Consider adding/maximizing ACEi/ARB and recheck K+ in 2 weeks

lisinopril (PRINIVIL,ZESTRIL) 10 mg tablet
Disp-30 tablet, R-1

losartan (COZAAR) 25 mg tablet
Disp-30 tablet, R-1

✓ Potassium, Serum / Plasma ■

Lab Collect, Routine, Expected: 9/8/2017, Expires: 8/25/2018
P Container details: Light green top preferred, Gold top acceptable
Resulting Agency - UCSF LAB

▼ Patient Instructions

- ✓ AVS - General CKD Education
- ✓ AVS - General CKD Diet Education
- ✓ AVS - NSAID Minimization

In addition to a reminder of BP targets in CKD, the SmartSet for patient participants classified as high risk for progression and/or complications of CKD used real-time EHR lab and medication data to recommend any of the following that applied:

1. Cardiovascular risk reduction: recommendation for use of statin in all individuals aged ≥ 50 years not already on a statin, as recommended by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [17].
2. Potassium management: diet and diuretic recommendations.
3. Proteinuria management: initiation or titration of renin-angiotensin blockade with angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB).
4. Nephrology referral for highest risk participants: highest risk was defined as one of: confirmed $eGFR_{Cys} < 30$ mL/min; potassium > 5.5 mEq/L; ACR > 300 mcg/mg, systolic blood pressure (SBP) > 150 millimeters of mercury (mm Hg) despite 3 agents including a diuretic; $> 3\%$ risk of five-year progression kidney failure based on Tangri equation [41].
5. Patient education: patient education materials to populate in the after-visit summary (AVS) focused on CKD general information, avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs), and dietary recommendations.

The second intervention arm (eCDSS+) included a pharmacist follow-up visit by telephone. If the SmartSet was signed during the PCP visit, a pharmacist would call the participant within 2 weeks of the visit to reinforce CKD-related teaching and medication changes from the visit as well as complete a

comprehensive medication review. Information on the telephone encounter was documented in the EHR and sent to the PCP; any urgent clinical issues identified during the call were highlighted for the PCP as needing their follow-up. Providers in the eCDSS+ group also were encouraged to make a warm handoff to the pharmacist by including anticipatory guidance about the pharmacist phone call within the after-visit summary and distributing a business card with the pharmacist's photo and phone number for their patient participants at the time of using the SmartSet.

Given that the study physician ordered labs at the start of the intervention period, safety checks were put into place to ensure adequate review of the laboratory results. A nephrologist (LL) from the study team reviewed weekly laboratory results specifically to identify the following: $eGFR_{Cr}$ decline $> 30\%$ from baseline, ACR ≥ 1000 mcg/mg, adherence to nephrology referrals, and any discordance $> 30\%$ between $eGFR_{Cr}$ and $eGFR_{Cys}$. In all of these situations, the nephrologist contacted the PCP to ensure appropriate follow-up. Specifically, in cases of discordance between the 2 types of eGFR levels, the nephrologist advised PCPs to dose medications based on $eGFR_{Cys}$ when the clinical scenario suggested that $eGFR_{Cr}$ may not be accurate.

Strategies to Encourage Intervention and Behavior Change

Implementation studies have shown that interventions designed with a theoretical basis are more likely to be successful [42,43].

Therefore, we utilized several theory-based strategies to encourage provider uptake of the eCDSS and participant uptake of provider and/or pharmacist recommendations. We classify these strategies using the capability, opportunity, motivation, behavior framework (or COM-B), which asserts that capability, opportunity, and motivation are essential conditions that impact behavior [44,45].

To encourage provider uptake and use of CKD guidelines, we addressed *capability barriers* (such as knowledge about the guidelines or the eCDSS or forgetting to discuss CKD owing to limited bandwidth). During the recruitment phase, we educated eligible PCPs about the prevalence of CKD within their panel by sending a list of their potentially eligible participants along with information about the importance of recognizing and managing CKD early. Shortly before intervention implementation, we sent a training video about the CKD guidelines and the eCDSS to the participating intervention PCPs. The eCDSS itself also served as a prompt to discuss CKD during the visits.

To address PCP *opportunity barriers*, we designed the eCDSS to fit into the physician workflow and to contain all the necessary CKD-related orders and patient education in one easily accessible place during a clinical visit.

To address PCP *motivation barriers*, we provided a small incentive to the participating intervention PCPs who watched the training video. Finally, to enhance use of the BPA, study personnel sent an individual email reminder to the intervention PCP the day before each eligible patient participant visit.

Although the eCDSS itself was a provider-facing intervention, we used strategies to encourage patient participant behavior change. To address *capability barriers* (such as knowledge of CKD or forgetting the provider recommendations), the CDSS SmartSet had CKD-based patient educational handouts in the patient's preferred language. The pharmacist phone call was also designed to reinforce the knowledge provided at the office visit and *motivate* the patient participant to adhere to medication and avoid NSAIDs.

Data Collection

For patient participants, the EHR was used to collect baseline data about demographic characteristics (age, sex, race-ethnicity, preferred language, and insurance status); medical

co-morbidities (cerebrovascular disease, congestive heart failure, coronary artery disease, diabetes mellitus, hyperlipidemia, and hypertension); current medication prescriptions (statin, ACEi/ARB, and diuretics); previous documentation of CKD on problem list and/or as a visit diagnosis, most recent blood pressure, eGFR_{Cr}, eGFR_{Cys} (if available), and urine ACR (if available) before enrollment.

Primary outcome data on BP will be extracted from the EHR. Baseline BP was defined as the most recent ambulatory BP measurement before final enrollment on October 4, 2017. All patient participant ambulatory BP measurements were collected during the intervention period and will continue to be collected for the 6 months after the end of the intervention.

Secondary outcomes will be collected primarily using automated EHR data extraction algorithms. The outcomes acquired through data extraction include all secondary outcomes except for provider and patient-centered outcomes, which are collected via surveys. Up to 25 participants in each of the 3 arms were surveyed to assess patient knowledge about CKD and NSAID avoidance. Patient participants in the eCDSS arm were surveyed 2 weeks after a visit in which the SmartSet was utilized; those in the eCDSS+ arm were surveyed 2 weeks after their pharmacist follow-up call, and those in the usual care arm were surveyed 2 weeks after a visit with their PCP during the study period. All participating intervention PCPs will be surveyed about their perception of the feasibility and utility of the eCDSS and pharmacist calls (for CDSS+ providers).

Outcomes

Primary Outcome

A summary of pre-planned study outcomes is shown in [Textbox 1](#). The primary clinical outcome of this study is BP change from baseline. This outcome will be assessed as a continuous variable (separately for both diastolic and systolic BP change from baseline) and dichotomous variable (sustained control, defined as BP <140/90 in 2 or more consecutive visits during the trial). As this study was initiated before the 2017 BP guidelines, <140/90 was used to define control; this value also aligns with current KDIGO recommendations [17,46]. Rates of control at the end of the intervention period and 6 months later will be assessed based on the most recent BP measurement carried forward.

Textbox 1. Outcome measures. ACEi/ARB: angiotensin converting enzyme inhibitor / angiotensin II receptor blocker; BPA: best practice advisory; CKD: chronic kidney disease; PCP: primary care provider; NSAID: nonsteroidal anti-inflammatory drug.

Primary outcome: blood pressure

- Systolic blood pressure change
- Diastolic blood pressure change
- Controlled blood pressure (defined as <140/90)

Secondary outcomes

- Process
 - PCP awareness of CKD diagnosis (CKD inclusion on problem list or visit diagnosis)
 - ACEi/ARB utilization for albuminuria
 - Statin therapy for eligible high-risk CKD patients
 - Initiation of statin therapy
 - Total use of statin therapy
- Patient-centered
 - Knowledge about CKD
 - Awareness of NSAID avoidance in CKD

Implementation outcomes

- Reach
 - Recruitment rate of providers and patients
 - Proportion that complete triple marker screen
 - Proportion with PCP visit after complete triple marker screening
 - Proportion of participants where BPA is available for PCP
 - Proportion of participants identified as high- vs low-risk CKD
- Adoption
 - Proportion where PCP signed Smart Set when BPA was available
 - Proportion of CDSS+ participants that received pharmacist phone call after PCP signed Smart Set
- Implementation
 - Proportion of orders signed or patient education provided by PCP after opening Smart Set
 - Proportion referred to nephrology and followed up with nephrology after signing Smart Set
 - Proportion of low-risk CKD patients that receive repeat triple screen
- Maintenance
 - PCP satisfaction with eCDSS
 - PCP intent to continue using eCDSS

Secondary Outcomes

Our main secondary outcome is PCP awareness of the patient participant's CKD diagnosis, as measured by inclusion of CKD-related International Statistical Classification of Diseases and Related Health Problems-10th Revision codes on the problem list or as a visit diagnosis. Additional secondary outcomes include process of care, patient-centered, and implementation outcomes.

There are 2 main process of care outcomes: (1) the proportion of patient participants with albuminuria prescribed ACEi/ARB and (2) appropriate use of statins. Appropriate statin use is defined both as the proportion of all patient participants aged ≥ 50 years prescribed statin therapy and the proportion of participants initiated on statin therapy after study start date.

Patient-centered outcomes include patient knowledge about CKD and NSAID avoidance as measured by patient surveys.

In addition to the effectiveness outcomes described above, the implementation outcomes are described in detail in [Textbox 1](#) using the reach, effectiveness, adoption, implementation, and maintenance (or RE-AIM) framework to highlight measures crucial to successful implementation [47]. In this paper, we report initial implementation results, including all of the Reach outcomes and the first Adoption outcome (PCP SmartSet use).

Analyses

Baseline demographic and clinical characteristics will be summarized and study balance by study arm will be assessed using descriptive statistics as well as methods that account for the lack of independence among patients in the same cluster [48]. Balance will be assessed with logit link generalized estimating equation (GEE) for categorical variables and linear GEE models for continuous variables. Clustering will be accounted for using an exchangeable correlation matrix with robust standard errors. We anticipate controlling for characteristics that are associated with outcomes but differ at baseline between arms and using multivariable regression analyses with GEE to account for cluster randomization in the reporting of the final outcomes of our study. Sensitivity analyses will include *as treated* analyses with inverse probability weighting to determine impact of participants changing providers/study arms as well as to determine impact of any differences in the number of assessments or clinic visits by study arm. Primary analyses will follow intention-to-treat principles.

Sample Size and Power Calculation

Based on preliminary data from our institution's EHR, it was determined that there would be a maximum of 1400 participants in the practice who could meet inclusion criteria. The study was powered for the clinical outcome of BP change, with calculations performed using the `clustersampsi` command for Stata version 11.2. We assumed a 2-tailed alpha level of 0.05, an intraclass correlation coefficient of 0.025 based on studies

in primary care settings [49,50], and a standard deviation of 5 mmHg. Assuming 23 clinicians per arm with at least 15 patients per clinician (ie, 345 patients per arm), we estimated that we would have 80% power to detect a difference as small as 1.27 mmHg between arms.

Results

Implementation Outcomes: Reach

Implementation outcomes at the end of the 12-month intervention period on October 4, 2018, are summarized below:

Recruitment Rate

At the provider level, all 81 eligible PCPs (47 faculty attending physicians, 31 resident physicians, and 3 NPs) agreed to participate (100%). In total, 79 of the 81 providers (98%) were included because 2 providers had no remaining eligible participants after exclusion and opt-outs. At the patient level, 995 patients who met the initial eligibility criteria were identified. A total of 316 / 995 (31.8%) potential patient participants were excluded using automated algorithms, and clinicians excluded another 90 patients ([Figure 1](#)). A total of 582 patient participants were distributed to the 3 arms based on provider randomization. After an additional 3 patients were excluded (owing to patient deaths not recorded in EHR before randomization) and 55 / 582 patients (9.5%) opted out or withdrew, 524 patient participants (90.0% of eligible 582 participants) were included in the study: 188 usual care, 165 eCDSS, and 171 eCDSS+.

Baseline patient participant characteristics are shown in [Table 1](#). The 55 patients that opted out/withdrew were similar to the patient participants across multiple traits—including age, gender, race/ethnicity, language preference, and co-morbidities—except they had lower renal function on average: eGFR_{Cr} (52.7 [SD 11.7] versus 56.0 [SD 11.8]; $P=.046$).

Table 1. Baseline characteristics of all included patients (N=524).

Patient characteristic	Values
Age (years), mean (SD)	70.3 (8.9)
Female, n (%)	236 (45)
Race/ethnicity, n (%)	
White	277 (53)
Asian	118 (23)
Black/African American	70 (13)
Hispanic	38 (7)
Other	20 (4)
Preferred language, n (%)	
English	469 (90)
Chinese	39 (7)
Spanish	16 (3)
Insurance, n (%)	
Private insurance	146 (28)
Medicare	215 (41)
Medicaid	163 (31)
Medical co-morbidities, n (%)	
Cerebrovascular disease	36 (7)
Congestive heart failure	40 (8)
Coronary artery disease	95 (18)
Diabetes mellitus	199 (38)
Hyperlipidemia	302 (58)
Hypertension	377 (72)
Medication use, n (%)	
Angiotensin converting enzyme inhibitor/angiotensin II receptor blocker	319 (61)
Diuretic	199 (38)
Statin	353 (67)
CKD-related outcomes, n (%)	
Chronic kidney disease (CKD) on problem list	61 (12)
CKD on problem list or primary care visit diagnosis by ICD-10 ^c codes	247 (47)
Systolic BP ^a (mm Hg), median (Q1-Q3)	128 (117-140)
Diastolic BP (mm Hg), median (Q1-Q3)	68 (62.5-75)
BP controlled ^b (<140/90), n (%)	373 (71)
Estimated glomerular filtration rate based by serum creatinine (mL/min), mean (SD)	56.0 (11.8)

^aBP: blood pressure.

^bBP control reported based on only the most recent measurement before the start of the study.

^cICD-10: International Classification of Diseases, Tenth Revision, Clinical Modification.

Completion of Triple Marker

Of the 336 patient participants in the intervention arms, 178 (53.0%) completed the triple-marker screening.

PCP Visits

Of the 178 patient participants who completed a triple-marker screen, 138 (77.5%) had a PCP visit during the 12-month intervention period. This was 41.1% (138/336) of all intervention participants.

PCP BPA Use

Of the 138 participants with a PCP visit, the BPA was opened for 102 participants (73.9%). This was 30.3% (102/336) of all intervention participants.

Implementation Outcomes: Adoption

SmartSet Use

Of the 102 participants in which the BPA was opened, orders were signed or patient education was given from the SmartSet for 83 participants (81.4%).

Discussion

Principal Findings

In this report, we describe the rationale, design, and initial implementation outcomes of a 3-arm pragmatic trial that assessed the feasibility and preliminary effectiveness of an eCDSS to improve CKD management in primary care compared with usual care. This study builds on previous pragmatic trials focused on EHR-based interventions to improve CKD management [28,29,51,52] and supports the feasibility of using EHRs to identify study participants, intervene in early CKD management, and measure study outcomes. Given its design as a pragmatic trial (per Pragmatic Explanatory Continuum Indicator Summary, or PRECIS, criteria [53]), we found high rates of participation by providers and low opt-out rates by patients. We also found high rates of eCDSS use by providers.

This study has many innovative components. We utilized a 3-armed trial design, which included a usual care group as well as a group with pharmacist-patient engagement after the provider-facing electronic intervention. In addition, our clinical eCDSS was mostly automated and individualized to patients based on laboratory results, rather than a generic CDSS for all participants. We also implemented the recommended triple-marker risk stratification approach to better characterize participants' risk for CKD progression. Our participants included non-English speakers, who have been excluded from many other trials. This trial also included multiple types of outcomes allowing for a deeper understanding of the intervention's impact on care processes. Reviews of eCDSS have found that few studies assess unintended consequences or adverse effects of a CDSS, which can be widespread as CDSS interventions often automate multiple actions [54,55]. This trial integrated safety measures and their tracking by a nephrologist allowing not only for measurement of safety but also the ability to ensure that any new concerning clinical findings found owing to the trial would be addressed. As previously recommended, it is important to first pilot interventions before widespread implementation to ensure there are no adverse effects in a small population where safety can be more easily assessed [56].

One of the greatest challenges of this trial was its dependence on data analysts experienced at working with the EHR to program and implement the intervention as well as extract outcomes data. The study team devoted substantial time to troubleshoot unanticipated problems with the eCDSS programming and capture of outcomes. Every update or change to the EHR processes had the potential to disrupt the trial

implementation. The team regularly validated the eCDSS and data capture through manual chart reviews. The inaccuracies of EHR data extraction are well-documented [57]. Despite the presence of an explicit trial infrastructure in our EHR, implementation of the intervention and data collection was far from seamless. Studies that rely on the EHR to deliver interventions and collect outcomes must ensure adequate time and resources for a multidisciplinary team to validate the intervention and review data inaccuracies in an ongoing manner for all EHR-based trials.

Comparison With Previous Work

In this trial, we found much higher reach and adoption of eCDSS by PCPs than previous studies where adoption rates were frequently <50% [55,58]. We believe there are multiple explanations. Few electronic alerts are currently used in this practice, so providers have not yet experienced fatigue associated with the growing presence of alerts [59]. Moreover, the eCDSS was designed by a multidisciplinary team, facilitating buy-in from all stakeholders and ensuring all perspectives were considered in determining how the eCDSS would impact workflow. Finally, study staff (including a lead investigator who works within the primary care practice) served as on-the-ground champions and made significant efforts to educate, remind, and incentivize PCPs.

We experienced many of the same challenges as other pragmatic trials during implementation of this EHR-dependent intervention. There was a period of time between provider recruitment, randomization, participants being contacted to opt out, and the study start date; as a result, 18 patients passed away before randomization and 2 additional patients passed away before the start of the study. Importantly, nearly half of the participants in the intervention arms never completed the triple-marker screen and therefore never had the opportunity to receive the eCDSS interventions. Another one-fifth of participants who completed the triple-marker screen did not have a PCP visit after the triple-marker screening and also did not receive the eCDSS. These barriers, common in many eCDSS trials, prevented the intervention group from receiving the desired intervention.

Limitations

As a pilot study, this study was limited by its inclusion of patients and providers from a single institution. Therefore, both the intervention and strategies to encourage intervention uptake were adapted to meet the needs of this single institution that uses Epic Systems' EHR. However, we have found that the patient population in this clinic is similar to others [60], and Epic is a widely used EHR in multiple health systems. As a pragmatic trial, our sample size was smaller than initially anticipated and will thus ultimately impact our power to detect changes in our primary outcome. The short follow-up period for this pilot study will also limit our ability to assess some clinical outcomes. However, we were still able to use this pilot study to determine the feasibility of this intervention.

Conclusions

As the prevalence of CKD grows, primary care teams will increasingly be responsible for management of CKD. Clinical

decision support tools may be a low-cost effective solution to enhance guideline-concordant care for this underdiagnosed disease. We describe the design and implementation of a pragmatic clustered randomized controlled trial to evaluate the

feasibility and effectiveness an EHR-embedded electronic clinical decision support tool to improve management of CKD in primary care. Results from this study can guide design of future pragmatic eCDSS trials to improve CKD care.

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Authors' Contributions

EK analyzed and interpreted data and drafted the manuscript. LK, LL, and MS conceived and designed the study; interpreted data; and substantively revised the manuscript. AR, SP, JS acquired and analyzed data. RS designed the study; analyzed data; and substantively revised the manuscript. CP conceived and designed the study; interpreted data; and substantively revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

CP is currently the chief medical officer of Cricket Health. The other authors declare they have no conflicts of interest.

Multimedia Appendix 1

CONSORT - EHEALTH checklist (V 1.6.1).

[\[PDF File \(Adobe PDF File\), 3MB - resprot_v8i6e14022_app1.pdf\]](#)

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Abbreviations

- ACEi:** angiotensin converting enzyme inhibitor
- ACR:** urine albumin-creatinine ratio
- ARB:** angiotensin II receptor blocker
- BP:** blood pressure
- BPA:** best practice advisory
- CKD:** chronic kidney disease
- eCDSS:** electronic clinical decision support system trial arm
- eCDSS+:** electronic clinical decision support system and pharmacist follow-up trial arm
- eGFR:** estimated glomerular filtration rate
- eGFR_{Cr}:** estimated glomerular filtration rate by serum creatinine
- eGFR_{Cys}:** estimated glomerular filtration rate by serum cystatin-c
- EHR:** electronic health record
- GEE:** generalized estimating equation
- ICD-10:** International Classification of Diseases, Tenth Revision, Clinical Modification
- KDIGO:** Kidney Disease: Improving Global Outcomes
- NP:** nurse practitioner
- NSAID:** nonsteroidal anti-inflammatory drug
- PCMH:** primary care medical home
- PCP:** primary care provider

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Protocol

Policies and Programs for the Prevention and Control of Breast Cancer in Mexican and Latin American Women: Protocol for a Scoping Review

Igor Martin Ramos Herrera¹, MD, PhD

Center for Research on Health Information Systems and Management, Department of Public Health, University of Guadalajara, Guadalajara, Mexico

Corresponding Author:

Igor Martin Ramos Herrera, MD, PhD

Center for Research on Health Information Systems and Management

Department of Public Health

University of Guadalajara

Sierra Mojada 950

Colonia Independencia

Guadalajara, 44340

Mexico

Phone: 52 (33)1058200 ext 33900

Email: iramos@cucs.udg.mx

Abstract

Background: Breast cancer has become a major public health problem around the world, especially in Mexico and Latin America. Screening for breast cancer, which involves self-examination, mammography, and clinical breast examination, is crucial for early diagnosis, which in turn is associated with improved outcomes and survival rates. Although breast cancer prevention and control activities are being implemented in Mexico and Latin America, as in many other countries, there are no comprehensive public reports that provide information on the number, type, and scope of these activities; the impact of the programs and actions implemented; and the policies that form the basis of these programs.

Objective: This study aims to present the design of a protocol for a scoping review on the policies and action programs for breast cancer care in Mexico and Latin America, as well as their objectives and implementation plans.

Methods: This scoping review is guided by the methodological reference framework proposed by Arksey and O'Malley. A systematic search of the following electronic databases will be performed: MEDLINE (PubMed), MEDLINE (EBSCOHost), CINAHL (EBSCOHost), Academic Search Complete (EBSCOHost), ERIC, ISI Web of Science (Science Citation Index) in English and Cochrane and MEDES-MEDICINA in Spanish. A search will be conducted to identify relevant studies published between 2000 and 2018. Data will be analyzed and presented in descriptive statistics and qualitative content analyses with analysis matrices and semantic networks. The selected studies will be arranged according to the Specific Action Program, Prevention and Control of Female Cancer 2013-2018.

Results: The intention is to perform this review during the first and second quarters of 2019 and present the results to health authorities by the first quarter of 2020. Results will also be sent for publication to an indexed journal by the second quarter of 2020.

Conclusions: We present a protocol for a scoping review—type literature revision based on the Arksey and O'Malley methodology to be performed during the first quarter of 2019. According to this 6-stage methodology, we will identify the scientific publications that present or analyze first-level action policies and programs for breast cancer care in Mexican women, as well as the results of these policies and programs, if any. The outcome of this review will be used to define the basis of a research project intended to design an educational intervention strategy for the general public in Mexico to enable them to deal with this public health problem.

