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High-Yield HIV Testing, Facilitated Linkage to Care, and Prevention for Female Youth in Kenya (GIRLS Study): Implementation Science Protocol for a Priority Population

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Abstract

Background: Sub-Saharan Africa is the region with the highest HIV burden. Adolescent girls and young women (AGYW) in the age range of 15 to 24 years are twice as likely as their male peers to be infected, making females in sub-Saharan Africa the most at-risk group for HIV infection. It is therefore critical to prioritize access to HIV testing, prevention, and treatment for this vulnerable population.

Objective: Using an implementation science framework, the purpose of this research protocol was to describe the approaches we propose to optimize engagement of AGYW in both the HIV prevention and care continuum and to determine the recruitment and testing strategies that identify the highest proportion of previously undiagnosed HIV infections.

Methods: We will compare two seek recruitment strategies, three test strategies, and pilot adaptive linkage to care interventions (sequential multiple assignment randomized trial [SMART] design) among AGYW in the age range of 15 to 24 years in Homa Bay County, western Kenya. AGYW will be recruited in the home or community-based setting and offered three testing options: oral fluid HIV self-testing, staff-aided rapid HIV testing, or referral to a health care facility for standard HIV testing services. Newly diagnosed AGYW with HIV will be enrolled in the SMART trial pilot to determine the most effective way to support initial linkage to care after a positive diagnosis. They will be randomized to standard referral (counseling and a referral note) or standard referral plus SMS text message (short message service, SMS); those not linked to care within 2 weeks will be rerandomized to receive an additional SMS text message or a one-time financial incentive (approximately US $4). We will also evaluate a primary prevention messaging intervention to support identified high-risk HIV-negative AGYW to reduce their HIV risk and adhere to HIV retesting recommendations. We will also conduct analyses to determine the incremental cost-effectiveness of the seek, testing and linkage interventions.

Results: We expect to enroll 1200 participants overall, with a random selection of 100 high-risk HIV-negative AGYW for the SMS prevention intervention (HIV-negative cohort) and approximately 108 AGYW who are living with HIV for the SMART design pilot of adaptive linkage to care interventions (HIV-positive cohort). We anticipate that the linkage to care interventions will be feasible and acceptable to implement. Lastly, the use of SMS text messages to engage participants will provide pilot data to the Kenyan government currently exploring a national platform to track and support linkage, adherence to treatment, retention, and prevention interventions for improved outcomes.

Conclusions: Lessons learned will inform best approaches to identify new HIV diagnoses to increase AGYW's uptake of HIV prevention, testing, and linkage to care services in a high HIV-burden African setting.

Trial Registration: ClinicalTrials.gov NCT02735642; https://clinicaltrials.gov/ct2/show/NCT02735642 (Archived by WebCite at http://www.webcitation.org/6vgLLHLC9)

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KEYWORDS

HIV; adolescents, female; youth; viral load; Kenya; self-testing; cash transfer; SMS message

Introduction

HIV in Adolescent Girls and Young Women

Adolescents are at significant risk for HIV infection, and despite the need to increase knowledge of HIV status in this priority population, access to and uptake of testing remain low [1-3]. Globally, sub-Saharan Africa remains the region with the highest HIV burden, and infections disproportionately occur among adolescent girls and young women (AGYW) in the age range of 15 to 24 years [4]. Adolescent girls and young women are twice as likely as their male peers to be infected, making females in sub-Saharan Africa the most at-risk group for HIV infection [4]. High fertility, early age of first intercourse, intergenerational sex, and low likelihood of partner circumcision put many young women at increased risk [5]. It is therefore critical to prioritize access to HIV testing, prevention, and treatment for this vulnerable population.