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KEYWORDS

breast neoplasms; public policies; primary health care; systematic review

Introduction

Background

Breast cancer has become a major public health problem all around the world, especially in Latin America. In 2015, Mexico reported an incidence rate of 14.8 cases per 100,000 women [1], and the mortality rate was 15 cases per 100,000 women aged 20 years and older. Though self-examination and mammograms were recommended in 2007 as the best ways to diagnose this type of cancer [2], the Canadian Task Force on Preventive Health Care obtained recent evidence that self-examination does not reduce breast cancer mortality compared with those who did not practice it [3]; thus, health education is extremely important so that women can learn about this disease and feel encouraged to attend their medical service immediately after identifying any anomaly in their breasts, as advised by the Mexican Official Norm for Breast Cancer Detection and Control for each age group [4]. As in most of the countries of Latin America, breast cancer prevention and control activities are also being implemented in Mexico [5], but there are no comprehensive public reports that could provide information on the number, type, and scope of these activities; the impact of the programs and actions implemented; and the policies that form the basis of these programs.

One approach to gather this information is by conducting systematic reviews of scientific literature. There are different types of reviews, but in this study, we will focus on the scoping review or systematic exploratory review [6], as it is known in Spanish. Although designing a formal implementation protocol before carrying out a scoping review is not considered a requirement because of the possibility of study duplication [7], at an international level, there has been a trend toward publishing these protocols in scientific journals to shed light on the review methodology and scope.

Theoretical and Evidence Base

Although protocols for scoping reviews regarding the prevention and control of chronic diseases such as obesity [8], breast cancer [9], or physical activity [10] have been published, at present, there is no reference in Mexico or Latin America of a scoping review about the policies and programs for the prevention and control of chronic diseases, including breast cancer. Therefore, a protocol was designed to perform a scoping review of the scientific publications that can identify the nature, extent, and range of breast cancer prevention and control policies and programs for Mexican and Latin American women to evaluate how both align with the existing actions on an international level and identify the gaps in this regard.

The Official Mexican Standard NOM-041-SSA2-2011 [4] recognizes that the main risk factors for this disease are grouped in 4 categories: (1) biological risk, including gender, age, inheritance, history of breast changes, extended menstrual cycle, and high breast density; (2) iatrogenic or environmental risk, including exposure to ionizing radiation and thorax radiation therapy; (3) risk in the reproductive history, including pregnancy absence, first pregnancy at an advanced age, and perimenopausal and postmenopausal hormone therapy lasting more than 5 years; and (4) high-risk lifestyles, including high-carbohydrate and

low-fiber diets, high-fat diet, obesity, physical inactivity, alcohol consumption of more than 15 g/day, and smoking. Early diagnosis is one of the most important elements for successful treatment, and its delay means that patients are diagnosed at advanced cancer stages [11-13], which results in poor prognosis and survival rates.

Current health policies regarding breast cancer, which are included in the official standards, state decrees, and clinical practice guidelines, are based on primary and secondary prevention [4,5]. These levels of prevention focus on minimizing lifestyle risks, but they also focus on early diagnosis and timely care, which leads to improved survival rate for those women who receive a timely breast cancer diagnosis.

The Specific Action Program, Prevention and Control of Female Cancer 2013-2018 [5] identifies breast cancer as a public health problem. This action program issues from the Sectorial Health Program, which derives from the National Development Plan in Mexico 2013-2018 [14]. The specific action program states the objectives and strategies that shall be followed by health authorities to (1) increase the joint responsibility of men and women in the prevention and early detection of cervical-uterine and breast cancer; (2) reinforce the detection, follow-up, and timely quality treatment of cervical and breast cancer cases, and (3) contribute to the convergence of cancer information systems between the institutions of the National Health System.

Prevention for breast cancer in women can be primary or secondary. Primary prevention includes all the activities that are aimed to reduce the onset of breast cancer by controlling the causal factors and the predisposing or determining factors [2,15], with the aim of reducing the incidence of this disease. According to the Official Mexican Standard 041-SSA2-2011 [4], primary breast cancer prevention actions include good health promotion, specific protection, and chemoprophylaxis.

Secondary breast cancer prevention, on the other hand, is completely oriented toward early disease diagnosis in an incipient stage (without clinical manifestations), which means looking for signs and symptoms of the disease in women who *appear to be healthy* [2]. The same Official Mexican Standard 041-SSA2-2011 identifies early diagnosis and timely treatment programs to limit the damage that cancer may cause, which can be achieved through periodic medical examination and planned case search. This official standard establishes that prevention activities, in general, include educating the population about the risk factors, promoting healthy lifestyles that may contribute to reducing breast cancer morbidity, as well as encouraging the demand of early detection to improve the opportunity of diagnosis and treatment.

Finally, breast cancer detection activities consist of 3 types of specific interventions that address the female population according to their age and vulnerability group: (1) self-examination to identify initial symptoms, (2) clinical examination for early identification, and (3) mammograms for preclinical phase identification. Therefore, educational actions at a preventive level must focus on orienting and educating women so that they perform these 3 types of intervention routinely from the age of 20 years onward and with the frequency established by the standards.

Objective

On this basis, in the words of Arksey and O'Malley [16], a scoping review would help to describe in more detail the actual primary and secondary prevention programs for breast cancer that have been implemented by the countries in the Americas, thereby providing a summary of those findings to policy makers, health authorities, and other researchers. Therefore, the objective of this study is to present the design of a scoping review protocol on the policies and action programs for breast cancer care in Mexico and Latin America, as well as their objectives and implementation plans.

Methods

Design

This scoping review protocol was based on the methodological framework proposed by Arksey and O'Malley [16], which was later modified by the Joanna Briggs Institute [17]. Though this work is based on Arksey and O'Malley's guidelines, other guidelines for systematic reviews were also examined, such as the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocols [18] or the Consolidated Standards of Reporting Trials [19], but these were intended for reviews on clinical evidence and not for primary health care programs or scoping reviews. However, we performed a checklist using the PRISMA Extension for Scoping Reviews (PRISMA-ScR) [20] guidelines.

A systematic search will be performed of the main electronic databases available internationally and that can be accessed in full text through the Digital Library of the University of Guadalajara [21], Mexico. The databases that will be consulted

are as follows: MEDLINE (PubMed), MEDLINE (EBSCOHost), CINAHL (EBSCOHost), Academic Search Complete (EBSCOHost), ERIC, ISI Web of Science (Science Citation Index) in English, Cochrane, and MEDES-MEDicina in Spanish. The searching period will be between 2000 and 2018. The protocol will be based on the 6 stages established by the Arksey and O'Malley's [16] methodology.

Some adaptations to these stages will be made as the process advances, with the intention of ensuring a feasible approach, consistent with the existing literature. Each one of these stages is described as follows.

Stage 1: Identifying Research Questions

According to the guidelines of the methodological framework, an initial iterative process of revisions must be carried out to raise 1 or more questions that may guide the research. For this purpose, the iterative process has already begun with the intention of identifying existing parameters that can give structure to the review as well as define in operational terms, database consultations about breast cancer diagnosis within the framework of the breast cancer prevention and control actions performed by the health authorities in Mexico and Latin America. This initial search yielded very few results, but among those, we found the Specific Action Program, Prevention and Control of Female Cancer 2013-2018 [5], whose guidelines we decided to take as an important preliminary finding to raise the base questions for the review because we consider that they reflect real actions that are developing in the region. [Textbox 1](#) shows the questions proposed for this scoping review following such guidelines, as well as the definitions that will be used to make this search operational.

Textbox 1. Research questions and their operational definitions (modified from the Specific Action Program, Prevention and Control of Female Cancer 2013-2018 [5]).

Which breast cancer prevention and control policies in Mexico and Latin America have been analyzed in the national and international scientific literature?

- Guaranteeing effective access to quality health services
- Improving the breast cancer detection and care process
- Establishing breast cancer risk communication strategies
- Focusing on breast cancer prevention and detection actions
- Developing and spreading performance evaluations of breast cancer screening programs

Which is the nature (type), extension, and range of these policies and/or programs according to those reports?

- Breast cancer prevention and control strategies: best practices in line with the sociodemographic characteristics of the populations to improve the access, coverage, and quality of the actions that promote health, detection, diagnosis, and follow-up of female cancer
- Implementation based on scientific evidence of national and international experiences and with gender perspective
- Interinstitutional coordination to universalize procedures, practices, efforts, and impacts; among those, the efforts to universalize breast cancer screening through mammography
- Participation of the organized civil society and the citizens in processes that improve access to services and politically influenced actions (citizen monitoring and oversight)
- Reducing health gaps, according to the epidemiological trends in female cancer and the sociodemographic characteristics of the populations
- Health service expense, as a responsible investment, regarding the sociodemographic characteristics of the populations
- Systematic monitoring and evaluation to continuously improve the program
- Coordinating together with the institutions of the National Health System to universalize an information registry and statistical sources with an ethnic focus and gender perspective to improve epidemiological vigilance.

Which is the existing frame of reference for female breast cancer prevention and control policies and/or programs on a national and international level?

- International Breast Cancer Prevention and Control Plans
- National Development Plans
- Sectorial Health Programs

Stage 2: Identifying Relevant Studies

Even though the objective of a scoping review–like revision work is to account for the research questions in the broadest sense, establishing parameters that guide the search strategy is necessary. By this logic, inclusion and exclusion criteria for the eligibility of the studies, the databases to be used and the key consultation words or terms were determined.

Eligibility Criteria

On the basis of the same methodology, eligibility criteria must be established for identified studies about breast cancer prevention and control policies and programs. Thus, the studies that will be selected in this review must comply with the following inclusion criteria:

1. Studies about public policies or programs regarding breast cancer prevention and control published between January 2000 and December 2018.
2. Studies published in English and Spanish preferably.
3. Works on public policies or programs applicable to female human subjects of any age group.
4. Review studies that include systematic revisions, meta-analysis, meta-synthesis, other scoping reviews, and gray literature (annual, research, technical, or project

reports; working papers, government documents, white papers and evaluations, etc).

Likewise, the following exclusion criteria shall apply:

1. Studies about public policies or programs addressing any other type of cancer.
2. Profit-seeking advertising documents.

Databases

Databases to be consulted are as follows: MEDLINE (PubMed), MEDLINE (EBSCOHost), CINAHL (EBSCOHost), Academic Search Complete (EBSCOHost), ISI Web of Science (Science Citation Index), and Scopus in English; and SciELO, Cochrane, and MEDES-MEDICINA in Spanish. The author considers that these databases are the ones that most probably contain the range and scope of the studies included in this review.

Search Strategy

In the indicated electronic databases, an initial search about breast cancer prevention and control policies and programs will be performed by 2 researchers. The following filter shall be applied to the initial search: Mexico or Latin America. By Latin America, we will include documents from the all the countries in Central, South America, and the Caribbean.

The search terms will be defined based on the initial database consultations; these words will include the Medical Subject Headings terms for the database search in English and the terms from Health Sciences Descriptors of the Virtual Health Library of the Pan American Health Organization for the database search in Spanish. The search terms shall include the words “policies,” “public policies,” “programs,” “strategies,” “laws,” “prevention,” and “control” combined with “breast cancer” and “malignant neoplasms,” both in English and Spanish languages.

Thereafter, a manual search of relevant documents that have not been enlisted in the electronic databases search will be implemented. Furthermore, literature will be searched in relevant sites such as the Pan American Health Organization and the World Health Organization, health departments in Mexico and Latin American countries, Academic Google, and abstract databases of specialized conferences and meetings. Finally, we will search for gray literature in the sites provided by the previous consultations. All references shall be handled through a bibliographic citation management software to organize references and eliminate duplicates.

Stage 3: Study Selection

Documents containing information about breast cancer prevention and control policies and programs are of interest to this review. Therefore, Mexican and Latin America’s public policies and health education campaigns, healthy lifestyle promotion, timely detection, and identification of environmental and genetic factors shall be included in this analysis. To this end, once we obtain the results from the previous stage, the titles, overviews, and executive summaries shall be reviewed to identify topic-relevant literature, which will be checked per the inclusion and exclusion criteria to verify their eligibility. The documents complying with the inclusion criteria shall be taken into account for this review. To this end, 2 assistant reviewers will select a first round of documents; afterwards, each one shall submit their work for consideration to the other reviewer. In case a discrepancy should arise among them, a third reviewer will be consulted to solve the differences in their criteria. The work will be done under constant supervision to ensure high standards during the scoping review.

Stage 4: Data Representation

The documents and reports selected in the previous step will be submitted to the data extraction process through specifically designed forms. Resulting data will be first analyzed with descriptive statistics and then through a qualitative content analysis, thus ensuring that the key elements of this search are reflected appropriately. For this, the 2 main reviewers will extract data independently, and the process of comparison will be performed thereafter.

Data extracted from the documents shall include the following: (1) authors, (2) year of publication, (3) document source (public

or private), (4) type of document (scientific, political, gray literature, etc), (5) targeted population, (6) subject (public policy or action program), (7) proposed action or activity, (8) level of application (federal, state, municipal, or local), (9) field of action (primary, secondary, or tertiary prevention), and (10) political emphasis (primary attention, treatment, or survival). The data format could be modified as the review progresses and as we become familiar with the data found in the documents.

Stage 5: Result Classification, Synthesis, and Report

Finally, the documents will be arranged according to the Specific Action Program, Prevention and Control of Female Cancer 2013-2018 [5] in a manner such that they can be categorized as shown in [Textbox 1](#) and the way in which each applicable policy or program—either in a geographic, economic, infrastructure or breast cancer detection process sphere—can be identified.

As no primary source data will be obtained, the approval of an ethics or research committee is not necessary. Finally, quantitative data will be reviewed and presented as descriptive statistics and qualitative data as analysis matrices and semantic networks. Stage 6, the consultation exercise, will be considered once stage 5 is finished.

Results

The report of this scoping review will be verified using the PRISMA-ScR Checklist for scoping review reports [20]. The intention is to perform this review during the first and second quarters of 2019. Results will also be sent for publication by the second quarter of 2020 to an indexed journal. The final aim is to present the results of this review to local and national health authorities by the first quarter of 2020, as well as present them in different scientific events and national conferences and meetings.

Discussion

We present a protocol for a scoping review–type literature revision based on the Arksey and O’Malley’s [16] methodology during the first and second quarters of 2019. According to this 6-stage methodology, we will identify the scientific publications that present or analyze first-level action policies and programs for breast cancer attention in Mexican and Latin American women, as well as their results. The outcome of this review will be used to identify and define the basis of a research project intended to design an educational intervention strategy for the general public in Mexico, to contribute toward raising the awareness for breast cancer and its prevention. Likewise, it attempts to identify the gaps that still exist in public health policies to contribute to the development of well-structured and well-financed comprehensive care programs [22,23].

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Conflicts of Interest

None declared.

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Abbreviations

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

PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Reviews

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Protocol

Adolescent Male Couples-Based HIV Testing Intervention (We Test): Protocol for a Type 1, Hybrid Implementation-Effectiveness Trial

Tyrel J Starks^{1,2,3}, PhD; Sarah W Feldstein Ewing⁴, PhD; Travis Lovejoy^{4,5}, PhD, MPH; Sitaji Gurung¹, MD, MPH; Demetria Cain¹, PhD, MPH; Carolyn A Fan¹, BA; Sylvie Naar⁶, PhD; Jeffrey T Parsons^{1,2,3}, PhD

¹Center for HIV Educational Studies and Training, Hunter College, City University of New York, New York, NY, United States

²Hunter College Department of Psychology, Hunter College, City University of New York, New York, NY, United States

³Health Psychology and Clinical Science Doctoral Program, Graduate Center, City University of New York, New York, NY, United States

⁴Department of Psychiatry, Oregon Health & Science University, Portland, OR, United States

⁵Center to Improve Veteran Involvement in Care, VA Portland Health Care System, Portland, OR, United States

⁶College of Medicine, Florida State University, Tallahassee, FL, United States

Corresponding Author:

Sylvie Naar, PhD

College of Medicine

Florida State University

Main Campus

1115 West Call Street

Tallahassee, FL, 32306

United States

Phone: 1 248 207 2903

Email: sylvie.naar@med.fsu.edu

Abstract

Background: Young men who have sex with men (YMSM), particularly those who are partnered, are at unique risk for HIV. YMSM are among those at highest risk for HIV. Meanwhile, despite the fact that primary partners account for many—possibly most—new HIV infections, partnered men who have sex with men perceive themselves to be at much lower risk for HIV infection and therefore test less often than single men. In response to the risk of primary partner HIV transmission, couples HIV testing and counseling (CHTC) procedures have been developed for use in adult populations. Although promising, YMSM couples may require additional support to complete CHTC given their developmental context in which sexual and romantic relationships are relatively new, and communication skills are emergent.

Objective: The aim of this study was to test the additive benefit of adjunct treatment components tailored for YMSM, which enhance communication skills before the completion of CHTC. The intervention tests a continuum of prevention packages including assertive communication training videos and motivational interviewing focused on assisting with identification and development (MI-AID) before entering into the dyadic intervention components. This protocol is part of the Adolescent Medicine Trials Network (ATN) Scale It Up program described in this issue.

Methods: This is a comparative effectiveness trial that will be executed in 3 phases. Phase 1 will gather qualitative data related to intervention development and implementation from partnered YMSM at 4 subject recruitment venues (SRVs). Phase 2 will compare a continuum of these interventions in a pilot randomized controlled trial (RCT) at 2 SRVs. Phase 3 will compare the most successful adapted intervention package from phase 2 to CHTC as usual in a larger RCT at 4 SRVs. This phase is focused on implementation and sustainment phases of the Exploration, Preparation, Implementation, and Sustainment framework.

Results: Phase 1 data will be drawn from qualitative interviews with partnered YMSM (n=24) and staff from ATN sites (n=20). Baseline enrollment for phase 2 is expected to begin across 2 SRVs in June 2018 (n_{couples}=36). In phase 2, survey data collection along with HIV and sexually transmitted infection (STI) testing will occur at baseline, and 1- and 3-month (postintervention) follow-ups. Phase 3 will begin enrollment across 4 SRVs in September 2019 (n_{couples}=144) and follow-ups will occur at 1, 3, 6, and 9 months postintervention.

Conclusions: Although MI-AID, video-based assertive communication training, and CHTC have established efficacy when administered on their own, this study will be the first to evaluate the strongest adjunctive version of these interventions to address the specific developmental needs of partnered YMSM.

Trial Registration: ClinicalTrials.gov NCT03386110; <http://clinicaltrials.gov/ct2/show/NCT03386110> (Archived by WebCite at <http://www.webcitation.org/75mlO7GCx>)

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KEYWORDS

men who have sex with men; adolescents; HIV; comparative effectiveness research

Introduction

Background

Partnered young men who have sex with men (YMSM) are a uniquely vulnerable population. Adolescents in relationships continue to be an underexamined subgroup, despite the fact that YMSM are at the highest risk of HIV infection. Youth aged 13 to 24 years made up more than a fifth of new HIV diagnoses in 2015 [1]. The vast majority (81%) included gay and bisexual males [1]. Among men who have sex with men (MSM) aged 18 years and older, 35% to 68% of new HIV infections are transmitted between partners in primary (vs casual) relationships [2,3]. Primary partners account for 79% of new infections within the youngest MSM cohort included in Sullivan et al [3].

A number of factors may collectively contribute to the elevated risk of HIV transmission between primary partners. Gay men have anal sex—and receptive anal sex specifically—more frequently with primary (vs casual) partners [3]. Concomitantly, MSM are less likely to use condoms with primary partners. Condom use may be suppressed with primary partners because condomless anal sex (CAS) is interpreted as an indicator of commitment and emotional closeness [4-7]. A strong, positive association between CAS and relationship seriousness has been observed among YMSM [8]. Despite the incidence of main partner HIV transmission, partnered MSM perceive themselves to be at much lower risk of HIV infection and test for HIV less often [9,10]. In addition, for adolescent MSM, relationship development is still new, and romantic partnerships tend to be of short duration [8]. Thus, frequent brief primary partnerships, low perception of CAS risk, and the relative novelty of negotiating close relationships during this developmental period may escalate HIV infection among partnered YMSM.

Less than half of partnered adolescents feel comfortable advocating for and discussing condom use before sexual intercourse, contributing to 50% of youth consenting to condomless sex, despite wanting to use a condom [11,12]. YMSM show even lower rates of assertive communication relative to heterosexual age-mates [13]. Enhancing communication skills is thus a route to improve sexual safety in this age group [14,15].

Theoretical and Evidence Base

Individual HIV prevention, including HIV testing, is conceptualized within the Self-Management Theory framework [16,17]. Problem solving, decision making, and access to care

predict health behavior engagement. This, in turn, develops positive provider relationships that facilitate behavioral skills development and access to care.

Although useful, the framework does not fully address or incorporate the inherently interpersonal nature of sexual health decision making for individuals in relationships. The dyadic processes that contribute to the establishment and attainment of sexual health goals have been conceptualized within the framework of couples interdependence theory (CIT) [18-20]. Of the processes described within CIT, 2 are particularly useful when thinking about HIV risk reduction with couples [18,21]. Accommodation refers to a couple's arrival at a shared or joint goal. Joint goals are more likely to be accomplished because they draw upon resources from both partners within the couple as they support each other in goal attainment. The transformation of motivation refers to the transition from considering primarily interpersonal gain and loss in decision making (and moments of conflict) to partners' consideration of the consequences of their actions—not only for their own outcomes but for their partner and the overall health of their relationship.

Within CIT, each partner in the relationship can be viewed as having his own initial HIV-risk reduction and sexual health maintenance goals. CIT would suggest that couples who are able to accommodate potentially divergent health and safety preferences and arrive at a shared goal and strategy for its attainment have a greater potential to maximize their health outcomes [18,21-23]. A sexual agreement defines the rules and boundaries related to sex with partners outside the relationship [20,24]. They potentially encompass both the broad issue of whether casual partners are permitted and the rules that govern sex with casual partners when it occurs [25].

Couples HIV testing and counseling (CHTC) utilizes the concept of sexual agreement negotiations to catalyze the accommodation of partners' sexual health goals. Over the course of a CHTC session, couples discuss their current HIV prevention practices, formulate a sexual agreement, and discuss how they might handle agreement violations. After receiving their HIV test result together, the couple formulates a shared HIV treatment or prevention plan in the context of their agreement [26,27].

Although a sound strategy, the negotiations inherent in the accommodation process assume that the individuals in the couple have adequate communication skills. To be effective, individuals must identify both their own and their partner's preferences and feelings, and then communicate those concepts in constructive ways. To date, CHTC has been tested with adults

[28]; this leaves the question of whether adolescents are similarly positioned to benefit from the intervention. As their communication skills are still very much in development [29], particularly in the relationship context [30,31], youth may need added support to effectively identify sexual goals and to learn to communicate them carefully and productively. Youth may need the support of additional communication and skills practice, both modeled (such as in assertive communication training, CT) or as shaped through actual role plays [32] to successfully convey their sexual and relationship goals to their likely, relatively new relationship partner.

Rosenthal and Starks [33] found that stigma directed at their relationship was associated with mental health functioning above and beyond stigma directed at gay men individually. Furthermore, their work showed that relationship functioning buffered against this negative association. Building on this work, there is evidence to suggest that providing models of YMSM communicating effectively with relationship partners may have beneficial effects on mood or anxiety. Studies of gay men in relationships suggest that being partnered may be associated with a range of mental health benefits [34-36]. A potential pathway for this links dyadic functioning and mental health. Dyadic research with gay couples has indicated that depression scores are predicted by both personal and the partner's relationship satisfaction scores [37]. To the extent that improvements in communication skills result in improvements in dyadic functioning, it is plausible that mental health outcomes may also result in similar improvements. A second pathway, which might conceivably result in secondary effects on mood and/or anxiety, lies in the potential to reduce the effects of stigma by challenging negative stereotypes about gay men and gay relationships [38,39].

In addition, the design of this study will be organized within the Exploration, Preparation, Implementation, and Sustainment (EPIS) framework [40]. The EPIS framework specifies internal and external factors that contextualize the adoption and delivery of services in complex systems such as research trials. Phases 1 and 2 of the study will focus on the exploration and preparation stages by creating adapted intervention packages and evaluating an optimal intervention package. Phase 3 will focus on implementation and sustainment phases of the model, and will primarily be informed by outcome analyses, cost analyses, and feedback from study participants.

The interventions to be adapted are video-based CT, delivered in a dyadic format, along with an individual-level single session of motivational interviewing focused on assisting with identification and development (MI-AID) of sexual goals and communication skills. Video-based communication skills training has received broad support in the literature [41]. The use of videos to reinforce skills related to the negotiation of sexual safety is supported by meta-analytic findings that video content enhances the effectiveness of HIV-prevention interventions that target behavioral skills [42]. This approach builds upon established cognitive-behavioral approaches to assertive communication skill building [43]. Consistent with the results of studies examining the effectiveness of behavioral models, our videos will depict models of positive (exemplary) and negative (nonexemplary) communication [41,44] exchanges

between YMSM couples in age-relevant contexts discussing issues related to sexual health and HIV prevention.

Motivational interviewing (MI) has empirical support for its success in reducing adolescent risky sex and sexually transmitted infections (STIs) [32,45-47], including earlier iterations of MI for adolescent HIV risk reduction that are now recognized as empirically supported programs by the Office of Adolescent Health [48]. In line with this team's prior work in this area [30,32], this intervention has been updated to enhance communication development, particularly for young adolescents who are new to the relationship context. Thus, new developments to this intervention specifically target enhancing nascent communication around HIV risk reduction within young dyads. A single-session MI intervention is used here because it has been shown to have the best possible reach with high-risk youth [45,47]. Not only does prior work underscore that individuals in this age group enjoy and are responsive to MI [46], meta-analyses continue to support the effectiveness of the approach for reducing youth health risk behaviors [49-51].

The MI-AID session begins with an initial introduction describing the session itself and its relationship to the upcoming dyadic HIV testing session with their sexual partner (CHTC). The youth is told that this is an opportunity to identify individual preferences and goals related to sexual agreements, biomedical prevention (pre-exposure prophylaxis, PrEP or post-exposure prophylaxis, PEP), thoughts and preferences on HIV/STI testing, and condom use before discussing these with their partner. The provider's objective is to both elicit, potentially for the first time, for some youth, the adolescent's goals and preferences in these domains, as well as to learn how to successfully express those goals and preferences in a relationship context. Active, iterative practice is utilized to ensure that the youth feels fully prepared to transition into the dyadic components of the intervention, including the CT and CHTC sessions.

Overview and Aims

The purpose of this comparative effectiveness trial (CET) was to test the additive benefit of adjunct treatment components tailored for YMSM, which enhance communication skills before completion of CHTC. The intervention tests a continuum of prevention packages including CT videos with MI-AID before entering into the dyadic intervention components, including CHTC.

Methods

Overview of Content and Delivery

This study (We Test, Adolescent Medicine Trials Network 156) is part of the Scale It Up program as described in the overview paper in this issue [52] and will take place in 3 phases. In phase 1, tailored CT videos and MI-AID modules will be developed for partnered YMSM aged 15 to 19 years using information gathered from qualitative interviews with YMSM and SRV site staff. In phase 2, a pilot randomized controlled trial (RCT) will compare a continuum of CHTC packages: CHTC alone; CT videos viewed by the couple in addition to CHTC; and an individually administered MI-AID, along with CT videos and CHTC. Phase 3 will test a sustainable model of CHTC

implementation in real-world adolescent HIV clinics. The phase 3 RCT will compare CHTC as usual to the intervention package found most effective in phase 2.

Eligibility

YMSM who express interest in We Test are assessed for eligibility by completing a brief screener. In phase 1, eligible participants must be (1) cis-male gender identity; (2) aged 15 to 19 years, (3) in a relationship, dating, or seeing a cis-gender male (regardless of relationship duration) with whom they have or anticipate having sex, (4) HIV-negative or status unknown, and (5) able to complete a qualitative interview by Skype, Facetime, or phone. YMSM aged 15 to 17 years must indicate that their partner is aged 15 years or older, and the age difference between partners cannot exceed 2 years. YMSM aged 18 or 19 years may participate if their partner is less than 2 years younger or older than 18 years. Potential participants will be excluded if they are unable to communicate in English; their mental, physical, or emotional capacity does not permit them to complete the protocol as written; they display current suicidal or homicidal ideation; or they are not exerting autonomy over participation (eg, they report that someone forced them to participate in the study).

In phases 2 and 3, study inclusion criteria include (1) at least one partner must be aged 15 to 19 years, (2) both partners identify as cis-male; (3) at least one partner must be HIV-negative or status unknown, (4) partners must be sexually active together or indicate that they plan to have sex together in the future, and (5) both relationship partners must agree to attend an assessment together at an SRV. Similar to phase 1, if either YMSM is aged 15 to 17 years, then the age difference between partners cannot exceed 2 years. YMSM who are aged 18 or 19 years may participate in the study with a partner who is less than 2 years younger or one who is older than 18 years. Potential participants will be excluded if either partner is unable to communicate in English; their mental, physical, or emotional capacity does not permit them to complete the protocol as written; they display current suicidal or homicidal ideation; or they report that someone forced them to participate in the study. Participants from phase 1 may be eligible for participation in later phases.

Recruitment and Screening

Leveraging existing Scale It Up infrastructure, participants will be recruited and screened for eligibility via 4 different SRVs in phase 1, 2 SRVs in phase 2, and 4 SRVs in phase 3 that provide HIV testing and prevention services to YMSM (Table 1). All SRVs have extensive relationships with the gay, lesbian, bisexual, and transgender communities; community service organizations; health service organizations; and providers for MSM. This may be supplemented by Web-based advertising conducted through Scale It Up's Recruitment and Enrollment Center (REC). Although advertising will be distributed through the REC, they will be targeted to the geographic areas surrounding the SRVs for this project and will contain information about participation at the SRV.

In phase 1, partnered YMSM will complete a brief Web-based screener. Eligible participants will subsequently be contacted via email or telephone to schedule a qualitative interview. YMSM will receive written consent information before completion of the screener. Those participants who screen eligible and schedule an interview will receive verbal consent information. Similarly, SRV staff will receive written information about the study as part of recruitment materials and will be provided verbal consent information before completion of their interview. A waiver of consent or assent will be obtained to reduce barriers to participation and prevent the need to capture a physical signature in a study conducted remotely. In phases 2 and 3, couples will be screened through an index-case approach. In this approach, 1 partner in the couple will be asked to provide screening information about himself and his partner. If the couple is preliminarily eligible based upon the report of the index partner being screened, that index partner will be asked to schedule a baseline appointment at a time both he and his partner can attend. A waiver of parental consent will be obtained for this study. At the baseline appointments, YMSM partners will be consented privately in separate rooms. A research assistant will review written consent information and obtain consent or assent from both partners before completion of the baseline assessment. Contact information for the recruited (nonindex) partner will be collected at this point and added in REDCap for tracking purposes.

In addition, the Center for HIV Educational Studies and Training (CHEST) will assist in referring potentially eligible participants to the We Test study through existing online recruitment efforts. CHEST utilizes the Hunter College Institutional Review Board (IRB)-approved online master screener (OMS) to preliminarily screen individuals who are interested in participating in studies being conducted through CHEST and live in 1 of the target cities. If an individual is preliminarily eligible for a study, the individual is asked to provide contact information to CHEST for follow-up. For phase 1, the OMS will be used to link potentially eligible participants to the study-specific screener; however, most participants will be recruited through ads that link potential participants directly to the study-specific screener, bypassing the OMS.

For phases 2 and 3, the OMS will only be used to refer potentially eligible YMSM to HIV testing sites by sending them an email referral informing them about the We Test study and where to go to determine eligibility after completing the OMS. The contact information collected through the OMS will not be provided to the SRVs. However, We Test SRVs will be made aware that a potentially eligible YMSM has been referred to their testing services for the study. The OMS, in this study, will primarily be used as a referral mechanism, directing participants to which study they may be eligible for, including We Test. YMSM who complete the OMS and screen preliminarily eligible and who then are referred and subsequently make contact with their SRV will take the We Test-specific screener via the SRV to further establish eligibility. It will be the duty of the SRV site staff to coordinate with the YMSM couples to schedule the baseline appointment.

Table 1. Scale It Up subject recruitment venues.

Sites	Location
Phase 1	
CHEST ^a	New York, NY
Wayne State University	Detroit, MI
University of Miami	Miami, FL
San Diego Lesbian, Gay, Bisexual, and Transgender Community Center	San Diego, CA
Phase 2	
CHEST	New York, NY
Wayne State University	Detroit, MI
Phase 3	
CHEST	New York, NY
Wayne State University	Detroit, MI
University of Miami	Miami, FL
San Diego LGBT Community Center	San Diego, CA

^aCHEST: Center for HIV Educational Studies and Training.

In phases 2 and 3, community health workers (CHWs) who conduct standard of care HIV testing services for the We Test SRVs will be trained to provide information about the We Test study after HIV-negative results are delivered at their site or in the field at mobile testing events. The CHW will be trained in appropriate and ethical methods of recruiting participants in clinical settings and in the field. To minimize the risk for coercion, the staff member and the study information will emphasize the optional nature of participation and that it will not affect, in any way, their access to health care services. If the potential participant is interested in finding out if he is eligible for We Test after learning about the study, the CHW will provide an iPad with a secure Web-based REDCap We Test Study Screener (IRB approved). The confidential We Test Study Screener will be completed on the iPad by the potential participant, and no one will be able to see the responses; the iPad will only indicate whether the potential participant is eligible.

YMSM who screen ineligible for the study do not need to provide contact information and may screen again after 30 or more days provided they tested HIV-negative at the site in the past 90 days or they again test HIV-negative at the site. Participants are also able to rescreen should they test HIV-negative at the site or through mobile testing efforts associated with the site.

Study Design

Phase 1

Phase 1 aims to develop tailored CT videos and MI-AID modules for partnered YMSM aged 15 to 19 years (see [Figure](#)

1). Qualitative interviews with 20 staff from SRVs and 24 partnered YMSM will be conducted to identify barriers and facilitative factors related to receipt of CHTC for youth as well as to examine sexual communication between primary relationship partners and its link to HIV/AIDS in this age group. Interviews with YMSM will focus on assessing youth's comfort and capacity to identify sexual goals and communicate about HIV testing and prevention. Interviews will be conducted remotely from CHEST via Skype, Facetime, or phone, based on participants' preference. Both interfaces have been approved by the IRB. Interviews will be audio-recorded using an external recording device. Recordings will be stored on a secure server and subsequently transcribed. Transcripts will be identified only by participant identification and all proper names will be removed. Participants will receive US \$50 each as a compensation for completing this component (see [Table 2](#)).

Data gathered from these staff and partnered YMSM qualitative interviews will inform the development of the CT videos and MI-AID. A codebook will be used to structurally and thematically code qualitative output from these interviews using established qualitative methodology. A total of 2 analysts will independently code a subset of the transcripts until intercoder agreement of >90% is reached. All transcripts will then be coded by one of the 2 analysts. Afterward, iterative thematic analyses will be conducted to identify major trends and themes from the interviews. Using this information, CT videos will be created and the individual-level MI-AID intervention will be adapted.

Figure 1. Phase 1 study design. YMSM: young men who have sex with men.**Table 2.** Compensation. All compensation is delivered either through Visa or Amazon Gift Card or cash depending upon subject recruitment venue restrictions.

Phase and appointment	Study component	Compensation amount (US \$)
1		
Qualitative phone interviews	SRV ^a staff focus group	20
	YMSM ^b screener and consent	50
	YMSM qualitative interview	— ^c
2 and 3		
Baseline	Baseline CASI ^d	30
	STI ^e testing	20
	Intervention session (including HIV testing)	20
1-month follow-up	CASI	50
3-month follow-up	CASI	30
	HIV testing	10
	STI testing	10
6-month follow-up ^f	CASI	50
9-month follow-up ^f	CASI	30
	HIV testing	10
	STI testing	10

^aSRV: subject recruitment venue.^bYMSM: young men who have sex with men.^cNot applicable.^dCASI: computer-assisted self-interview.^eSTI: sexually transmitted infection.^fIndicates phase 3 only.

Phase 2

In this phase, a pilot RCT will be conducted to evaluate the acceptability and feasibility of adjunct intervention components. This initial trial will recruit 36 couples who will be randomized to 1 of 3 conditions: (1) CHTC only; (2) couples’ joint observation of CT videos and CHTC; (3) each individual within a couple receiving MI-AID, in addition to joint observation of CT videos and CHTC. Youth will then complete follow-up assessments at 1 and 3 months postintervention (see Figure 2).

The main measures that will be tracked are the 4 behavioral indicators of HIV transmission risk behavior (TRB). Two of these are at the individual level: the number of CAS acts with a casual partner in the absence of PrEP and any positive chlamydia or gonorrhea diagnoses in the absence of PrEP. The other 2 behavior indicators of TRB are at the couple level: any sex in the absence of PrEP with a primary partner who reports CAS with a casual partner and any sex in the absence of PrEP with a primary partner who receives a positive chlamydia or gonorrhea diagnosis.

This phase will be completed in 4 steps at 3 time-points—baseline and intervention delivery, followed by 1- and 3- month follow-ups (see Table 3). At the baseline assessment, both members of the couple will attend their local SRV in tandem. Each partner will have STI biomarker specimens collected separately and will independently complete a baseline computer-assisted self-interview (CASI). Each participant will receive US \$70 (payable as cash, Visa Gift Card, or Amazon Gift Card based upon SRV restrictions) for completing all components of the baseline assessment (see Table 2). Upon completion of the baseline assessment, couples will

be randomized to 1 of 3 study conditions via stratified randomization procedure using Qualtrics. Youth will be stratified by city, age (whether or not both members of the couple are younger than 18 years), and racial composition (if 1 member of the couple identifies as a racial or ethnic minority).

After randomization, the interventions will be delivered by CHWs, former providers of individual HIV counseling and testing services, health educators, and/or trained program peers. The CHTC protocol [53,54] consists of a 25- to 40-min session made up of 8 steps that couples will complete together: (1) description of CHTC, (2) description of HIV testing procedures, (3) exploration of the couples’ relationship, (4) assessment of the couples’ reasons for testing and HIV risk concerns, (5) clarification of sexual agreements, (6) reporting HIV test results, (7) prevention planning or linkage to HIV care, and (8) referral.

The second study condition adds on the CT video intervention. In this intervention, couples will view the 20-min CT video together. This is to provide an added layer of communication training around sexual agreements and HIV testing. The partners will then work together on a brief, 5-min survey about the video content to evaluate treatment receipt.

The third condition adds individually received MI-AID, in addition to the jointly viewed CT video and joint CHTC. In MI-AID, each partner will meet one on one with the CHW for 30 min to address the development of sexual communication. Using the MI-based protocol, the CHW will assist the youth in identification of their own goals for sexual agreement, HIV testing, STI testing, and PrEP/PEP use and assertive communication. In addition, they will use iterative role playing practice in communicating target goals.

Figure 2. Phase 2 study design. CASI: computer-assisted self-interview, CHTC: couples HIV testing and counseling; CT: communication training; MFU: monthly follow-up; MI-AID: Motivational Interviewing focused on Assisting with Identification and Development; STI: sexually transmitted disease.

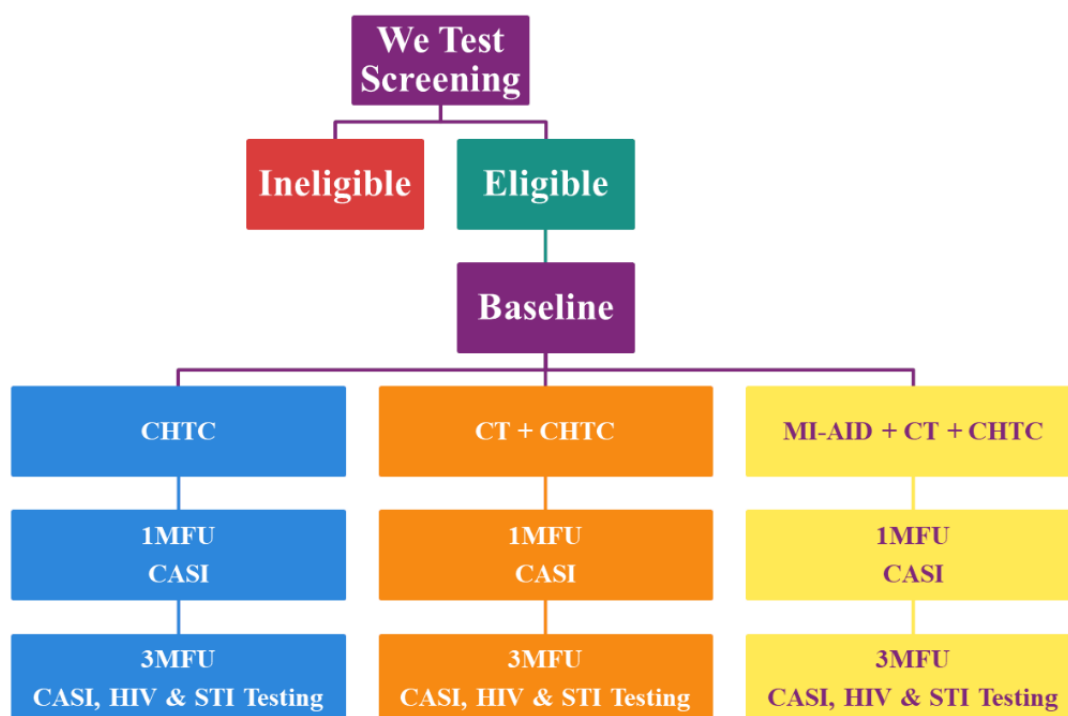


Table 3. Schedule of assessments, phases 2 and 3.

Component	Baseline	1-month follow-up	3-month follow-up	6-month follow-up ^a	9-month follow-up ^a
Informed consent	X ^b	— ^c	—	—	—
CASI^d	X	X	X	X	X
HIV testing	X	—	X	—	X
STI^e testing	X	—	X	—	X
Randomization	X	—	—	—	—

^aPhase 3 only.

^bX: relevant protocol components at each assessment point.

^cNot applicable.

^dCASI: computer-assisted self-interview.

^eSTI: sexually transmitted infection.

Follow-ups will occur at 1 and 3 months post-intervention in phase 2. In the follow-up assessments, participants will complete a Qualtrics CASI, with the 3-month follow-up including rapid HIV testing and STI testing. These follow-ups will be completed individually to facilitate the retention of all participants even if the relationships dissolve. Participants will receive US \$50 at both the 1- and 3-month follow-up upon completion of all follow-up components (payable as cash, Visa Gift Card, or Amazon Gift Card based upon SRV restrictions). Those participants who test positive for STIs will be referred for treatment following the standard procedures of the SRV.

Phase 3

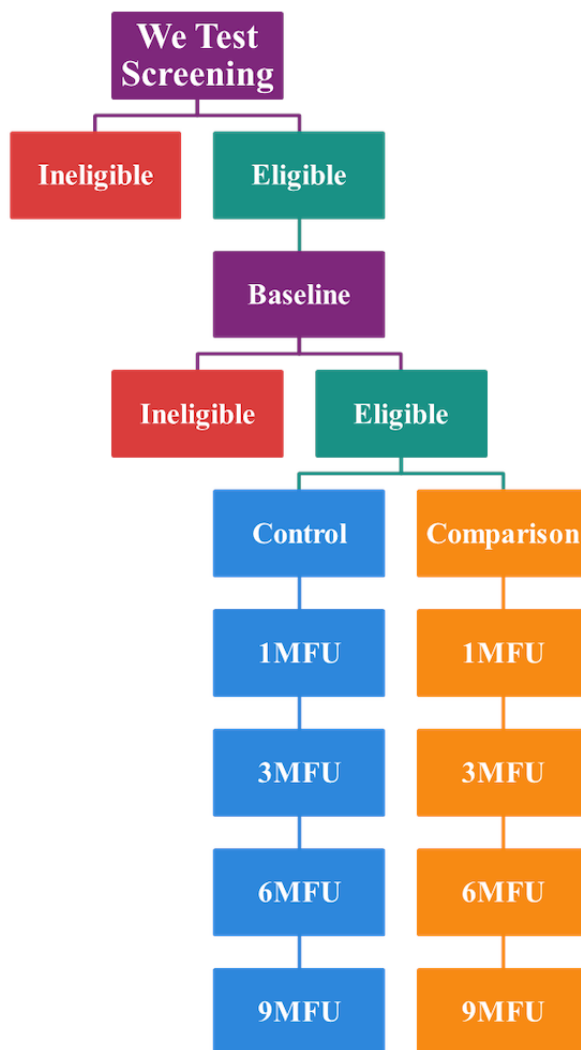
Phase 3 will build upon the results of the pilot RCT conducted in phase 2. Phase 3 will also gather feedback from staff at our SRVs. EPIS qualitative interviews will be conducted with staff (n=20) from 4 SRVs, namely CHWs, providers, supervisors, and administrators who have experience with the partnered YMSM and CHTC. The objective of these interviews is to elicit staff perspectives on (1) the nature of content included in adapted CT and MI-AID interventions, (2) structural considerations that must be accommodated in the intervention protocol, and (3) developmental concerns of delivering CHTC to youth younger than 18 years. The focus will be on identifying

factors that can ultimately enhance intervention acceptability and sustainability, while retaining core elements of all intervention components. The EPIS protocol paper in this issue [55] outlines how these components are captured for analysis. SRV staff will receive US \$20 as compensation in the form of an Amazon Gift Card for their time for completing the EPIS interview and survey (see Table 2).

Phase 3 will enroll 144 couples from 4 SRVs into the full RCT (see Figure 3). In phase 3, couples will be randomized to 1 of only 2 conditions. Although the control condition will be CHTC delivered as usual, the comparison condition will include the optimal intervention package indicated during our phase 2 adaptation. This condition may therefore involve viewing CT videos only before CHTC, individual MI-AID before CHTC only, or both depending upon results and feedback obtained in phase 2. Youth in this RCT will complete follow-up assessments at 1, 3, 6, and 9 months (see Table 3).

Eligibility criteria during phase 3 are the same as phase 2. The same recruitment, consent, and baseline assessment procedures will be utilized in both phases. Although there are additional 6- and 9-month follow-up assessments in phase 3, the procedures remain the same.

Figure 3. Phase 3 study design. MFU: monthly follow-up.



Training of Interventionists

Following phase 1, to prepare for the rollout of the CET, there will be a week-long in-depth training on all study procedures. This training will include members of the 2 SRVs who will participate in phase 2. Any staff who cannot attend because of nonresolvable travel restrictions will participate via Skype. This training will include 2-day training in CHTC, 2-day training on MI-AID, and 1 day dedicated to reviewing and practicing protocol delivery, including administration of the CT videos. Throughout training and fidelity-monitoring activities, the implementation team will work to document CHW and supervisor performance and feedback on intervention materials and delivery (reflecting the exploration and preparation phases of EPIS). At the conclusion of the CET, the project implementation team will work closely with the implementation science core to package training and intervention materials in a manner that supports the dissemination of CHTC and adjunct components shown to be effective.

We will use a train-the-trainer model, where centralized training will be conducted for CHWs and their supervisors on the implementation and delivery of the intervention materials, with the goal that supervisors will serve as local implementation *champions* by instructing and overseeing implementation within

their SRV. To maximize accuracy, consistency, and fidelity of intervention delivery, each intervention (CHTC, CT, and MI-AID) will be codified into manuals. This training sequence will be offered again before phase 3 to bring the 2 new SRVs into the study and update staff at existing SRVs.

Fidelity Monitoring

All sessions will be audio-recorded for the purposes of systematic supervision so that fidelity can be assessed and interventionist drift prevented. A team of Motivational Interviewing Treatment Integrity (MITI) [56] coders trained in the assessment of MI, along with research assistants trained in the assessment of CHTC fidelity, will ensure the fidelity of intervention packages. These MITI coders will review the first 10 sessions completed by each CHW and a random selection of sessions for the remainder of the trial (approximately 1 in 4 of sessions completed by each CHW over the entire trial). Coding of all initial sessions will ensure fidelity across interventionists at the start of the trial, and subsequent coding will identify any interventionist drift that occurs for the remainder of the trial. Tapes will be coded to ensure the presence of essential elements of the intervention. When interventionists exhibit low levels of intervention integrity or significant drift, the feedback will be relayed to their on-site supervisors. The training team will then work with the local supervisor to develop

a remediation plan to bring the CHW back up to parity with other interventionists.

Reporting Adverse Events

In addition, the site protocol lead (PL) is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Data for monitoring participants' safety will be captured within the REDCap database as part of the required study data. Site study staff may ask questions concerning AEs via the Scale It Up query system but must formally report them via email and REDCap. Information on unexpected events including SAE will be reported as per the policy of Scale It Up's single IRB.

Information to be collected includes the nature, date of onset, stop date, intensity, duration, treatment, causality, and outcome of the event. Site PLs should follow usual clinical practices at their institutions for reporting serious, unexpected events related to standard of care. SAEs that occur after 30 days after completion of the study will be collected only if they are considered by the PL to be related to study participation. In addition, any AE resulting in potential participant withdrawal must be reported to the Scale It Up REC before participant withdrawal when possible.

Results

Participant recruitment for phase 1 qualitative interviews with partnered YMSM occurred between December 2017 and October 2018. The target start date for the phase 2 enrollment is November 2018, phase 3 to begin in September 2018, and all 3 phases will finish by 2021.

Quantitative Analysis Plan

The primary hypothesis is that because of developing skills in self-management and assertive communication, inclusion of adjunct components will be associated with clinically significant decreases in HIV TRB as compared with partnered YMSM who receive CHTC (only). Secondly, we propose that these intervention effects will be mediated by assertive communication skills. As stated above, we focus on 4 behavioral indicators of TRB. At the individual level, we examine (1) number of CAS acts with a casual partner in the absence of PrEP and (2) any positive chlamydia or gonorrhea diagnoses in the absence of PrEP. At the couple level, we will examine (1) any sex in the absence of PrEP with a primary partner who reports CAS with a casual partner and (2) any sex in the absence of PrEP with a primary partner who receives a positive chlamydia or gonorrhea diagnosis. Any missing data and additional covariates will be informed by attrition analyses before primary analyses.

Analytic Plan

All primary outcome variables will be tested in the context of a multilevel growth model, which accounts for the nesting of individuals within couples. To capture within-individual change over time, we will utilize a latent growth curve approach to modeling follow-up data. At the individual level (level I), models will include an intercept and linear slope component to represent the initial value and change over time in each participant's outcome. We will explore the inclusion of quadratic

components as indicated by model fit. Mplus provides the flexibility to accommodate count and dichotomous outcomes. Growth factors will then be regressed on intervention condition at the couple level (level II), and the effect of the intervention will be evaluated by examining the regression coefficient (and associated *P* value) associated with intervention condition for each of these factors.

Secondary analyses of individually reported self-management and dyadic functioning as potential mediators of the intervention's effect on and TRB will specify growth factors for self-management, dyadic functioning, and communication skill scores during the follow-up period [57]. In this manner, growth factors for the outcome can be regressed on growth factors for the putative mediator. Intervention effects (a couple-level predictor) will be determined by examining regression coefficients associated with intervention in the prediction of growth factors for both the outcome of interest and mediator. For significant direct effects, indirect pathways from intervention communication will be tested using bootstrapping tests of mediation. Where outcome distributions prevent bootstrapping, we will utilize a model constraint approach to evaluate the significance of indirect effects. The product of constituent direct effects is constrained as zero. The overall model fit under this constraint is compared with one where the constraint is not specified. A statistically significant reduction in fit associated with constraint represents evidence that indirect effects differ from zero [58].

Power Analysis

Consistent with the intervention development goals of phase 2, we are not powered to detect significant between-condition differences in primary outcomes for that phase. Power analyses for phase 3 were conducted based on our preliminary pilot data extracted from a similar study (R34 DA036419; PI Starks) testing adjunct CHTC components in emerging adult gay male couples aged 18 to 29 years. Preliminary results from the 3-month wave of data collection (the most distal available with sufficient data to estimate effects at the time of this submission) suggested that viewing CT videos before CHTC was associated with a 56% decrease in the odds of CAS with a casual partner (relative to CHTC alone) among HIV-negative participants not on PrEP. Of particular relevance to our mediation hypotheses, viewing CT videos before CHTC was associated with a 5- to 6-point decrease in avoidant communication as measured by the Communication Patterns Questionnaire (CPQ). In turn, CPQ avoidant communication scores had a significant positive association with CAS with casual partners among HIV-negative men not on PrEP ($expB=1.06$, $P<.01$). Separately, our previous study of brief MI interventions with YMSM suggests that the receipt of MI is associated with as much as an 83% within-condition reduction in CAS over time and a 24% reduction in the odds of CAS with a casual partner compared with an attention-matched psychoeducation control condition [59].

These preliminary effect sizes were utilized as parameters in power analyses using a Monte Carlo simulation approach in Mplus (version 7.3) [58]. This approach provides a direct estimation of power while modelling both the multilevel

structure of the data (individuals are nested within couples) and the longitudinal design of the study (each individual provides data at 3 follow-up points). The program generates random samples from the specified population and, within each sample, examines the significance of freed parameters. Power is defined as the proportion of simulated samples in which the freed parameter has a P value of less than .05. All models specified a random seed and used 10,000 sample replications. Power analyses conducted based on these preliminary effect sizes suggest that 144 couples ($N=288$ individuals), anticipating a minimum of 232 individuals retained at 9 months, is adequate to achieve power $>.80$ for all hypothesized direct effects as well as indirect pathways.

Equivalency Tests

We will follow standard procedures in cleaning data and examining initial distributional properties (means, SDs, medians, skew, and kurtosis) in addition to graphical summaries (boxplots and density plots). Subsequently, we will evaluate the suggestions of randomization by testing between-condition differences with respect to demographic covariates and primary outcomes reported at baseline. Note, because participants are nested within dyads, these analyses will utilize the generalized estimating equations (GEEs) module within SPSS to control for the nonindependence of observations and specify outcome distributions that are appropriately matched to the variables of interest.

Finally, we will conduct an analysis of attrition to determine if dropout at each follow-up timepoint is associated with (1) demographic variables assessed at baseline and/or (2) drug use or TRB outcomes assessed at baseline. At each wave, we will utilize GEE models to evaluate whether those participants retained at the given wave differ significantly with respect to demographic or baseline outcome values compared with those who were not retained. As with the analyses of randomization success, the use of GEE permits analyses to control for the nesting of participants within couples and specify outcome distributions that are matched to variables of interest. Factors that are observed to covary significantly with attrition will be incorporated as covariates in outcome analyses. Mplus has a variety of options for handling partial attrition including full-information maximum likelihood estimation [60]. Nonrandom and consequential missingness can also be modeled directly through the addition of latent variables, which account for the probability of missingness at any timepoint. Where indicated, we will explore the use of these procedures in the analyses described below.

Discussion

Summary of Key Innovations

The primary innovation of this multilevel CET lies in the novel packaging of existing interventions in a manner that addresses the specific developmental needs of YMSM. Although MI-AID, video-based CT, and CHTC have individually established

efficacy, this study will be the first to evaluate a continuum of prevention packages, which combine these components.

In addition, this multilevel intervention seeks to leverage the power of the dyadic processes to enhance motivation for HIV testing and prevention (including biomedical prevention). Our adjunctive components (CT and MI-AID) are specifically intended to enhance self-management skills (eg, assertive communication), which are essential to effectively engage relationship partners in collaborative sexual goal development and problem solving. The underlying assumption of this strategy is that improvements in dyadic functioning will lead to reductions in sexual risk for both individuals within the relationship.

Another strength lies in the inclusion criteria, which were constructed to accommodate the broadest possible range of sexual partnerships at this exciting developmental stage. The study does not impose any requirement on relationship duration. Given the dynamic and potentially experimental nature of relationships at this stage, we have utilized a liberal definition of relationship. YMSM are not required to identify their partner as a boyfriend or indicate *being partnered*. Instead, they may identify themselves as dating, or experimenting with a relationship, and still be eligible as long as the other person involved is a cis-gender male with whom they either are or may be sexually active. This inclusive stance toward relationships is consistent with the CHTC protocol [53,54], created to be applicable for any couple who has or *intends to have* a sexual relationship.

Limitations and Conclusions

There are a few limitations to this study. First, this study requires that participants are able to communicate in English. As a result, nonfluent English speakers—such as those who have recently immigrated or those who live in predominately non-English speaking communities—are unable to participate. This misses out on key sectors of the YMSM population, particularly as our SRVs located in New York, Detroit, Miami, and San Diego are racially, ethnically, and linguistically diverse areas. In particular, Spanish-speaking YMSM cannot participate in this study.

In addition, this study is limited in its location. The study takes place in 4 major cities. Although these cities are geographically diverse, the study is unable to adapt its interventions for partnered YMSM from other cities. In particular, YMSM from rural areas away from these cities are unable to participate. The effectiveness of these intervention packages may or may not vary depending on a YMSM's locale.

Ultimately, this study is an innovative design which not only incorporates community feedback to develop interventions but also uses 2 CETs to determine the most effective continuum of interventions for partnered YMSM. This study will be the first to combine MI-AID, CT video, and CHTC. Packaging these trainings with CHTC may enhance prevention for the uniquely vulnerable population of partnered YMSM.

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Conflicts of Interest

None declared.

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Abbreviations

- AE:** adverse event
- ATN:** Adolescent Medicine Trials Network
- CAS:** condomless anal sex
- CASI:** computer-assisted self-interview
- CET:** comparative effectiveness trial
- CHEST:** Center for HIV Educational Studies and Training
- CHTC:** couples HIV testing and counseling
- CHW:** community health workers
- CIT:** couples interdependence theory
- CPQ:** Communication Patterns Questionnaire
- CT:** assertive communication training
- EPIS:** Exploration, Preparation, Implementation, and Sustainment
- GEE:** generalized estimating equation
- IRB:** Institutional Review Board

MI: motivational interviewing

MI-AID: motivational interviewing focused on assisting with identification and development of sexual goals and communication

MITI: Motivational Interviewing Treatment Integrity

MSM: men who have sex with men

OMS: online master screener

PEP: post-exposure prophylaxis

PL: protocol lead

PrEP: pre-exposure prophylaxis

RCT: randomized controlled trial

REC: Recruitment and Enrollment Center

SAE: serious adverse event

SRV: subject recruitment venue

STI: sexually transmitted infection

TRB: transmission risk behavior

YMSM: young men who have sex with men

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Protocol

Testing a Motivational Interviewing Implementation Intervention in Adolescent HIV Clinics: Protocol for a Type 3, Hybrid Implementation-Effectiveness Trial

Sylvie Naar¹, PhD; Karen MacDonell², PhD; Jason E Chapman³, PhD; Lisa Todd², MSc, JD; Sitaji Gurung⁴, MPH, MD; Demetria Cain⁴, MPH, PhD; Rafael E Dilones⁴, BSc; Jeffrey T Parsons^{4,5}, PhD

¹College of Medicine, Florida State University, Tallahassee, FL, United States

²Department of Family Medicine and Public Health Sciences, Wayne State University, Detroit, MI, United States

³Oregon Social Learning Center, Eugene, OR, United States

⁴Center for HIV Educational Studies and Training, Hunter College, City University of New York, New York, NY, United States

⁵Health Psychology and Clinical Science Doctoral Program, Graduate Center, City University of New York, New York, NY, United States

Corresponding Author:

Sylvie Naar, PhD

College of Medicine

Florida State University

Main Campus

1115 West Call Street

Tallahassee, FL, 32306

United States

Phone: 1 248 207 2903

Email: sylvie.naar@med.fsu.edu

Abstract

Background: Motivational interviewing (MI) has been shown to effectively improve self-management for youth living with HIV (YLH) and has demonstrated success across the youth HIV care cascade—currently, the only behavioral intervention to do so. Substantial barriers prevent the effective implementation of MI in real-world settings. Thus, there is a critical need to understand how to implement evidence-based practices (EBPs), such as MI, and promote behavior change in youth HIV treatment settings as risk-taking behaviors peak during adolescence and young adulthood.

Objective: This study aims to describe the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) protocol of a tailored MI (TMI) implementation-effectiveness trial (ATN 146 TMI) to scale up an EBP in multidisciplinary adolescent HIV settings while balancing flexibility and fidelity. This protocol is part of the Scale It Up program described in this issue.

Methods: This study is a type 3, hybrid implementation-effectiveness trial that tests the effect of TMI on fidelity (MI competency and adherence to program requirements) while integrating findings from two other ATN protocols described in this issue—ATN 153 Exploration, Preparations, Implementation, Sustainment and ATN 154 Cascade Monitoring. ATN 153 guides the mixed methods investigation of barriers and facilitators of implementation, while ATN 154 provides effectiveness outcomes. The TMI study population consists of providers at 10 adolescent HIV care sites around the United States. These 10 clinics are randomly assigned to 5 blocks to receive the TMI implementation intervention (workshop and trigger-based coaching guided by local implementation teams) utilizing the dynamic wait-listed controlled design. After 12 months of implementation, a second randomization compares a combination of internal facilitator coaching with the encouragement of communities of practice (CoPs) to CoPs alone. Participants receive MI competency assessments on a quarterly basis during preimplementation, during the 12 months of implementation and during the sustainment period for a total of 36 months. We hypothesize that MI competency ratings will be higher among providers during the TMI implementation phase compared with the standard care phase, and successful implementation will be associated with improved cascade-related outcomes, namely undetectable viral load and a greater number of clinic visits among YLH.

Results: Participant recruitment began in August 2017 and is ongoing. As of mid-May 2018, TMI has 150 active participants.

Conclusions: This protocol describes the underlying theoretical framework, study design, measures, and lessons learned for TMI, a type 3, hybrid implementation-effectiveness trial, which has the potential to scale up MI and improve patient outcomes in adolescent HIV settings.

Trial Registration: ClinicalTrials.gov NCT03681912; <https://clinicaltrials.gov/ct2/show/NCT03681912> (Archived by WebCite at <http://www.webcitation.org/754oT7Khx>)

International Registered Report Identifier (IRRID): DERR1-10.2196/11200

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KEYWORDS

implementation science; motivational interviewing; youth living with HIV

Introduction

Background

The National Institutes for Health Office of AIDS Research called for implementation science (IS) to address the behavioral research-practice gap [1]. IS is the scientific study of methods to promote the uptake of research findings and evidence-based practices (EBPs) to improve the quality of behavior change approaches in health care settings [2]. A primary challenge of scaling up EBPs is the balance of flexibility (adaptation to context) and fidelity (provider adherence and competence) [3]. Despite the success of the Centers for Disease Control's dissemination program of HIV-related EBPs, there are substantial barriers to the effective implementation of these interventions in real-world settings [4]. To date, considerably less attention has been paid to IS in HIV care settings [5] and even less in HIV adolescent and young adult care settings, an age group hardest hit by new infections [6]. Youth aged 16-24 years have the highest rates of new HIV infections compared with all other age groups [7]. Rates of new and existing infections continue to be disproportionately higher in racial and ethnic minorities, particularly among African American and Latino adolescents and young adults [8]. With current clinical guidelines, youth living with HIV (YLH) increasingly will be initiating antiretroviral treatment, yet rates of adherence are notoriously poor [9]. Racial and ethnic minority youth are at particular risk of poor adherence to antiretroviral therapy and, therefore, of having detectable viral load [10,11]. Thus, an understanding of how to implement EBPs to promote behavior change in HIV treatment settings is critical and timely, particularly in youth treatment settings, as adolescence and young adulthood are the developmental periods where risk behaviors, including nonadherence, peak. Yet, to the best of our knowledge, there have been no IS studies of behavioral EBPs in adolescent HIV treatment settings.

Motivational Interviewing

Motivational interviewing (MI) is a collaborative, goal-oriented method of communication designed to strengthen intrinsic motivation in an atmosphere of acceptance, compassion, and autonomy support [12]. MI was adapted by the protocol chair for adolescents and young adults [13] and chosen as the EBP of the study because (1) MI-consistent behaviors promote behavior change and treatment engagement across multiple behaviors, in multiple formats, and by multiple disciplines and has shown effectiveness with minority populations [14]; (2) MI

was also the only EBP to demonstrate success across the youth HIV prevention and care cascades [15-18], and a recent meta-analysis found that MI was the only effective EBP for behavior change in YLH [19]; (3) MI is already embedded in the clinical guidelines for HIV care [20-23] and HIV risk reduction [24]; (4) MI may provide a foundation for patient-provider communication in the delivery of other EBPs; and (5) MI has been found to have even larger effect sizes in minority populations [14].

Balancing Flexibility and Fidelity

A key tension in IS lies between strict fidelity to EBP program requirements and flexibility in adapting to the community context [25]. Fidelity refers to adherence to the program requirements as well as EBP competence of implementers. Adaptation is the process of making a new program "fit" in the targeted inner context (organization) and outer context (service system). Aarons et al [26] developed the Dynamic Adaptation Process for adapting an EBP to a new context while maintaining fidelity to core elements during 4 phases of the Exploration, Preparation, Implementation, and Sustainment (EPIS) model [27]. The process involves identifying core elements and adaptable characteristics of EBP implementation, then supporting implementation by guiding allowable adaptations to the model, fidelity monitoring and support, and identifying the need for and solutions to system and organizational adaptations. This guidance occurs in collaboration of with local stakeholders who meet regularly as an implementation team (iTeam).

Promoting Sustainability

An EBP is considered sustained if core elements are maintained with fidelity—typically 1 year postimplementation [12]. Fidelity-maintenance strategies such as ongoing audit and feedback and booster training are particularly important for sustainability [28]. While it is clear that ongoing coaching is necessary to sustain MI fidelity, it remains unclear whether this facilitation is best delivered by facilitators who are internal to the organization or by outside experts. Our pilot work suggests that at least 6 months are needed in HIV care settings for even a subset of providers to achieve expert competency sufficient to provide coaching [29]. Furthermore, in these multidisciplinary medical settings, one provider is not typically providing supervision to other providers. Preselecting internal facilitators may be counter to the structure of the team, and preselected staff may not have set aside time to provide such supervision, particularly in an era of shrinking resources. Alternatively, a

more feasible model could use the Dynamic Adaptation Process to guide internal facilitation (IF) after a year of external facilitation with data collection on staff competency, time, and interest.

Communities of practice (CoPs) are another strategy to promote the uptake and sustainability of EBP. A CoP is a group of people who learn together and create common practices based on (1) a shared domain of knowledge, tools, language, and stories that creates a sense of identity and trust to promote learning and member participation; (2) a community of people who create the social fabric for learning and sharing, inquiry, and trust; and (3) shared practice made up of frameworks, tools, references, language, stories, and documents that community members share. They can vary in the level of formality, membership (shared discipline or across disciplines), and method of communication (eg, face-to-face and Web-based). They are supposed to be nonhierarchical and can change their agenda to suit the needs of members. While the study of CoPs to promote fidelity in the implementation of EBPs is in its infancy, preliminary findings are promising [30].

Efficient fidelity measurement can aid sustainability by providing supervisors with easily used tools for ongoing quality assurance [31]. A fidelity instrument with strong established psychometric properties will not be used in real-world clinics if it is too costly or difficult to integrate into routine practice; therefore, developing fidelity measures that can be feasibly used by internal or external facilitators to provide rapid, accurate feedback and that have a high likelihood of being sustained to support the ongoing implementation is an important component of a successful implementation strategy. We have tested the efficiency and validity of a trainer or coach rating scale for fidelity monitoring, feedback, and systematic coaching. In addition, we have learned in our preliminary studies that recording actual patient-provider interactions in some HIV clinic settings is not feasible. As a result, we have developed a standard patient interaction model of fidelity monitoring using our trainer or coach rating scale as an alternative choice for implementation [32].

Linking Cost-Effectiveness Research With Implementation Science

In the face of competing demands for health care resources, the importance to establish not just the efficacy of EBPs but also their relative economic value has increased. A recent editorial noted that despite the prevalence of economic evaluation in health services research, there is a dearth of studies on the cost-effectiveness of implementing EBPs [33]. The authors note that the number of economic evaluations contrasts sharply with

the number of studies on implementation strategies assessing only their effect on behavior change and health outcomes. To further emphasize this, the National Institutes for Health has established the cost-effectiveness analysis as a key priority for 2016 [34].

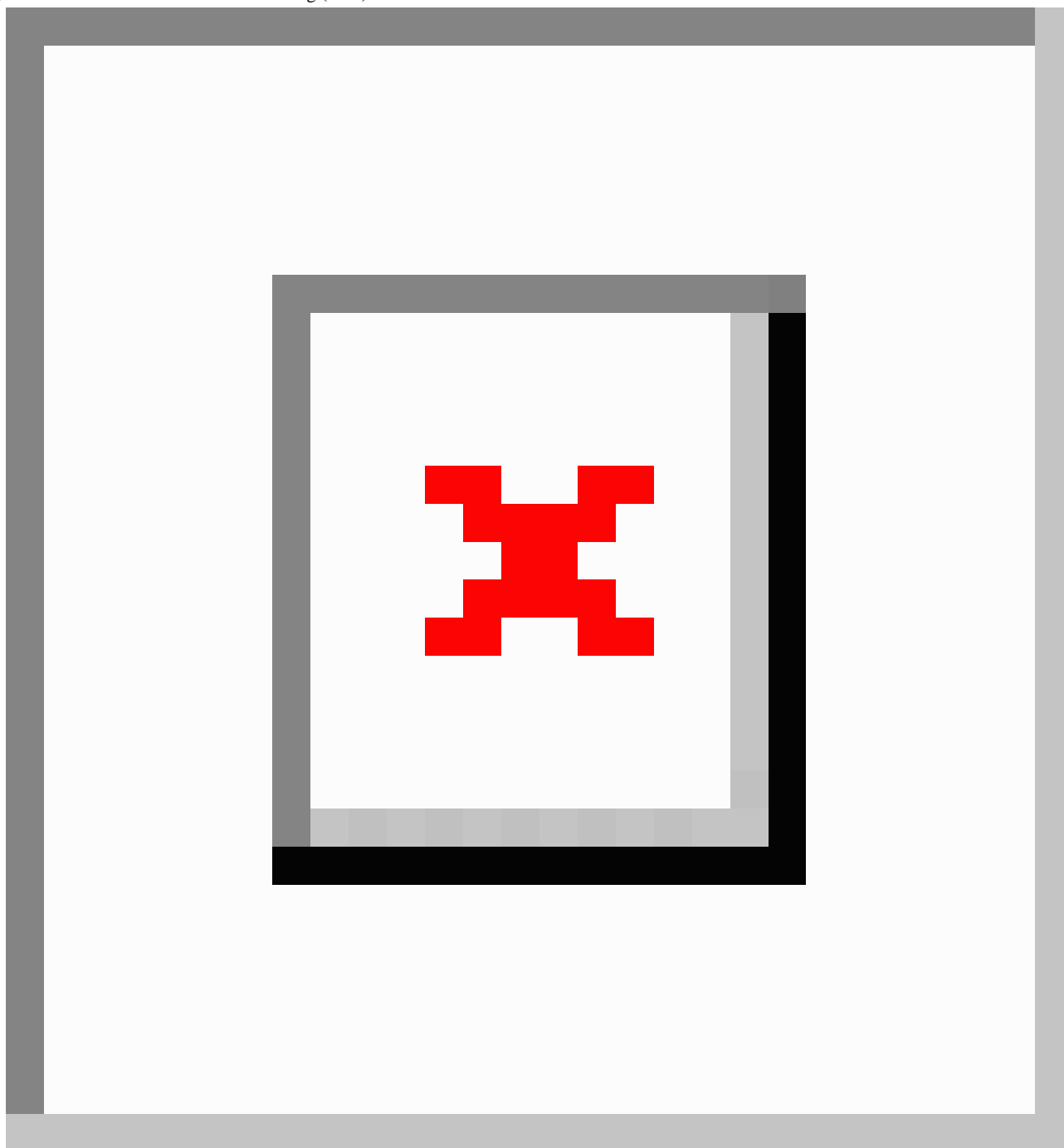
Aims

The aim of this paper is to describe Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) 146 Tailored Motivational Interviewing (TMI) to study the scale up of an EBP in multidisciplinary adolescent HIV care settings while balancing flexibility and fidelity. The protocol is part of the *Scale it Up* research program focusing on implementation of self-management interventions to impact the adolescent HIV prevention and care cascades [35]. The study seeks to determine primarily the effect of the TMI implementation intervention (set of strategies) on provider fidelity (adherence plus competence) and secondarily HIV care continuum outcomes (collected as part of ATN 156 described in this issue). Another objective of this study is to compare IF plus CoPs with CoPs alone in sustaining fidelity and to explore the role of the barriers and facilitators to implementation (see ATN 153 EPIS protocol paper in this issue), as these impact fidelity in study sites. Finally, this study also seeks to determine the cost-effectiveness of TMI with or without IF sustainment by combining fidelity and cascade outcomes with money spent on implementation strategies.

Methods

Design

ATN 146 TMI is part of the *Scale It Up* Program as described in the overview paper in this issue [35]. TMI is a type 3, hybrid implementation-effectiveness trial [36] that tests the effect on fidelity to MI, using a dynamic wait-listed design [37] with 150 providers (an average of 15 providers and 100 patients each) nested within 10 HIV clinical sites (subject recruitment venues) in the United States. A type 3, hybrid implementation design focuses primarily on the effect of the implementation intervention strategies on implementation outcomes, such as fidelity, and secondarily on patient outcomes and the effect of these outcomes on adaption and fidelity. This design allows for all clinics to receive the implementation intervention (set of implementation strategies), but randomization and implementation intervention phase occur in staggered blocks (in pairs of clinics). Although fidelity assessments occur throughout the study period at each site, a new block enters into the implementation phase every 3 months (Figure 1).

Figure 1. Tailored motivational interviewing (TMI) schedule of assessments.

Participants and Recruitment

Eligible participants include all youth HIV care providers (eg, physicians, nurses, mental health clinicians, and paraprofessional staff) who have at least 4 hours of contact with youth for HIV prevention or care. Study coordinators at each clinic work with the research team to introduce the project and recruit participants by scheduling and conducting introductory meetings. After the introductory meetings, a study coordinator from each site sends provider contact information (email and phone number) to the research team that contacts potential participants to provide information and schedule quarterly assessments. A participant is considered enrolled once he or she reviews the information sheet and completes a research element (ie, at least one fidelity

assessment). A central institutional review board (IRB) is used to establish a master reliance agreement via the “SMART” or Streamlined, Multisite, Accelerated Resources for Trials IRB Reliance platform. This is designed to harmonize and streamline the IRB review process for multisite studies, while ensuring a high level of protection for research participants across sites. Participants (medical providers) at each site provide informed consent before any study activities. This study has been approved as an expedited protocol at the central IRB site. HIV care and prevention providers may choose to opt out of the study without penalty. A participant meets the criteria for premature discontinuation upon withdrawal of consent before the project’s completion or stops working in the clinic during the study.

Implementation Intervention

The implementation intervention strategies follow the phases of the EPIS model [38].

Exploration Phase


The exploration phase involves a multilevel assessment of system, organization, provider, and client characteristics using qualitative and quantitative assessments. ATN 153 EPIS [39] is utilized for this purpose as providers complete qualitative interviews and quantitative surveys related to the following: (1) anticipated barriers and facilitators of adoption and use of MI and proposed implementation intervention strategies within the inner (provider, clinic, and organization) and outer (system) contexts; (2) ideas to promote sustainability in terms of integration into program and clinic policies; and (3)

identification of key stakeholders for the iTeam. In addition to these data, baseline quantitative data on provider competency is collected in this phase.

Preparation Phase

In the preparation phase, a continuous information feedback loop is created such that information gathered during the assessments are used by the iTeam to make adjustments to the implementation strategies while maintaining fidelity to the EBP and mandatory implementation intervention components. The iTeam has monthly conference calls during this period to member-check the barrier and facilitator data and iteratively draft locally customized implementation strategies. Figure 2 shows the mandatory and adaptable components of the implementation intervention.

Figure 2. Dynamic Adaptation Process to balance fidelity and flexibility using monthly implementation team meetings. MI: motivational interviewing.



Component	Required	Adaptable
Initial Workshop	12 hours of tailored MI workshop	Hours may be spread over 2-3 days to avoid clinic closure; up to 6 hrs virtual (up to two hours individual)
Fidelity Monitoring	Quarterly	Audiorecordings or standard patient model (standard patients developed)
Coaching Feedback	Written feedback of competency ratings; Triggered coaching	Format of written feedback and delivery; Scheduling preferences (automated appointment reminders and feedback developed)
Organizational Supports	Leadership monitoring of adherence, \$3000 incentives, options of youth feedback	Who monitors and how frequently; delivery of program adherence feedback; corrective actions and supports; incentives structure

Implementation Phase

Implementation begins with a 12-hour skills workshop [40] delivered by members of the Motivational Interviewing Network of Trainers. The workshop was tailored for adolescent HIV in our prior studies [29,41]. MI training relies on experiential activities developed by the network while minimizing didactic presentations. Cooperative learning methods [42] allow staff members to coach each other in small groups to promote experiential learning and group cohesion. Group MI methods are included to increase intrinsic motivation for implementation strategies [43]. A recent review of 10 studies in health care settings [44] suggested that MI workshops markedly improved MI skills compared with controls; however, as in mental health settings [40,45,46], workshops were not sufficient for trainees to achieve MI competency. There are two mandatory coaching sessions in the 3 months following training. Subsequently, providers complete a quarterly competency assessment (see the schedule of assessments below). Coaching feedback is triggered

by a provider falling below the intermediate competency threshold on this measure. Providers receive an autogenerated report based on their scores with recommendations for mandatory coaching for scores below intermediate competency and optional maintenance coaching for scores in the intermediate or advanced range. The duration of coaching sessions is 45-60 minutes, and they are delivered by a member of the Motivational Interviewing Network of Trainers. The standardized coaching includes a brief interaction to elicit change talk around MI implementation, feedback on two highest and two lowest ratings, and review of the audiorecording and coaching activities (eg, fidelity assessments) targeting the lowest ratings.

The iTeam continues to monitor adaptations at the provider and inner and outer organizational contexts as well as any fidelity drift and plan for sustainability.

Sustainment Phase

In the sustainment phase, the iTeam is encouraged to meet without external facilitation to review client and system data

and address barriers and facilitators to ongoing EBP fidelity. The iTeam guides the site to develop a CoP and are given a manual of possibly group activities to support MI fidelity. The sites randomized to IF receive .1 full time equivalent for the facilitator who must achieve advanced competency by the end of the implementation period and complete a 5-session facilitator training.

Site Randomization

The research design requires randomization of sites in blocks to the MI implementation intervention. The 10 clinics receive random assignment to 5 blocks to receive the TMI implementation intervention. Every 2 months, 2 clinics are randomized to begin the implementation intervention and the others remain in the wait-listed condition. This continues until the last block is randomized. To allow sufficient time for scheduling and planning the initial workshop component, each wave of randomization occurs 6 months prior to the initiation of implementation. After 1 year of implementation (1-year postworkshop), regardless of the block, sites receive rerandomization to IF plus CoP or CoP alone.

Schedule of Assessments and Compensation

Fidelity is assessed on a quarterly basis for 36 months throughout the study (preimplementation, 12 months of implementation, and sustainment). Provider competence ratings (primary outcome) are collected quarterly preimplementation, once a week for the first 2 weeks of implementation (to support the coaching process), and quarterly during the rest of the year of implementation and, then, quarterly during sustainment. Across clinics, providers preceding the implementation intervention will form the control or comparison group, and the providers following the start of the implementation intervention will form the intervention group. After 1 year of implementation, regardless of the block, sites receive rerandomization to either IF monitoring and coaching plus the encouragement of CoPs or CoP alone.

Each site receives the same incentive budget (the equivalent of US \$50 per staff member, or approximately US \$3000 in total) and will determine whether incentives will be provided episodically or after program completion. The iTeam decides whether incentives should be delivered directly to individuals for completion of program requirements, utilize a lottery system, or provide a group reward when all site providers adhere to program requirements.

Assessment Scheduling

Appointy, a Web-based scheduling system, is used to schedule fidelity assessments and coaching sessions. Providers are sent an invitation link through Appointy to create an account. Providers can view the hours that are available from the research team to schedule their roleplay and a coaching session. A confirmation email is sent to providers to confirm their booking. In addition, providers have the advantage of rescheduling or canceling their appointments if needed. Canceled or “no show” appointments are tracked along with completed appointments in REDCap, a Web-based database management program. If providers fail to schedule through Appointy, the research team

uses direct contact methods (phone or email) to schedule their roleplay or coaching session.

Primary Outcome: Competency Ratings

Every 3 months over the 36 months of the study, providers complete a 15-minute, phone-based standard patient interaction developed in our previous studies [32]. There is a growing body of literature supporting the educational use of standardized patients in teaching and learning [47,48], including teaching MI skills and practice [49,50]. Standard patients' profiles were developed by actual clinical encounters and delivered by trained actors. In addition to a specified target behavior (eg, medication adherence, appointment attendance, and risk behavior), a detailed patient history is provided to the actor including living situation, pregnancy status, relationship status, drug use, willingness to take medications, talkativeness, and mental health symptoms such as depression. Each scenario also includes 3 unique “must say” statements or questions (eg, “*I hate that I have to deal with this [HIV]. That's why I don't date, or get close to people or anything.*”) to be included in the acting session. The supervisor listens to randomly selected recordings on a monthly basis to provide feedback on accuracy and consistency. Standardized profiles are delivered on a schedule, meaning that only 1 profile is used for all interactions conducted in each quarter. We attempt to keep actors and coders blind to the condition by assigning each participant a unique participant identification number (9 digits) that does not reflect participant location or randomization status.

A trained independent rater codes the interactions with the MI Coach Rating Scale [51,52] developed using Item Response Theory item development and evaluation methods [51,53,54]. The scale includes 12 items (Figure 3) assessing MI competence on a 4-point Likert scale (1=Poor, 2=Fair, 3=Good, and 4=Excellent). Overall, 20% interactions are recoded to confirm interrater reliability. In addition, coders attend a monthly coding lab to discuss discrepancies in a randomly selected recording. Competency thresholds were defined using a Rasch-based objective standard setting procedure [55]. Fifteen MI content experts used the instrument's 4-point scale to select the minimum rating scale category reflecting beginner, intermediate, and advanced competence. The selected categories were combined with the results of a Many-Facet Rasch Model [56], including item estimates, SEs, and rating scale thresholds. From this information, the average item “difficulty” was computed across raters and items, with separate scores for the beginner and solid competency thresholds. These values were then adjusted for the experts' ratings of overall competency, from 0% to 100%, required for “somewhat acceptable” and “acceptable” competency. The resulting logit-based criterion scores were then converted to raw scores (using information from the Many-Facet Rasch Model) that correspond to the instrument's 4-point scale. Applied to datasets from previous studies, including ATN 128, a large proportion of ratings fell in the Beginner category, and based on (1) expert review and (2) the wide range from Beginner to Advanced, the Beginner category was divided into 2 parts, to reflect “Beginner” and “Novice.” Thus, the final categories and associated threshold scores were as follows: Beginner (<2.0); Novice (2.0-2.6); Intermediate (2.7-3.3); and Advanced (>3.3).

Figure 3. Motivational Interviewing Coach Rating Scale.

Item- The Provider....	Definition
1. cultivates empathy and compassion with client.	The provider understands or makes an effort to grasp the client's perspective and feelings, and conveys that understanding to the client.
2. fosters collaboration with client.	The provider negotiates with client and avoids an authoritarian stance. A metaphor for collaboration is dancing instead of wrestling.
3. supports autonomy of client.	The provider emphasizes client's freedom of choice and conveys an understanding that the critical variables for change are within the client and cannot be imposed by others.
4. works to evoke client's ideas and motivations for change.	The provider conveys an understanding that motivation for change, and the ability to move toward that change, reside mostly within the client and therefore focuses efforts to elicit and expand it within the therapeutic interaction.
5. balances the client's agenda with focusing on the target behaviors.	The provider maintains appropriate focus on a specific target behavior or concerns directly tied to it while still addressing the client's concerns.
6. demonstrates reflective listening skills.	The frequency of reflective statements in balance with questions
7. uses reflections strategically.	The quality of the reflections - low quality reflections are inaccurate, lengthy, or unclear. High quality reflections are used to express empathy, develop discrepancy, reinforce change talk, reduce resistance, and generally strategically increase motivation.
8. reinforces strengths and positive behavior change with affirmations/affirming reflections.	The provider affirms personal qualities or efforts made by the client that promote productive change or that the client might harness in future change efforts.
9. uses summaries effectively.	Summaries are used to pull together points from two or more prior client statements. At least two different ideas must be conveyed, as opposed to two reflections of the same idea. Summaries are a way to express active listening and reflect back to the client the "story." Summaries are also used to structure the session as well as to guide clients in the direction of change.
10. asks questions in an open-ended way.	An open question is one that allows a wide range of possible answers. Closed ended questions may be answered with a one word response. Multiple choice questions are considered open particularly with clients who struggle with open and more abstract questions.
11. solicits feedback from client.	The provider asks clients for their response to information, recommendations, feedback, etc. This is analogous to the Ask-Tell-Ask or Elicit-Provide-Elicit strategy in Motivational Interviewing.
12. manages counter change talk/sustain talk and discord.	The provider responds to discord and sustain talk (i.e., counter change talk) either reflectively or strategically. Client may make statements against change either directly about the target behaviors, about engaging in the treatment program or discord in the relationship. Discord refers to tension between the client and provider (wrestling).

Secondary Outcome: HIV Cascade Variables

ATN 154 Cascade Monitoring [57] examines the trends in treatment cascade, including whether patients are receiving antiretroviral treatment, adhering to regimens, attending care appointments, and maintaining suppressed viral loads, to guide the new protocol development and to facilitate community engagement.

Measures of the Context of Implementation

ATN 153 EPIS [39] assesses the barriers and facilitators to implementation with qualitative interviews and qualitative surveys to address the following: (1) why were some providers and not others able to integrate competent use of MI into their practice with adolescent patients? (2) Why did some providers sustain MI over time? And (3) why were some sites good host settings for an initiative designed to promote the use of MI in routine clinical practice? There are distinct factors that position an organization well for succeeding in implementing a new practice, and there are also distinct provider and organizational influences that can impede or facilitate successful integration of a new practice into providers' daily routines [58].

Analysis Plan

Aim 1: Effect of Tailored Motivational Interviewing on Provider Motivational Interviewing Competence and Cascade Outcomes

We will confirm the distribution for outcome modeling using graphical or descriptive procedures. The descriptive trajectory for each provider on each outcome will be plotted using "spaghetti plots" [59]. The plots will illustrate the patterns of change over time, including the specific patterns during the preimplementation, implementation, and sustainment phase, and this will inform the specification of the growth models.

Analyses will be conducted using mixed-effects regression models (eg, Raudenbush and Bryk [60]). For the MI competence outcome, aims 1 and 2 will be evaluated using the same base model. The slope term for the preimplementation phase is expected to be nonsignificant; that is, MI competence is expected to be relatively low and stable prior to the implementation interventions. Upon entering the implementation phase, the competence slope is expected to shift markedly, becoming more positive. Likewise, the implementation phase indicator should reflect a marked increase in the overall level of competence from the preimplementation phase to the implementation phase. Furthermore, follow-up models will be conducted to determine whether MI competence is higher for clinics in the implementation phase relative to clinics that, at the same time, are still in the preimplementation phase.

The cascade outcomes will be analyzed using a similar approach. For the viral load and appointment adherence outcomes, the model will be specified as described for the provider competence outcome, testing for changes in the viral load and appointment adherence slopes from the preimplementation to implementation to sustainment phases. For the outcomes that are cross-sectional within phases—new diagnosis and receipt of counseling and testing services—phase-level indicators will test for changes in the rate of new diagnoses and receipt of C&T. Furthermore, planned comparisons will be specified to compare the rates between the implementation and sustainment phases.

Because there are multiple phases over time for each provider and clinic, the primary question is whether provider competence slopes change from phase-to-phase. The approach used to estimate the statistical power is recommended by Hox [61] and Hedges and Rhoads [62]. Specifically, there are 3 steps

1. Estimate power for a single-level regression model as the *targeted* sample size. In this case, power is .80 to detect a

- small-to-medium effect of $R^2=0.10$ with 75 single-level, independent observations.
2. Compute the *actual* sample size for the proposed study. For the primary outcome of provider competence, focusing on the implementation phase only, with 10 clinics that have 15 providers each and 6 measurements of competence, there are 900 nonindependent observations.
 3. Penalize the actual sample size for the nesting effects using the design effect formula (ie, $n_{\text{eff}} = n / (1 + \{n_{\text{clus}} - 1\} \rho)$, where n_{eff} is the effective sample size, n is the total sample of observations, n_{clus} is the cluster size, and ρ is the intraclass correlation), providing the effective sample size. The observations provide the statistical power of 225 independent observations, and adjusting for nesting within clinics, they provide the statistical power of 71 independent observations. As such, the proposed sample is sufficient for detecting a small-to-medium effect of $R^2=0.11$.

For aim 2, the power estimate reflects the ability to detect a difference in the overall level of the primary outcome of provider competence between groups. Power was estimated as detailed for aim 1. With 10 clinics that have 15 providers each and 4 measurements of competence, there are 600 nonindependent observations. These observations provide the statistical power of 214 independent observations, and adjusting for nesting within clinics, they provide the statistical power of 70 independent observations. As such, the proposed sample is sufficient for detecting a small-to-medium effect of $f^2=0.11$.

Aim 2: To Compare Internal Facilitation Plus Communities of Practice to Communities of Practice Alone in Sustaining Competence

For the provider competence outcome, the data structure is identical to that described for aim 1. For the adherence to program requirements outcome, the data are from the sustainment phase only, with repeated measurements of adherence to fidelity assessments and coaching sessions (level 1) nested within providers (level 2) nested within clinics (level 3).

To evaluate the outcomes for aim 2, including provider competence, completion of fidelity assessments, and completion of coaching sessions, a dichotomous indicator will be added at clinic level to differentiate clinics randomized to CoP plus IF from those randomized to CoP alone. For the provider competence outcome, in the model detailed for aim 1, cross-level interactions will be specified between this condition indicator and the level-2 sustainment phase indicator, along with the level-1 growth term for the sustainment phase. This will test the extent to which changes in provider competence during the sustainment phase differ for clinics receiving CoP plus IF and those receiving CoP alone. Likewise, the model can be simplified to test for a difference in the average level of provider competence, rather than change over time, during this phase. For the adherence to program requirements outcomes, the data are dichotomous, and as such, analyzed according to a binomial outcome distribution, reflecting each provider's completion of planned fidelity assessments and coaching sessions. The clinic-level condition indicator will test for a difference between

CoP plus IF and CoP alone in the average rate of adherence to program requirements during the sustainment phase.

For aim 2, the power estimate reflects the ability to detect a difference in the overall level of the primary outcome of provider competence between groups. Power was estimated as detailed for aim 1. With 10 clinics that have 15 providers each and 4 measurements of competence, there are 600 nonindependent observations. These observations provide the statistical power of 214 independent observations, and adjusting for nesting within clinics, they provide the statistical power of 70 independent observations. As such, the proposed sample is sufficient for detecting a small-to-medium effect of $f^2=0.11$.

Aim 3: To Understand Barriers and Facilitators to Implementation

Our research questions for this component of the project are as follows: (1) why were some providers and not others able to integrate the competent use of MI into their practice with adolescent patients? (2) Why did some providers sustain MI over time? and (3) why were some sites good host settings for an initiative designed to promote the use of MI in routine clinical practice? To address these questions, data coding and analysis will proceed in a 3-phase process. First, consistent with Morgan's [63] recommendations for qualitative content analyses and Hsieh and Shannon's [64] directed qualitative content analytic approach, standard definitions of the concepts to be coded in the text will initially be developed on the basis of the EPIS model. We will systematically review each interview at each time point for all thematic mentions of (1) features of the inner and outer context per EPIS that have the potential to influence the implementation of MI; (2) all mentions of people; and (3) all mentions of personal perceptions of MI and other behavioral EBPs that have the potential to improve patient outcomes. Within these longer thematic lists, we will then separate specific categories of work setting characteristics, participants' roles, and perceptions of evidence-based interventions, initially using existing theory to guide categorization but also allowing themes to emerge from the data through open coding procedures [65,66]. This combined inductive and deductive coding approach will allow us to both *validate* and *extend* the EPIS framework through our analysis. In addition to identifying categories within the data, we will also note whether providers' mentions of particular categories of persons, organizational characteristics, and perceptions are positive or negative.

All coding will be conducted using NVivo Version 10. For reliability, a random selection of 30% of the interviews will be independently coded. Coding will be monitored to maintain a kappa coefficient of ≥ 0.90 [67,68]. In our third step, we will engage in comparative analyses both within and across time so that we may examine differences at the setting and provider levels in the quality and extent of MI implementation. Once all data are coded across all time points, we will adapt the innovation profile approach by Leithwood and Montgomery [69], originally developed for classroom research. The approach results in a multidimensional rubric to classify where a site is in the process of developing its capacity to engage in the integration of EBPs into routine patient care. These data will

be integrated with quantitative fidelity data and EPIS surveys using a sequential mixed-method design [70,71] with equal weight given to qualitative and quantitative data sources [72]. We will develop an intervention profile and implementation resources for replication and sustainment of the intervention. The profile will synthesize intervention components and implementation analyses into intervention-specific practical guidance for further scale up.

Cost-Effectiveness Analysis

We will specify costs of implementation for budgeting further scale up as well as the incremental benefit of TMI and the addition of an internal facilitator on provider TMI competence and cascade outcomes over time. The cost-effectiveness analysis for the study is designed to measure costs and consequences of changes in the implementation over the 36 months of study follow-up to help inform the investigators of the economic consequences of the varying amount of resources used in the EPIS components of the study. Data will be collected on resource use and costs using a modification of the Drug Abuse Treatment Cost Analysis Program method [73] based in the approach described by Kim et al [74] to estimate the standard costs of personnel, training, and clinic space and time logs from the workshops, coaching, and fidelity monitoring processes to capture resources used. The units of measurements specified in the analysis will be used to assess cost-effectiveness. We will

calculate the cost per provider trained in TMI to competency level and incremental cost-effectiveness of using different coaching approaches and will estimate the cost per provider trained for each site to explore potential for efficiencies that may be relevant to further dissemination of the interventions. Furthermore, we will use a previously developed cost utility model to estimate the cost per quality adjusted life years over a 10-year time horizon expected from cascade outcomes of viral suppression and retention in care.

Results

TMI was launched in August 2017 and is ongoing. Currently, blocks 1-3 (see Table 1 for the list of randomization blocks) are participating in the implementation phase of TMI, while blocks 4 and 5 are still in their baseline period. (The clinic in New Orleans, LA, has decided to withdraw from the study, prior to randomization to TMI, and will not be collecting follow-up data.) From these current 10 sites, a total of 172 providers were invited to participate (excluding those that declined participation or left the clinic); of these 172 potential participants, 146 have consented as of early mid-May 2018. Consented participants have completed at least one quarterly assessment in the preparation phase. This protocol allows for the addition of more participants until a site receives the TMI workshop so the consented participant number may continue to increase.

Table 1. Clinic site block numbers, target enrollment, and consenting participants.

Clinical site	Block number	Target enrollment (N=165)	Consenting participants (N=146)
Memphis	1	15	16
Philadelphia	1	15	11
Brooklyn	2	15	16
Miami	2	15	14
Baltimore	3	15	11
San Diego	3	15	12
Birmingham	4	15	15
Tampa	4	15	17
Los Angeles	5	15	14
Washington DC	5	15	20

Discussion

Principal Findings

ATN 146 tests the effect of an MI implementation intervention on fidelity (primary outcome) and patient appointment adherence and viral suppression. The proposed design not only has the potential to expand MI to multidisciplinary adolescent HIV settings but may also provide opportunities to improve the implementation of other EBPs by providing a cost-effective implementation schematic. It is true that some, if not most, care providers have already received some exposure to MI; however, adequate competence is essential for successful implementation. The study also tests 2 approaches to sustainability. Finally, using mixed methods from the ATN 156 (EPIS protocol paper) [39],

we will be able to understand the variability in implementation success.

Lessons learned thus far include the following:

1. Although the sites have a strong history of research participation, IS studies are new to the network. Sites required significant education prior to the study initiation to ensure a complete understanding of the protocol and delineation of site staff responsibilities while avoiding coercion for what are optional IS studies.
2. There appears to be marked variability in adherence to program requirements across sites, which we hypothesize will be explained by data collected regarding implementation factors guided by the EPIS model [39]

3. Sufficient resources must be allocated to provider recruitment and retention as would be done in a traditional efficacy trial with patients.
4. iTeams need significant guidance from protocol staff (external facilitators) throughout the phases of implementation.
5. It is difficult to obtain patient perspectives in an expedited protocol without resources to obtain patient consent. However, we are supporting sites to collect deidentified client satisfaction ratings from all youth who attend clinic during the course of the study.

Limitations

The real-world clinical context of TMI presents a number of challenges to be addressed by the research design, including the small number of available sites, budget limitations for travel for site training, and inability to randomize providers within sites because of contamination. As such, traditional randomized

and cluster randomized designs are not viable options. Utilizing a dynamic wait-list controlled design addresses these barriers, while a second randomization provides a targeted test of the implementation and sustainment interventions.

Conclusions

In conclusion, the TMI study addresses the gap between behavioral research and clinical practice with a type 3 hybrid effectiveness-implementation trial. This protocol describes the study's underlying theoretical framework, design, measures, and lessons learned. If successful, TMI will have a considerable impact on provider MI competence and positive outcomes on the youth HIV care cascade. Although this intervention is being implemented with MI at multidisciplinary adolescent HIV settings, it can be adapted for delivery of other EBPs in this setting as well as MI implementation in other health care contexts.

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Conflicts of Interest

None declared.

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Abbreviations

- ATN:** Adolescent Medicine Trials Network for HIV/AIDS Interventions
- CoP:** communities of practice
- EBP:** evidence-based practice
- EPIS:** Exploration, Preparation, Implementation, and Sustainment model
- IF:** internal facilitation
- IRB:** institutional review board
- IS:** implementation science
- iTeam:** implementation team
- MI:** motivational interviewing
- NIH:** National Institutes of Health
- TMI:** Tailored Motivational Interviewing Implementation Intervention
- YLH:** youth living with HIV

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Protocol

An Electronic Pre-Exposure Prophylaxis Initiation and Maintenance Home Care System for Nonurban Young Men Who Have Sex With Men: Protocol for a Randomized Controlled Trial

Aaron J Siegler¹, PhD; James B Brock², MD, MSc; Christopher B Hurt³, MD; Lauren Ahlschlager⁴, MPH; Karen Dominguez¹, MPH; Colleen F Kelley⁵, MD; Samuel M Jenness⁴, PhD; Gretchen Wilde¹, MPH; Samuel B Jameson⁶, PhD; Gina Bailey-Herring¹, APRN; Leandro A Mena^{2,6}, MD, MPH

¹Department of Behavioral Sciences and Health Education, Rollins School of Public Health, Emory University, Atlanta, GA, United States

²Division of Infectious Diseases, Department of Medicine, University of Mississippi Medical Center, Jackson, MS, United States

³Institute for Global Health & Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

⁴Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, United States

⁵Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, United States

⁶Department of Population Health Science, John D Bower School of Population Health, University of Mississippi Medical Center, Jackson, MS, United States

Corresponding Author:

Aaron J Siegler, PhD

Department of Behavioral Sciences and Health Education

Rollins School of Public Health

Emory University

1518 Clifton Rd NE

Atlanta, GA, 30030

United States

Phone: 1 4047129733

Email: asiegler@emory.edu

Abstract

Background: Pre-exposure prophylaxis (PrEP) is highly efficacious for preventing HIV but has not yet been brought to scale among at-risk persons. In several clinical trials in urban areas, technology-based interventions have shown a positive impact on PrEP adherence. In rural and small-town areas in the United States, which often do not have geographically proximal access to PrEP providers, additional support may be needed. This may be particularly true for younger persons who are more likely to face multiple barriers to accessing PrEP services. Home-based care, accomplished through a tailored mobile phone app, specimen self-collection (SSC), and interactive video consultations, could increase both PrEP initiation and persistence in care.

Objective: The goal of this study is to assess the initiation and persistence in PrEP care for those randomized to a home-care intervention (electronic PrEP, ePrEP) relative to those assigned to the standard of care (control) condition. We will conduct additional assessments, including quantitative and qualitative analyses, to contextualize trial results and facilitate scale-up.

Methods: This 2-arm, randomized controlled trial will enroll young men who have sex with men (YMSM) aged between 18 and 24 years from rural areas of Georgia, Mississippi, and North Carolina. The trial will seek to recruit a diverse sample, targeting 50% participation among highly impacted groups of black or Latino men who have sex with men. Intervention participants will receive a study app that incorporates a messaging platform, a scheduling and milestone-based tracking system for PrEP care progress, electronic behavioral surveys, and interactive video consultations with a clinician. Complemented by SSC kits mailed to laboratories for standard PrEP-related monitoring, the ePrEP system will allow participants to access PrEP care without leaving their homes. YMSM randomized to the control condition will receive a listing of nearest local PrEP providers to receive standard PrEP care. Both groups will complete quarterly electronic surveys. The primary outcome, assessed at 6 and 12 months after randomization, will be the difference in the proportion of intervention versus control participants that achieve protective levels of the active metabolite of oral PrEP (tenofovir diphosphate in dried blood spots).

Results: Enrollment will begin in May 2019, with study completion in 2022.

Conclusions: This trial will determine whether home PrEP care provided through an app-based platform is an efficacious means of expanding access to PrEP care for a diverse group of YMSM in rural and small-town areas of the United States.

Trial Registration: ClinicalTrials.gov NCT03729570; <https://clinicaltrials.gov/ct2/show/NCT03729570> (Archived by WebCite at <http://www.webcitation.org/78RE2Qizf>)

International Registered Report Identifier (IRRID): PRR1-10.2196/13982

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KEYWORDS

pre-exposure prophylaxis; sexual and gender minorities; prevention; smartphone; mobile apps; telemedicine; telehealth; mHealth

Introduction

Men who have sex with men (MSM) continue to account for the majority of new HIV diagnoses in the United States [1]. HIV prevalence among MSM in rural counties is high, with many counties exceeding 15% prevalence [2]. Oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) was approved by the US Food and Drug Administration (FDA) for HIV pre-exposure prophylaxis (PrEP) in 2012. Large-scale clinical and pragmatic trials of oral FTC/TDF demonstrated high efficacy and effectiveness in preventing sexual HIV acquisition when taken consistently [3-5], yet a national database of PrEP-prescribing clinics developed by the authors indicates a substantial lack of providers in rural areas [6]. There are a number of rural areas in the United States in which residents live in *PrEP deserts*, with no nearby PrEP-prescribing clinics [7]. An estimated 38,000 MSM eligible for PrEP would require a ≥ 2 -hour round trip drive to their nearest clinic; over 100,000 would require ≥ 1 -hour round trip drive to access PrEP services [7].

Within the elevated risk group of MSM, black MSM and young MSM (YMSM) aged between 15 and 24 years bear disproportionate burdens of incident HIV infection [1] and represent priority populations for interventions. Several successful technology-based interventions have been shown in clinical trials to increase PrEP adherence [8,9], yet these efforts have been conducted predominately in urban areas. The premise for this study is that a tailored approach for rural YMSM, addressing known barriers of transportation, access to knowledgeable providers, and privacy, is likely to yield demonstrable improvements in initiation of PrEP and persistence in PrEP care.

The focus of this project is the delivery of home-based PrEP care. Such a strategy has the potential to quickly make PrEP services available to MSM in rural areas who currently lack access. Using a mobile phone app, participants assigned to the intervention may initiate PrEP and be retained in follow-up care without leaving their home. This will be achieved through the *electronic PrEP (ePrEP)* system that combines app-based surveys and screening tools, interactive video consultations, and home specimen self-collection (SSC).

The primary aim of this efficacy trial is to determine the impact of the ePrEP system on the levels of PrEP protection achieved

by MSM interested in initiating PrEP in rural and small-town areas. The hypothesis is that a higher proportion of ePrEP intervention participants will achieve biomarker-determined protective levels of tenofovir diphosphate (TFV-DP) relative to those randomized to standard of care (control). Secondary aims include conducting additional assessments to contextualize trial results, including adjusted analyses of the primary outcome, as well as cost effectiveness and cost-utility analyses.

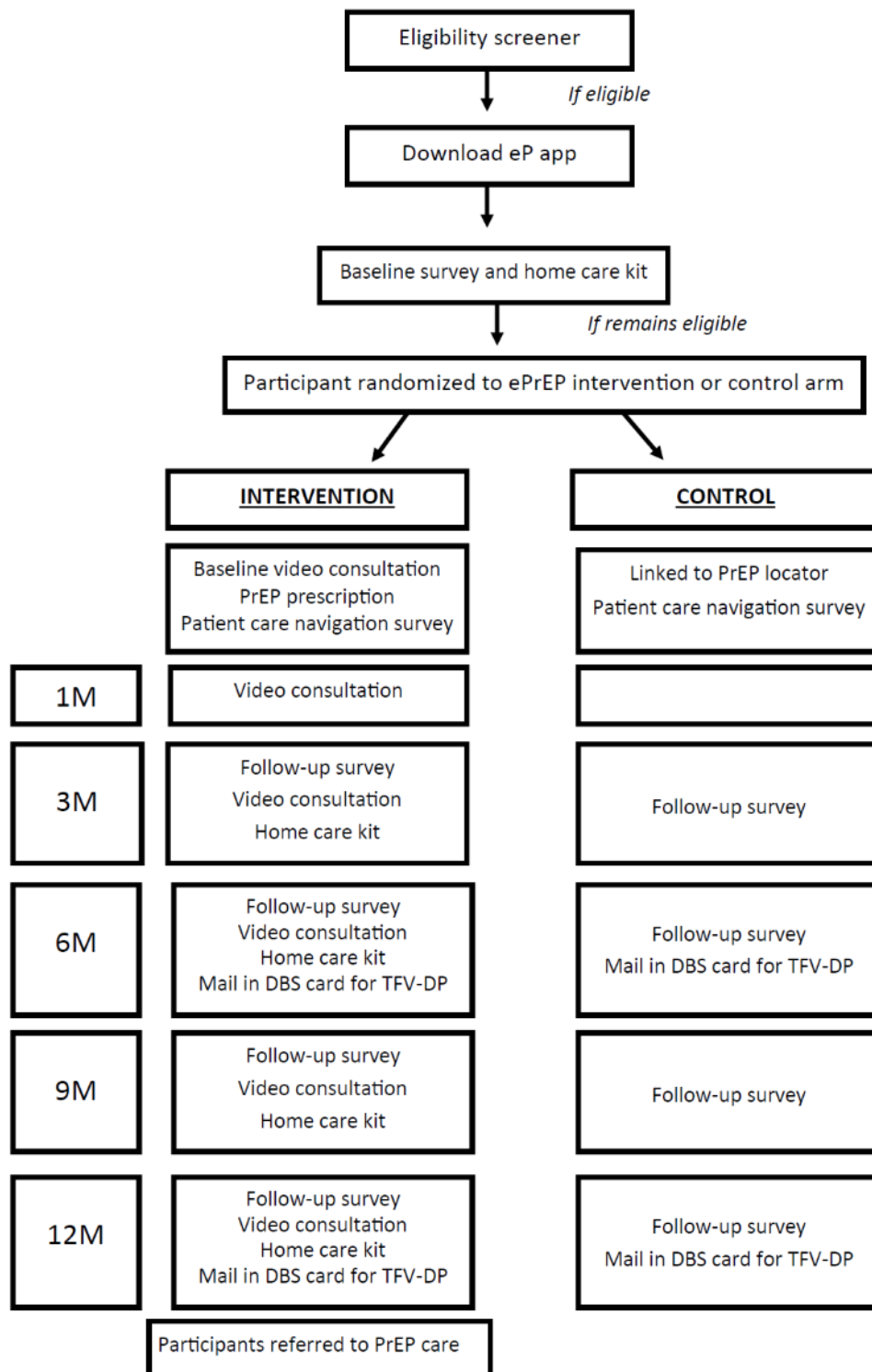
Methods

Study Design

PrEP-naïve MSM will be recruited into the study, with black and Latino MSM to comprise half of all participants. Initial screening will be conducted online; eligible individuals will complete an electronic consent ([Multimedia Appendix 1](#)) and a baseline survey ([Multimedia Appendix 2](#)), and then will receive an SSC kit to verify clinical appropriateness of oral FTC/TDF use. The home SSC kit will comprise supplies needed to produce microtube and dried blood spot (DBS) samples for central laboratory testing, detailed instructions, and directions for mailing specimens to the laboratory. MSM determined to be eligible, including clinical eligibility to receive oral FTC/TDF as PrEP, will be enrolled and randomized to either intervention or control conditions. Randomization, conducted using the study's electronic data capture (EDC) system, will be stratified by study site to decrease the likelihood of type I error because of the expected association between covariates and the primary study outcome.

Those assigned to the intervention ePrEP condition (n=120) will have an app-based interactive video consultation with a site study clinician who will prescribe PrEP as indicated [10]. At months 1, 3, 6, 9, and 12 postrandomization, participants complete *virtual* study visits that include app-based surveys, video consultations, and quarterly SSC for laboratory testing (per current practice guidelines) [11]. Participants assigned to the control condition (n=120) will be referred to a publicly available website that geolocates the nearest PrEP provider, using PrEP Locator [6]. All participants will mail-in self-collected DBSs for the determination of the primary outcome assessment of TFV-DP at month 12 postrandomization. All participants will also complete electronic surveys for secondary outcome assessment at baseline and months 3, 6, 9, and 12 postrandomization ([Figure 1](#)).

Figure 1. Electronic pre-exposure prophylaxis (ePrEP) study flow chart. DBS: dried blood spot; M: month; TFV-DP: tenofovir diphosphate.



Study Population and Recruitment

We will randomize 240 participants in Georgia, North Carolina, and Mississippi. Target recruitment is 50% among highly impacted groups of black or Latino MSM. To be eligible, a potential participant must (1) have been assigned male sex at birth, (2) be aged between 18 and 24 years, (3) live in a rural or small-town zip code based on the Centers for Disease Control and Prevention’s (CDC) urbanicity classifications [12], (4)

provide informed consent, (5) be able to complete study consent and survey processes in English, (6) be willing to provide complete contact information (including 2 alternate contacts), (7) be able and willing to provide identification for verification, (8) own an iOS or Android mobile phone capable of running the study app, (9) be willing to use study-provided PrEP financial navigation services, (10) be willing to self-collect specimens, (11) be HIV-uninfected, as determined by laboratory testing using an antigen/antibody combination assay, (12) have

a serum creatinine level that suggests creatinine clearance ≥ 60 mL/min, as determined by the Cockcroft-Gault equation, (13) be hepatitis B virus uninfected, as determined by laboratory testing, (14) have an indication for PrEP based on current guidance, including consideration of epidemic conditions [11], and (15) be interested in and willing to take daily FTC/TDF. Potential participants are excluded from enrollment if they (1) are currently taking oral FTC/TDF as PrEP, (2) have a medical contraindication to the use of FTC/TDF, (3) have symptoms of acute HIV infection, (4) are currently enrolled in any HIV prevention trials, (5) have a self-reported acquired or inherited disorder preventing the normal clotting of blood, such as hemophilia, or (6) have insurance coverage through a closed network system in which study clinicians cannot prescribe. Individuals with signs of acute HIV infection who are HIV antigen/antibody negative may, upon the discretion of study clinicians based on additional laboratory testing and/or discussion with the participant, be determined to be eligible for the study. Due to the additional clinical follow-up needed for persons with hepatitis B infection, we excluded those testing positive from this telemedicine study.

Primary participant recruitment will be conducted using banner advertisements and brief electronic messages on geospatial networking apps and social media platforms. Our target of 50% recruitment of highly impacted groups will be sought through study advertisement placement and content strategies. Although the target is not a hard cap, we anticipate that we will be able to meet it based on past recruitment experience and will seek alternative recruitment strategies as needed. Recruitment, led by the Emory Center for AIDS Research, which has led similar work previously [13-15], will target ads to nonurban zip codes that would indicate potential eligibility for the study. Secondary methods for recruiting participants, such as peer referral, will be used if needed.

Screening, Consent, and Enrollment Procedures

Individuals responding to electronic ads will be directed to a secure electronic platform to view a brief introductory statement, consent to be screened, and complete a brief eligibility screener. Screener-eligible participants will provide personal contact information and complete the full study consent by using mouse drag/touchscreen features to capture and document their signature. Study staff will review name, contact information, and other data, such as internet protocol address, for ineligible individuals to detect any instances of rescreening. Staff will call participants to answer any questions they might have about the

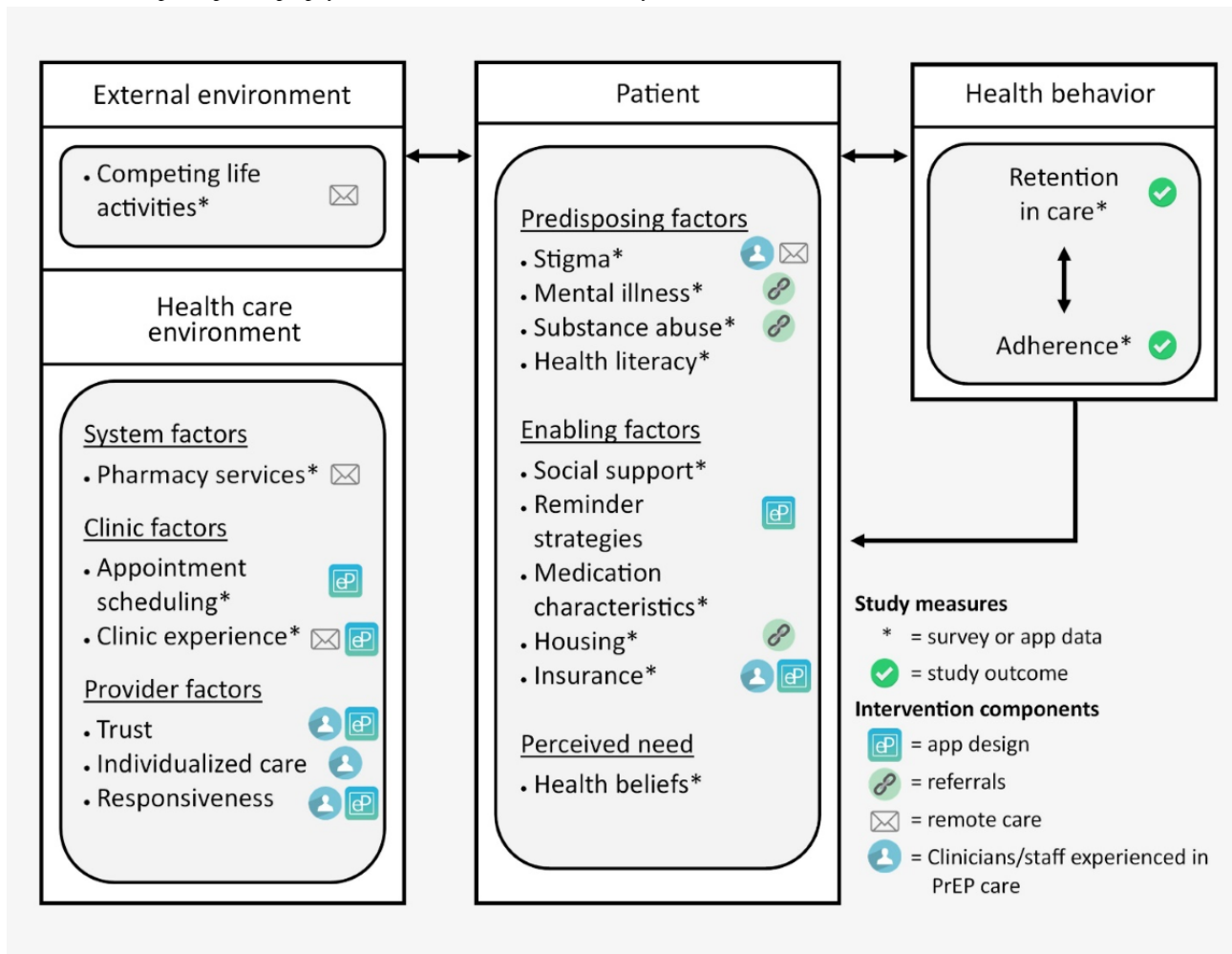
study and to reassess screener eligibility. Eligible and consenting participants will download the study app on their personal mobile phone from an *app store* and create a personal, password-protected app account. Both intervention and control participants will use research-assessment components of the app (eg, access to the survey platform and reminders); however, only intervention participants will have access to the app components relevant to PrEP care. The baseline survey will be immediately available for completion in the app, and the staff will receive an automated notification to mail an SSC kit to the participant to determine study eligibility. Participants will be enrolled in the trial and assigned a randomization code, if they return the SSC kit and complete the required study surveys within 1 month and the laboratory test results indicate eligibility. If these activities are not completed within 1 month, participants will be asked to repeat the appropriate previous step. Throughout the consent and enrollment process, study staff will be available by email and by phone during study hours to answer participants' questions. Study recruitment and retention activities will be conducted centrally by the staff at Emory University.

Intervention

The ePrEP intervention, developed based on Andersen behavioral model adapted to HIV care (ABMH), is designed to ease the burden of initiating and maintaining PrEP care by providing home SSC kits and telemedicine through a custom-built app for patients and Web portal for clinicians.

Theoretical Model

ABMH explicitly incorporates the biomedical nature of the intervention and also directly addresses patient experiences in health care and lived environments [16,17]. This multilevel model, with a focus on health care settings, describes how environmental and patient-level factors impact both retention in care and medication adherence (Figure 2). ABMH informs the development of a number of intervention components, such as an app-based scheduler to lower barriers to making appointments, an app-based message portal to increase provider responsiveness, use of PrEP-experienced pharmacies to facilitate PrEP prescriptions, use of interactive video consultations with lesbian, gay, bisexual, transgender, queer-friendly clinicians to facilitate provider trust, and referral strategies to address predisposing factors such as substance abuse or mental health problems. The model informs intervention assessment plans, including selection of appropriate measures and construction of multivariate models to assess intervention performance.

Figure 2. Electronic pre-exposure prophylaxis (ePrEP) intervention and study measures in Andersen behavioral model.

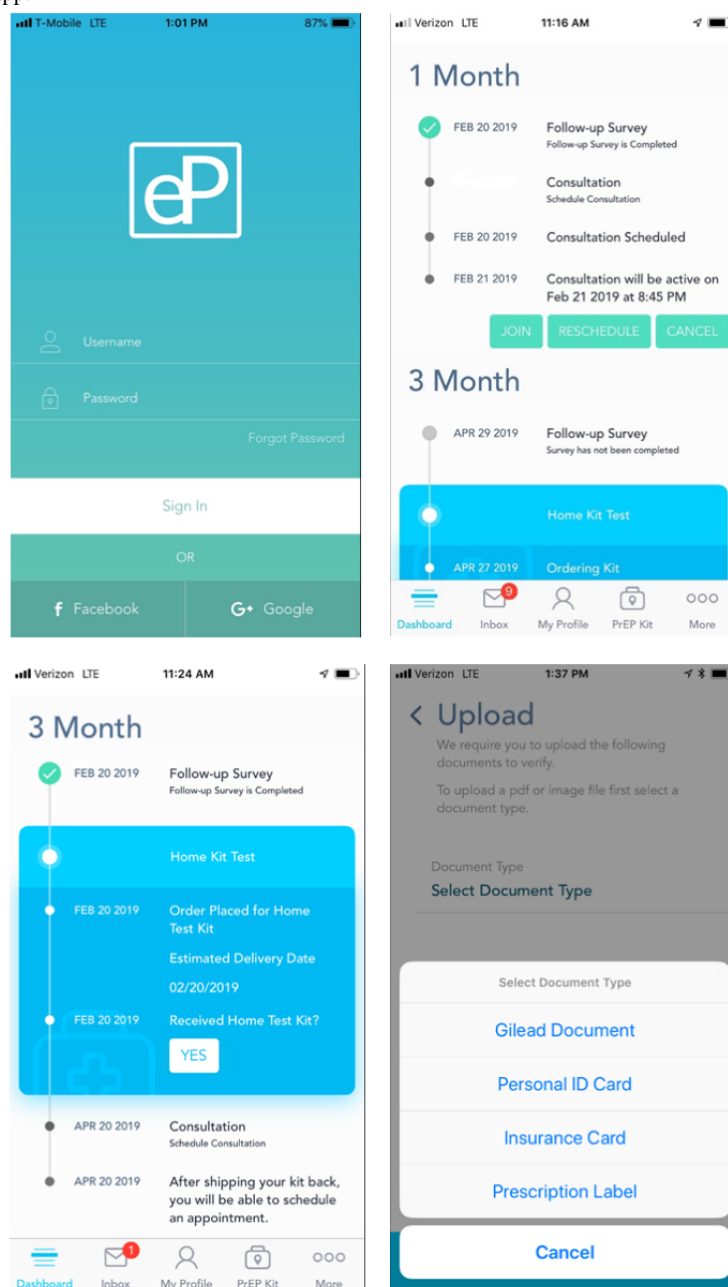
Specimen Self-Collection Kit

To allow for laboratory testing for PrEP care and for the study outcome, ePrEP will use an SSC kit that has previously been pilot tested [18]. Participants will receive a plain box via standard mail that includes video and written instructions, materials for each specimen to be collected, and a call-in help line. After specimen collection, participants will enclose them in a prepaid mailer to be sent directly to a study laboratory. On the basis of the results from the pilot assessment, we anticipate that most participants will be able to self-collect specimens. Our study laboratory will perform a visual assessment for the sufficiency of self-collected specimens based on the study requirements for quantity (eg, enough blood in a card spot) and quality (eg, properly sealed containers). For specimens determined to be insufficient or with indeterminate results, we will give participants an option of completing a second SSC or receiving a referral to a local health department or a commercial laboratory. Testing of all specimens will be performed at Clinical Laboratory Improvement Amendments–certified laboratories, with costs covered by the study. FDA-approved tests will be used for all tests used for PrEP care.

Study App

The study app, generically named *eP* to protect participant privacy on their mobile phones, will be the primary participant-facing component of the intervention. *eP* will be structured around a *dashboard* timeline (Figure 3) that visually depicts successful completion of past steps (green *check marks*), proximal future steps that require immediate action (activity buttons), and distal future steps needed for maintenance in ePrEP care (grey dots next to an anticipated future due date). The adaptive dashboard will refresh as tasks are completed. For instance, once an SSC is returned, scheduling of the next interactive video consultation will become available. An *inbox* screen (bottom navigation bar) will feature a variety of automated messages for required actions, reminders, and updates to facilitate the participant's progress in ePrEP care. This messaging system also allows for custom messages to be sent to and from study staff and clinicians. A *profile* screen will allow participants to alter their personal information, such as changing their preferred pharmacy or home shipping address, and a *PrEP kit* screen will allow participants to track shipping status of their SSC.

Figure 3. Screenshots of the eP app.



To initiate PrEP care, electronic surveys embedded in the eP app will collect behavioral information recommended by current practice guidelines [11]. Photo upload functionality will be used for the communication of documents such as those needed for financial navigation of access to PrEP, such as insurance- or employment-related documents required for assistance or copayment programs. Interactive video consultations with study clinicians will be scheduled by patients through an electronic calendaring function. Initiated in the dashboard, the consultations will be conducted on a secure, encrypted and Health Insurance Portability and Accountability Act (HIPAA)-compliant video platform within eP. A secure *inbox* text message system will increase access to and streamline communication with the clinical care team regarding questions such as medication side effects.

When participants initially download eP, they will only be able to access app information relevant to the overall research

process. Once randomized, the intervention group will be able to see and use all eP components. A modified version of the app will be used by control participants, which includes only components applicable to research participation such as processes around the primary and secondary outcomes data collection. Both eP app versions will be hosted in a secure environment that uses Single Socket Layer technology for encryption of online information transfer. Access to all systems will require authentication through individual log-ins and passwords, and all data will be stored on secure and HIPAA-compliant servers.

Administration/Clinical Portals

Study staff and clinicians will manage participant interactions through website *portals* developed for the study that use a cloud platform to exchange data with the participant-facing eP app. Both administration and clinician platforms will share a number

of key features, including automatic alerts when activity is required, such as a patient needing an additional reminder to schedule their video consultation. A secure text message platform will allow staff and clinicians to send messages to the participant's eP inbox. The administrative portal will allow for tracking of the participant's progress in completing research-related activities, including visualizations of each participant's movement through milestones essential to successful study retention. The clinical portal will allow clinicians to view clinically relevant information for study participants, including lab results, self-reported sexual behaviors, and self-reported PrEP adherence and side effects. Clinicians will specify their available time slots for the interactive video consultations in an electronic calendaring function. The clinical portal will allow the collection of nuanced care information during consultations—general assessments, adherence assessments, referrals, prescriptions (PrEP and other as needed), and notes. Clinicians will also be able to use the portal to track pre-existing medical conditions and concomitant medications, as well as provide referrals for treatment as needed, including sexually transmitted infections (STI), HIV, and others such as mental health or substance use disorders. Finally, the clinical portal will be used by the clinicians to track and monitor the progress of each participant in PrEP care, including the results of SSC kits and scheduling of future consultations. The portal is not currently connected to electronic medical records for each study site, although such functionality could be added later if the trial indicates utility of the intervention.

Statistical Analysis

Primary Outcome

The primary outcome measure will be protective levels of the active metabolite of oral PrEP (TFV-DP) drug levels at the 12-month study visit, using an intention-to-treat analysis. Using a pharmacological model developed in a cohort study of FTC/TDF use among MSM and transgender women [19], the concentration of TFV-DP as determined from a DBS can be used to infer the mean number of days per week FTC/TDF is ingested over approximately 1 month preceding specimen collection. The threshold used for the primary outcome measure will be a TFV-DP concentration considered to be a surrogate for substantial HIV protection: >700 fmol/punch, a level indicating ≥ 4 doses per week [20]. The intervention efficacy measure will be quantified as the difference in proportions of the intervention arm with this outcome compared with the control arm.

Secondary Outcomes

We will assess initiation into PrEP care based on self-report and pill bottle photos. Maintenance in PrEP care at the study midpoint will be assessed with the 6-month TFV-DP drug level measure. We will also track changes in PrEP indication, determined by the CDC and United States Public Health Service guidelines, over the course of each participant's involvement in the study. Other secondary outcome measures will be harmonized with Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) measures, when possible. Demographic, socioeconomic, and sexual behavioral risk measures are derived from the National HIV Behavioral

Surveillance (NHBS) instrument and our previous research instruments [10,21]. Adherence will be assessed with self-reported number of pills taken in the past week. Safety outcomes will include acute HIV symptoms assessed with a checklist of 17 symptoms and criteria identified by Braun [22] and the presence of more common adverse effects identified on the medication label. A number of domains of the study's theoretical model will be assessed to explore the context of the intervention performance: PrEP perceptions and PrEP use adapted from NHBS and other sources [10,23], depression [24], illicit and nonprescription drug use [25], sexual stigma [26], HIV severity and risk perceptions [27], HIV knowledge [25], medication adherence self-efficacy [28], the Systems Usability Scale [29,30], insurance coverage [14], use of social and geosocial networking sites [14], and the depth of clinician-patient relationship [31,32]. We will also seek to understand rationales for those who fail to persist in PrEP, assessing perceptions of PrEP barriers and concerns [33,34].

Power Estimates

Power analyses assumed 80% power to detect a difference at a 2-sided 5% significance level, using a 2-sample comparison of proportions. On the basis of retention in our past trials, we assumed a 20% attrition rate in both arms, with calculations assuming independent censoring. If 5% of participants in the control arm are above cut point levels of the outcome measure (TFV-DP), we will have sufficient power to detect a minimum detectable effect size of 13% absolute difference in the outcome measure (eg, $\geq 18\%$ of the intervention participants have TFV-DP above cut point threshold). To allow for the detection of a scenario where intervention outcome proportion is equal to control+20% absolute increase, our study would remain sufficiently powered with any control participant uptake level $\leq 15\%$.

Statistical Analysis Plan

Logistic regression and log-linear models will be used to estimate the association between the intervention arm and primary study outcome, TFV-DP level. If prognostic factors associated with the outcome remain insufficiently balanced through stratified randomization, we may adjust for these factors in our models. Potential confounding factors that may be included are medication self-efficacy and motivation to take PrEP. Per protocol assessments that account for potential changes in intervention as delivered will be conducted. For instance, this would account for participants assigned to the intervention condition opting to instead receive standard of care PrEP from a nonstudy clinician.

A number of secondary analyses will be conducted using regression models. Intervention impact on the secondary outcomes of PrEP initiation and PrEP persistence will be determined using analogous regression models. We will model \log_{10} TFV-DP levels as the outcome variable to potentially detect significant smaller, subclinical, differences in adherence between the intervention and control study arms. An additional analysis will account for the changes in each participant's PrEP eligibility over time, per CDC guidelines. The primary outcome measure and its intent-to-treat analysis assume daily oral PrEP dosing with FTC/TDF. Medications indicated for PrEP, as well

as commonly prescribed PrEP dosing, may change over the course of the study. Informed by new approvals and developments, we will measure self-reported medication use and dosing strategy, and a secondary analysis will be performed to account for the influence of these factors on study outcomes. Specific and aggregate measures of safety will be assessed, including renal function, HIV incidence, and incident bacterial STI.

Exploratory analyses of intervention effectiveness across subgroups and analysis of potential mediators of initiation or persistence in PrEP care across both study arms, such as self-efficacy will also be conducted. Understanding variables associated with success or failure in the intervention will inform future research and potentially guide clinician recommendations or policy regarding bringing remote PrEP care to scale. For participants who seroconvert during the study, levels of TFV-DP, PrEP persistence, and other clinically relevant study data will be analyzed.

Cost-Effectiveness and Cost-Utility Analyses

We will employ standard methods of cost analyses as recommended by the U S Panel on Cost-Effectiveness in Health and Medicine [35] and as adapted to HIV/AIDS programs [36]. This will be accomplished by conducting an economic analysis from the payer and societal perspectives to estimate the cost, cost-effectiveness, and cost-utility of the intervention relative to standard of care.

Comprehensive cost analysis will be conducted to assess the cost of developing and implementing the ePrEP intervention, using a microcosting approach to estimate net costs. Cost-effectiveness analyses will include calculating the incremental cost-effectiveness ratio for the cost per HIV infection averted compared with standard of care as follows: $(\text{Cost}_{\text{Intervention}} - \text{Cost}_{\text{StandardofCare}}) / (\text{Infections averted}_{\text{Intervention}} - \text{Infections averted}_{\text{StandardofCare}})$. The health effect will be defined as the projected reduction in HIV infections over time associated with adopting the intervention relative to standard of care. The base, standard of care, model will estimate the number of infections expected in the absence of the intervention and may vary under different assumptions of baseline and clinic-based PrEP coverage outside of the intervention [37]. In the cost-utility analysis, we will calculate the cost per quality-adjusted life year (QALY) saved. QALYs saved by averting an HIV infection will be up-to-date estimates from the literature.

Qualitative Assessment

In-depth interviews will be conducted after the completion of 12-month assessments with key participants to explore the experience of intervention participants (up to 10) and standard of care participants (up to 5) over time. Participants will be selected using purposive sampling methods, seeking to gain a diverse set of trajectories in PrEP care. Topics will include (1) barriers and facilitators to PrEP care, (2) problems with and benefits of ePrEP or standard of care, (3) ways to address problems and amplify success of ePrEP or standard of care, and (4) factors that influence successful persistence in or falloff from PrEP care.

Safety Data

Safety data will be collected throughout the study for reports of adverse events, social harms, and side effects. Reportable events will be captured through EDC. A safety monitoring committee (SMC) will convene biannually and receive data reports on a quarterly basis. The SMC will be tasked with stopping the study if the intervention proves to be significantly outperforming the standard of care, or if the inverse occurs. We will conduct 1 interim analysis comparing the efficacy of the intervention in the active arm with the control arm, with efficacy based on differences in trial success versus failure using the primary outcome definition (detectable TFV-DP at 12 months). If the intervention is significantly outperforming the standard of care, the study will seek to adjust study design and supplements to open the intervention arm. The SMC will monitor several other factors, including HIV seroconversion, changes in kidney function, behavioral disinhibition, medication adherence, and differential loss to follow-up.

Trial Registration, Ethics, Consent, and Institutional Board Approval

This study has been approved by the University of North Carolina Institutional Review Board (number 18-0107). Clinical trial best practice will be followed in accordance with National Institutes of Health (NIH) guidance. The trial has been registered with ClinicalTrials.gov, trial number NCT03729570. Informed consent will be obtained before any study procedures are initiated.

Results

We anticipate that the study will begin enrolling in May 2019. Our targeted enrollment period is 12 to 18 months. Therefore, we anticipate the completion of study data collection in mid to late 2021 and study results being available in 2022.

Discussion

PrEP is highly effective in preventing HIV transmission. Similar to the predominant mode of biomedical prevention preceding it (condoms) [38], the most frequent failure is because of nonuse rather than the failure of the intervention itself [39]. The challenge for PrEP is therefore how to promote uptake and persistence in care among those groups at highest risk of HIV transmission. The delivery of PrEP services at a distance (and without the need for a provider visit) has the potential to overcome not only the geographic and transit-related barriers to care, but also the reluctance to seek care because of documented barriers to care such as stigma [40]. Pilot data from other studies indicate a strong interest in home-based PrEP service access [18] and survey data indicate an overall interest in PrEP [41]. Yet, there may be some disadvantages of PrEP home care. For instance, individuals may not develop strong bonds with clinicians via video, potentially leading to higher levels of discontinuation than standard care. This clinical trial will allow for the determination of whether telemedicine care increases or decreases initiation of and maintenance on PrEP. Provided that the ePrEP system provides gains relative to standard care, it will be important to develop strategies to sustain

the program. The CDC's high impact HIV prevention program [42] currently supports several mobile phone apps, and similar investment will be needed to support the coming wave of technology-based interventions such as ePrEP. Cost-effectiveness analyses, such as that proposed for this study, should inform health system investments.

As electronic, mobile phone-based communications emerge to be the predominant form of social interaction among youth [43], it is only natural that the health care systems reflect this change.

The custom PrEP provision platform of the study will allow for an exploration of how youth can be retained in preventive care through an app-based telemedicine system. The recruitment of YMSM, with a focus on black and Latino participation, will provide an important perspective regarding how these highly impacted groups perform in telemedicine care relative to standard care. Provided that the study finds advantages of telemedicine, future work will be needed to understand how to best incorporate such a customized intervention into the broader health care system.

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Conflicts of Interest

AJS is an investigator on a grant from the Gilead Foundation, which is paid to his institution. He is an investigator on a study for which Gilead Sciences has donated the study drug. CBH is the University of North Carolina site investigator of record for an industry-sponsored clinical trial of PrEP (DISCOVER; NCT02842086), under an interinstitutional contract between the UNC and Gilead Sciences. LAM has received an honorarium from Gilead Science as consultant and member of their Speakers Bureau.

Multimedia Appendix 1

Electronic pre-exposure prophylaxis (ePrEP) study consent form.

[[DOCX File, 103KB - resprot_v8i6e13982_app1.docx](#)]

Multimedia Appendix 2

Electronic pre-exposure prophylaxis (ePrEP) study baseline form.

[[DOCX File, 92KB - resprot_v8i6e13982_app2.docx](#)]

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Abbreviations

- ABMH:** Andersen behavioral model adapted to HIV care
- ATN:** Adolescent Medicine Trials Network for HIV/AIDS Interventions
- CDC:** Centers for Disease Control and Prevention
- DBS:** dried blood spot
- EDC:** electronic data capture
- ePrEP:** electronic pre-exposure prophylaxis
- FDA:** Food and Drug Administration
- FTC:** emtricitabine
- HIPAA:** Health Insurance Portability and Accountability Act
- MSM:** men who have sex with men
- NHBS:** National HIV Behavioral Surveillance
- NIH:** National Institutes of Health
- PrEP:** pre-exposure prophylaxis

QALY: quality-adjusted life year
SMC: safety monitoring committee
SSC: specimen self-collection
STI: sexually transmitted infections
TDF: tenofovir disoproxil fumarate
TFV-DP: tenofovir diphosphate
YMSM: young men who have sex with men

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Protocol

Pre-Exposure Prophylaxis Integration into Family Planning Services at Title X Clinics in the Southeastern United States: A Geographically-Targeted Mixed Methods Study (Phase 1 ATN 155)

Jessica M Sales¹, PhD; Cam Escoffery¹, PhD, MPH; Sophia A Hussen¹, MD, MPH; Lisa B Haddad², MD, MPH; Ashley Phillips¹, MPH; Teresa Filipowicz³, MPH; Maria Sanchez³, BS; Micah McCumber³, MS; Betty Rupp³, MPH; Evan Kwiatkowski³, MS; Matthew A Psioda³, PhD; Anandi N Sheth¹, MD, MSc

¹Department of Behavioral Sciences and Health Education, Rollins School of Public Health, Emory University, Atlanta, GA, United States

²Department of Gynecology and Obstetrics, School of Medicine, Emory University, Atlanta, GA, United States

³Collaborative Studies Coordinating Center, Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

Corresponding Author:

Jessica M Sales, PhD

Department of Behavioral Sciences and Health Education

Rollins School of Public Health

Emory University

1518 Clifton Road

Room 570

Atlanta, GA, 30322

United States

Phone: 1 404 727 6598

Email: jmcderm@emory.edu

Abstract

Background: Black adolescent and young adult women (AYAW) in the Southern United States are disproportionately affected by HIV. Pre-exposure prophylaxis (PrEP) is an effective, scalable, individual-controlled HIV prevention strategy that is grossly underutilized among women of all ages and requires innovative delivery approaches to optimize its benefit. Anchoring PrEP delivery to health services that AYAW already trust, access routinely, and deem useful for their sexual health may offer an ideal opportunity to reach women at risk for HIV and to enhance their PrEP uptake and adherence. These services include those of family planning (FP) providers in high HIV incidence settings. However, PrEP has not been widely integrated into FP services, including Title X-funded FP clinics that provide safety net sources of care for AYAW. To overcome potential implementation challenges for AYAW, Title X clinics in the Southern United States are uniquely positioned to be focal sites for conceptually informed and thoroughly evaluated PrEP implementation science studies.

Objective: The aim of this study is to assess inner and outer context factors (barriers and facilitators) that may influence the adoption of PrEP prescription and treatment services in Title X clinics serving AYAW in the Southern United States.

Methods: Phase 1 of Planning4PrEP is an explanatory sequential, mixed methods study consisting of a geographically-targeted Web-based survey of Title X clinic administrators and providers in the Southern United States, followed by key informant interviews among a purposively selected subset of responders to more comprehensively assess inner and outer context factors that may influence adoption and implementation of PrEP in Title X FP clinics in the South.

Results: Phase 1 of Planning4PrEP research activities began in October 2017 and are ongoing. To date, survey and key informant interview administration is near completion, with quantitative and qualitative data analysis scheduled to begin soon after data collection completion.

Conclusions: This study seeks to assess inner and outer contextual factors (barriers and facilitators) that may influence the adoption and integration of PrEP prescription and treatment services in Title X clinics serving AYAW in the Southern United States. Data gained from this study will inform a type 1 hybrid effectiveness implementation study, which will evaluate the multilevel factors associated with successful PrEP implementation while evaluating the degree of PrEP uptake, continuation, and adherence among women seen in Title X clinics.

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KEYWORDS

HIV; pre-exposure prophylaxis; implementation science; women's health

Introduction

Women of childbearing age comprise a majority of adults living with HIV globally. They account for 20% of the 40,000+ new infections in the United States every year, with disproportionate impact on adolescent and young adult women (AYAW) in the South [1]. Black women in the South are disproportionately affected by HIV: 1 in 48 black women is diagnosed with HIV over their lifetime, nearly 20 times the risk for white women [2]. Southern states account for nearly half of new HIV diagnoses despite having only 37% of the population [3]. Effective prevention efforts tailored to the needs of AYAW are therefore needed not only to curb the epidemic among women but also to protect their sexual partners and prevent perinatal infection. Furthermore, scalable approaches that utilize individual-controlled prevention tools are required, as many AYAW are unable to successfully negotiate mutual monogamy or condom use and are unaware of their partner's HIV status [4-6]. Pre-exposure prophylaxis (PrEP) is an effective [7,8], scalable, and individual-controlled HIV prevention strategy that is underutilized among women of all ages and requires innovative delivery approaches to optimize its benefit [9].

The few available studies among US women report low knowledge and awareness of PrEP [9]. For example, in a US, multi-site study conducted in 2014, less than 10% of women at risk for HIV had heard of PrEP, but once informed, most women found the option to be attractive [10]. Although Centers for Disease Control and Prevention (CDC) estimates that 176,670 US women may benefit from PrEP to prevent sexual HIV acquisition [11], its use among US women remains low [12]. Despite CDC's clinical guidance for offering PrEP to individuals at substantial risk, data from a national prescription drug database suggest that women, individuals younger than 25 years, and residents of the South have lower levels of PrEP use relative to new HIV diagnoses [13]. Thus, innovative delivery approaches are required to optimize access to PrEP for AYAW, particularly in the Southern United States.

Anchoring PrEP delivery to health services that AYAW already trust, access routinely, and deem useful for their sexual health is of great appeal, as it may offer an ideal opportunity to reach women at risk for HIV and enhance their PrEP uptake and adherence. Family planning (FP) clinics in high HIV incidence settings may be ideal PrEP delivery settings as they are accessed by sexually active women of childbearing age and already provide sexual health services, including HIV testing and prevention counseling. Rather than standard primary care or sexually transmitted infection clinics, most (60%) AYAW utilize FP clinics for sexual health and preventative services [14], and they are viewed with trust among this group [10]. Importantly, shared decision making, a framework promoted in the Quality Family Planning recommendations [15] used by FP providers,

is ideal for identifying AYAW at substantial risk of HIV and offering them comprehensive HIV prevention services, including PrEP. Shared decision making is a process in which clinicians and patients work together to make decisions about care (eg, birth control) based on clinical evidence that balances risks and expected outcomes with patient preferences and values. However, not all FP providers provide services to large enough numbers of AYAW at high risk of HIV to justify the potential costs associated with preparing for on-site PrEP provision and monitoring. Therefore, efforts to integrate PrEP in FP services should focus on clinics with the highest anticipated impact.

Specifically, Title X-funded FP clinics may be an ideal setting for integrating PrEP into FP services given that they (1) are important safety net sources of care for AYAW, (2) serve clients at risk for HIV infection, and (3) are expected to offer HIV prevention services as part of Quality Family Planning recommendations. The Title X National Family Planning Program provides grants to health department or county hospital-based programs, non-profit stand-alone clinics, and community health clinics such as federally qualifying health centers. Title X supports an extensive network of approximately 4000 nationwide service sites that serve over 4 million clients, 90% of whom were women, and over two-thirds of whom are younger than 30 years [16]. The program is designed to ensure access to contraception, particularly for low-income individuals, but serves as the usual source of medical care for the majority of female clients [17]. Title X clinics serve as safety net providers, particularly in regions without Medicaid expansion [18], which closely overlap with regions that would most benefit from expansion of HIV prevention services [13].

Despite its appeal as an effective, individual-controlled HIV prevention strategy, PrEP has not been widely integrated into FP services in the United States, or specifically, in Title X clinics in the Southern United States. A 2015 national survey of FP providers in the United States, many of whom were Title X clinic providers, found low PrEP knowledge and use; FP providers in the South had lower PrEP knowledge than those in the Northeast or West [19]. Only one-third of respondents could correctly define PrEP and its efficacy, and less than 5% had ever prescribed PrEP. The majority felt uncomfortable prescribing PrEP because of lack of training, revealing an additional challenge to PrEP delivery for women, especially in the South. Although this study showed high provider willingness to prescribe, little is known about provider education and training needs as well as the prioritization, capacity, barriers, and facilitators to integrate PrEP across clinical settings, including Title X funded clinics.

Knowledge gaps exist that prevent optimal implementation of PrEP in real world settings for AYAW in the United States. Limited PrEP implementation science research has been published to date, and most PrEP demonstration projects and

implementation studies in the United States have not included cis-gender women [20]. Limited available data suggest that significant implementation challenges exist, particularly for AYAW. Data from a recent (2013-2016) study highlighted missed opportunities for PrEP delivery during care visits that preceded an HIV diagnosis; individuals with missed opportunities for PrEP were more likely to be female, black, and younger than 30 years [21]. A recent PrEP implementation project at a publicly funded community health center in Philadelphia showed that, while more than one-third of potential PrEP clients were women, only 15% of men and 8% of women who expressed interest and were referred ultimately started PrEP [22,23]. Although women were as likely as men to express interest, they were less likely to start, and attrition at each stage of the PrEP engagement process was higher for women [22], suggesting potential unique implementation challenges for women that need to be investigated.

Finally, few models exist describing the organizational processes and strategies associated with successful integration of PrEP delivery in new clinic settings, and none exist specifically for FP clinics [24,25], including those supported by Title X funding. To overcome the aforementioned potential implementation challenges for AYAW, Title X clinics in the Southern United States are uniquely positioned to be focal sites for conceptually informed and thoroughly evaluated PrEP implementation science studies in the United States because (1) FP providers in these clinics may more readily adapt skills used in contraceptive counseling and provision (ie, shared decision making) to PrEP counseling and provision [15]; (2) they are a regular, trusted source of care for AYAW with HIV risk, including black AYAW [10]; (3) they routinely screen and make referrals for intimate partner violence [26] and other known barriers to adherence [27]; and (4) there are virtually no data on PrEP implementation among US women [24]. To address multiple gaps in our understanding of how to optimally provide PrEP and support its use among AYAW in the Southern United States, we devised a multiphase study (Phase 1 study and Phase 2 study). Phase 1 is a mixed methods assessment of Title X clinics across the South to ascertain critical elements of the inner and outer contexts of various Title X clinics relevant for integrating PrEP into FP services. Phase 2 is a hybrid type 1 effectiveness implementation study in 3 Atlanta Title X clinics to evaluate multilevel factors associated with PrEP reach, level of adoption, and implementation (eg, HIV testing and risk assessment screening and PrEP counseling and prescription) within and across clinics, while also thoroughly evaluating the effect on PrEP uptake, continuation, and adherence over a 6-month follow-up period.

The Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) is a research program that aims to defeat the rising HIV epidemic among adolescents and young adults in the United States. The overarching goal of the ATN is to increase awareness of HIV status in youth and, for those diagnosed with HIV, increase access to health care. The ATN develops and conducts behavioral, community-based, translational, therapeutic, microbicide, and vaccine trials in youth who are at risk for or living with HIV, with a focus on the inclusion of minors. Our study (ATN 155) is funded as part

of the ATN. The combined findings and resulting tools and trainings will be valuable for PrEP integration in Title X-funded or similarly structured FP clinics and could inform future interventions to optimize PrEP delivery for AYAW. In this paper, we describe the research protocol for the Phase 1 study only.

Methods

Study Design

Phase 1 of this study utilizes an explanatory sequential, mixed methods design consisting of geographically-targeted surveys and key informant interviews among clinic administrators and providers in Title X FP clinics in the South. The Consolidated Framework for Implementation Research (CFIR) is used to provide a comprehensive set of constructs associated with effective implementation to facilitate evaluation of inner and outer contextual factors (barriers and facilitators) that may influence the adoption of PrEP prescription and treatment services in Title X clinics serving AYAW in the Southern United States.

Consent and Institutional Review Board Approval

Phase I of this study has been reviewed and approved by the Emory University Institutional Review Board (IRB# 00098606) and University of North Carolina at Chapel Hill Institutional Review Board (IRB#17-2595). Written consent for the Web-based survey will be obtained for all willing participants before survey start. Written consent is asked within the survey. Survey responses are deidentified to protect participants' privacy. Participants indicate interest in a follow-up qualitative interview during the consent process. Verbal consent is obtained over the telephone before the start of the qualitative interview.

Participants

Survey administration targets a convenience sample of approximately $n=600$ clinic providers and administrators ($n=400$ providers, $n=200$ administrators) at Title X FP clinics in the Department of Health and Human Services (DHHS) regions III (Washington District of Columbia, Delaware, Maryland, Pennsylvania, Virginia, West Virginia), IV (Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee), and VI (Arkansas, Louisiana, New Mexico, Oklahoma, Texas). This sample size was selected based on a previous study of PrEP knowledge and attitudes among FP clinicians [19]. From the pool of respondents who express interest in participating in key informant interviews, a subset of approximately $n=60$ will be purposefully selected for interviews to ensure broad representation of providers and administrators from each of the DHHS regions.

Recruitment

Online recruitment of participants is supported by the National Clinical Training Center for Family Planning (NCTCFP). Their assistance includes emailing the survey to a Title X clinic listserv, filtering for recipients from DHHS regions III, IV, and VI. Listserv members will receive 1 to 2 email reminders per month. A total of 7 large-scale emails to the Title X clinic listserv will be sent.

Additional recruitment efforts include an electronic link or banner advertisement for the survey posted on the NCTCFP website, engagement with State Title X Grant holders who oversee Title X funding and implementation in clinics within their state, and in-person recruitment at the biannual NCTCFP national meetings for Title X staff and providers.

Participants interested in taking part in key informant interviews indicate their interest during Web-based survey completion. To evenly represent participant types for these interviews, selection of interviewees is based on the following demographics: DHHS region, clinic type, role in the clinic, and current PrEP delivery in the clinic.

Incentives

Survey participants are offered compensation for their time with a US \$30 Amazon gift card, and those who complete the key informant interviews receive an additional US \$50 gift card. Participants provide contact information at survey completion to receive the gift cards.

Data Collection

Data are collected via a Web-based Qualtrics survey. Participants are aware of the survey's approximate 20-min duration. Key informant interviews are conducted either in person or via telephone based on participant preference. Interviewees are informed the interview will take approximately 45 min to complete. Surveys ([Multimedia Appendix 1](#)) and interviews ([Multimedia Appendix 2](#)) include questions aimed at identifying and exploring inner and outer factors that may influence the adoption and integration of PrEP into FP services in Title X clinics in the South.

Theoretical Frameworks

The CFIR [28] was selected as the framework through which inner and outer contextual factors (barriers and facilitators) that influence adoption of PrEP prescription and treatment services in Title X clinics serving AYAW in the Southern United States will be assessed. The CFIR provides a menu of constructs that have been identified as important for implementation success [28]. The CFIR captures the complex, multilevel nature of implementation and posits that successful implementation of a new innovation (PrEP delivery in FP clinics) will likely require the use of multiple strategies (eg, training, technical assistance, and an internal champion) at multiple levels of the implementation context. The CFIR comprises 39 constructs organized into 5 domains (*intervention characteristics, outer/inner setting, characteristics of individuals, and process*).

Consolidated Framework for Implementation Research Constructs Assessed

Implementation-related constructs are developed from the CFIR [28] guided data collection (both quantitative and qualitative). On the basis of a review of the US-focused PrEP implementation literature [29-40], a subset of the 39 CFIR constructs [41] are selected for their likelihood of being a potential barrier (or facilitator) to implementation and/or having sufficient variation across the units of analysis (eg, clinics) [42]. On the basis of the findings from the limited PrEP implementation literature [29-40], we have selected 17 implementation-focused constructs from the CFIR model to assess in the quantitative (from the Qualtrics survey) and qualitative (from key informant interviews) data collection; these pertain to all 5 CFIR domains. Qualtrics survey items are mapped to these 17 CFIR constructs for analysis. The 17 CFIR constructs targeted for quantitative data analysis are described in [Table 1](#).

Table 1. Targeted Consolidated Framework for Implementation Research constructs.

Consolidated Framework for Implementation Research construct	Description of construct	PrEP ^a specific example
Intervention characteristics [43,44]		
Evidence strength and quality	Stakeholders' perceptions of the quality and validity of evidence supporting the belief that the intervention will have desired outcomes.	To what extent do you think female patients on PrEP have a decreased risk of acquiring HIV?
Relative advantage	Stakeholders' perception of the advantage of implementing the intervention versus an alternative solution.	Advantage to onsite PrEP provision verses referral to off-site PrEP for your patients/staff?
Trialability	The ability to test the intervention on a small scale in the organization, or partial implementation, and to be able to reverse course (undo implementation) if warranted.	Providing PrEP at my clinic seems possible
Adaptability	The degree to which an intervention can be adapted, tailored, refined, or reinvented to meet local needs	Are screening guidelines for PrEP tailored for women? Adaptable to Quality Family Planning framework?
Complexity	Perceived difficulty of implementation, reflected by duration, scope, radicalness, disruptiveness, centrality, and intricacy and number of steps required to implement.	I am confident that I or someone in my clinic can provide risk reduction and medication-adherence counseling to patients on PrEP.
Cost	Costs of the intervention and costs associated with implementing the intervention including investment, supply, and opportunity costs.	Concerns about whether insurers/Medicaid will cover the cost of PrEP and monitoring
Outer Setting [43,44] (ie, outer context, factors external to the organization that may influence implementation)		
Patient needs and resources	The extent to which patient needs as well as barriers and facilitators to meet those needs are accurately known and prioritized by the organization.	PrEP is compatible with the needs of patients at my clinic.
Cosmopolitan	The degree to which an organization is networked with other external organizations.	Individuals in my clinic are connected with other community organizations that provide HIV prevention services to patients.
Peer pressure	Mimetic or competitive pressure to implement an intervention; typically because most or other key peer or competing organizations have or will be implementing intervention.	Other doctors (clinics) in my specialty area will prescribe PrEP to at-risk HIV-negative individuals in the next year.
Inner setting [43,44] (ie, inner context, factors internal to the organization that may influence implementation)		
Implementation climate [14]	The absorptive capacity for change, shared receptivity of involved individuals to an intervention, and the extent to which use of that intervention will be rewarded, supported, and expected within their organization.	Leadership values evidence-based HIV practices such as PrEP
Networks and communications	The nature and quality of webs of social networks and the nature and quality of formal and informal communications within an organization.	My clinic works effectively together as a team with community organizations to promote HIV prevention practices in our community.
Compatibility	The degree of tangible fit between meaning and values attached to the intervention by involved individuals; how those align with individuals' own norms, values, and perceived risks and needs; and how the intervention fits with existing workflows and systems.	PrEP seems like a good match for patients at my clinic.
Leadership engagement	Commitment, involvement, and accountability of leaders and managers with the implementation.	My clinic manager would be supportive of PrEP implementation
Relative priority	Individuals' shared perception of the importance of the implementation within the organization.	This is a high priority area for Title X clinics in my region.
Readiness for implementation	Tangible and immediate indicators of organizational commitment to its decision to implement an intervention.	Do you think PrEP education is an essential part of HIV prevention education at family planning visits?

Consolidated Framework for Implementation Research construct	Description of construct	PrEP ^a specific example
Available resources	The level of resources dedicated for implementation and on-going operations, including money, training, education, physical space, and time.	We have the necessary support in terms of budget or financial resources
Characteristics of Individuals [43,44]		
Knowledge [19]	Individuals' beliefs and value placed on the intervention as well as familiarity with facts, truths, and principles related to the intervention.	Before taking this survey, were you aware of Centers for Disease Control and Prevention guidance on PrEP?
Self-efficacy [15]	Individual belief in their own capabilities to execute courses of action to achieve implementation goals.	I am confident that I can identify individuals at-risk for HIV infection with assistance from an HIV risk screener.
Attitudes	Individuals' attitudes toward the intervention.	It is more suitable to provide PrEP in sexually transmitted disease clinics than in family planning clinics.
Process [43,44]		
Executing	Carrying out or accomplishing the implementation according to plan.	Providing HIV test results within 1 week of testing
Implementation strategies [16]	Most implementation frameworks, including the Exploration, Preparation, Implementation, Sustainment Framework, have 4 components in common: planning (training, tools), engaging (champions, implementation teams), executing, and reflecting and evaluating (monitoring and deciding about continuation/refinements).	The last time you integrated a new method (such as intrauterine devices) into your services, please describe the steps taken to implement that practice at your clinic.

^aPrEP: pre-exposure prophylaxis.

Quantitative Data Analysis

The primary outcome from quantitative data analysis for the Phase 1 study is the CFIR *Inner Setting: Readiness for Implementation* construct. The analysis end point is a semi-continuous composite score derived from 19 and 23 Likert-scale survey items for clinic providers and administrators, respectively.

Analyses of the primary outcome will evaluate associations with the following key secondary construct outcomes: (1) *Inner Setting: Implementation Climate*, (2) *Characteristics of Individuals: Knowledge and Beliefs*, (3) *Characteristics of Individuals: Self-Efficacy*, (4) *Inner Setting: Leadership Engagement*, and (5) *Inner Setting: Available Resources*, to explore drivers of implementation readiness. Each of these secondary construct outcomes are semi-continuous composite scores derived from collections of related Qualtrics survey items.

Analyses of primary and secondary construct outcomes will be performed using generalized linear mixed models that account for their being multiple respondents from the same clinic and will adjust for potential confounders including race/ethnicity of the respondent, age, ability to prescribe medication (ie, PrEP), years worked at the clinic, primary role at the clinic, HIV prevalence in the clinic's catchment area, and census tract data linked to the respondents clinic as relevant for the respective analysis.

Full details on the statistical analysis plan (SAP) for quantitative data are provided in the SAP provided in [Multimedia Appendix 2](#) to this paper.

Qualitative Data Analysis

For coding purposes, "Clinic Type" is considered a case in our qualitative analysis of key informant interviews. We selected this as our "case" as the findings from our study may be especially informative for the provision of Title X support for PrEP scale-up in the clinics that may systematically vary based upon their clinic type (health department/hospital, where multiple health services are available but not always coordinated on-site or during a single visit; community health centers, where multiple health services may be available on-site and same day but specialized expertise may be lacking; and stand-alone FP clinics, where specialized FP services are available on-site but other health services may not be readily available). Coding of the interview will follow a content analysis and deductive approach [45], using the CFIR to guide coding. We will remain open to new themes that may arise inductively from the data as well. Our coding process will follow a consensual research approach, where multiple judges are used throughout the data analysis to ensure multiple perspectives, then consensual validation is achieved through a process of deliberation and consensus among judges, and then an individual "external" to the team (an outside qualitative expert) will review the process to maximize validity of the findings [46]. After the codebook is finalized, the qualitative coding will be conducted in 3 phases: (1) Organize data by CFIR codes and build foundation for case-based analysis, (2) Using Nvivo 11 (QSR International Pty Ltd), a pair of analysts will code transcripts and meet to reach consensus then final codes applied for each transcript, and (3) Pairs of analysts will draft a case memo, organized by constructs. The case will be developed iteratively as each transcript is coded, added to, and used to refine the memo. Rigor for qualitative research will be employed by having verbatim

transcripts, structured codebook and coding training, double coding, and team consensus on data themes [47,48].

Results

Phase 1 of Planning4PrEP research activities began in October 2017 and are ongoing. To date, survey and key informant interview administration is near completion, with quantitative and qualitative data analysis scheduled to begin soon after data collection completion.

Discussion

Although FP clinics may be an ideal setting for PrEP delivery, there is a lack of available data from health care providers and

administrators to guide optimal integration of PrEP into various clinical settings, and in particular, for women's health care settings [24,25]. These data are critical to improve PrEP access and delivery for women. Data gained from this study will facilitate the development of general and context-specific logic models to guide implementation for the adoption of the innovation (PrEP) in a new setting (Title X-funded FP clinics). Furthermore, these data are needed to develop PrEP implementation plans across women's health care settings and to allow for gathering future data from women on PrEP uptake, adherence, and continuation to develop future interventions to support women's successful use of PrEP.

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Conflicts of Interest

JMS and ANS receive grants from Gilead Sciences.

Multimedia Appendix 1

Survey items for primary outcome.

[DOCX File, 14 KB - [resprot_v8i6e12774_app1.docx](#)]

Multimedia Appendix 2

Statistical analysis plan for integrating PrEP into family planning services at title X clinics in the Southeastern US-phase 1 (ATN 155).

[PDF File (Adobe PDF File), 528 KB - [resprot_v8i6e12774_app2.pdf](#)]

Multimedia Appendix 3

Lead questions from provider key informant interview guide (for non-PrEP providing clinics)—excludes sub-questions and probes.

[DOCX File, 18 KB - [resprot_v8i6e12774_app3.docx](#)]

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Abbreviations

ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions

AYAW: adolescent and young adult women

CDC: Centers for Disease Control and Prevention

CFIR: Consolidated Framework for Implementation Research

DHHS: Department of Health and Human Services

FP: family planning

NCTCFP: National Clinical Training Center for Family Planning

PrEP: pre-exposure prophylaxis

SAP: statistical analysis plan

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