HIV testing services (HTS) and knowledge of HIV status are key steps toward accessing HIV care, treatment, and prevention services. HIV self-testing (HIVST) is a promising approach to increase HTS access and overcomes many of the barriers to HIV testing, especially among young people. With self-testing, an individual collects his or her own sample (oral fluid or blood), performs the test, and interprets the result. A major development in the rapidly growing field of HIVST occurred in December 2016 when the World Health Organization (WHO) recommended HIVST as an additional approach to HTS [6]. For individuals living with HIV, HTS is a critical entry point to life-sustaining care. Successful HIV treatment through antiretroviral therapy (ART) is also essential for prevention of secondary transmission [7]. For those who are HIV negative, HTS provides information about risk reduction strategies and the importance of maintaining HIV negative status. In the 2012 Kenya AIDS Indicator Survey, among those who had not been tested for HIV, 36.7% of women in the age range of 15 to 64 years felt they did not need to be tested, and 17.5% of women were never offered an HIV test [5]. The focus area for the study, Homa Bay County, Nyanza region, is the epicenter for HIV in Kenya, with prevalence at 26% (vs 5.9% for Kenya overall) [8]. Additionally, HIV prevalence in this area is higher for women than men (27.8% vs 24%) [8]. In Nyanza region, 21% of young women and 27% of young men have had sex before the age of 15 years. By 18 years of age, this is two-thirds of both young women and men [9]. From these data, it is evident that there exists a crucial window between 15 and 18 years of age during which young people should access HTS. Highlighting the importance of HTS, WHO recommends it as an important HIV prevention priority, crucial to HIV programmatic success globally [10].

In this GIRLS Study protocol, we describe our planned approaches to address the HIV prevention and treatment continuum that will inform best practices to increase young women's uptake of HIV prevention, testing, and linkage to HIV treatment services in a high HIV-burden African setting. As this study will be conducted within the framework of implementation science, data generated will help determine which study elements can be scaled up to a national level and will directly inform and support Kenya's HIV epidemic control targets and approaches [11]. Lessons learned will be shared with stakeholders, including policy makers, implementation scientists, and nongovernmental agencies elsewhere in sub-Saharan Africa who are exploring how best to enhance the HIV prevention and treatment cascade for AGYW.

The study aims are organized by primary and secondary objectives. The primary objectives are to (1) identify the preferred recruitment venue and testing modality that targets and finds the highest number of previously undiagnosed HIV infected and at-risk AGYW in Homa Bay County, Nyanza region, western Kenya (aim 1), and (2) conduct cost-effectiveness analyses to determine the relative utility of the different seek, testing and linkage interventions (aim 3).

The secondary objectives are to (1) pilot and evaluate adaptive interventions to link newly diagnosed HIV positive female youth to treatment and care services (aim 2a), (2) identify barriers and facilitators to seeking HIV care services after receiving a positive diagnosis (aim 2b), (3) identify barriers and facilitators to seeking HIV prevention services for high-risk female youth after receiving a negative test result (aim 2c), and (4) deliver a primary HIV prevention intervention to high-risk HIV negative female youth (aim 2d).

GIRLS Study Components

We describe in this section the components of the GIRLS Study. Our study is conducted in partnership with the local community in conjunction with an implementing partner, Impact Research and Development Organization (IRDO), which has already successfully delivered combination HIV prevention services to youth in many counties in Nyanza and most recently completed a gender-specific combination HIV prevention study (MP3 Youth; R01AI094607) [12].

Mobile Health Delivery of HIV Testing Services

Our implementing partner has utilized health teams in mobile settings for service delivery, and useful community engagement lessons have been learned [12]. Mobile health clinic teams will

be composed of a driver, mobilizer, receptionist, laboratory technologist, and research assistant or HTS counselor. Their role will be to do community mobilization and refer potential participants to the mobile event; obtain consent, assess eligibility, perform HTS, and administer computer-assisted personal interviewing (CAPI); draw, process, and ship to external laboratory samples of those who test positive; and refer participants for HIV care and treatment or prevention services, as appropriate. We expect that our study will also ascertain whether mobile health clinic teams or home-based recruitment strategies are preferred by AGYW and which strategy identifies the highest number (yield) of HIV-positive female youth.

Home-Based Delivery of HIV Testing Services

Home-based HTS has been provided in Kenya to individuals and families since 2006 and was piloted in Nyanza Province, with a high general acceptance rate above 90% [13]. The home-based and community-based recruitment strategies used in the study is a departure from the more passive approach to HTS that is conducted in antenatal clinics, health facilities, and research clinic settings. HTS and recruitment for research has traditionally been done in health facilities. Due to financial, health system, cultural, and knowledge barriers experienced by adolescents, young women may be less likely to access standard facility-based HTS. Therefore, our study offers HIV testing and recruitment in different settings to inform best practices regarding recruitment and testing strategies targeting this population.

HIV Self-Testing

Youth are least likely to get HIV testing, and innovative strategies are needed to reach young women. HIV self-testing has the potential to overcome many of the barriers to HIV testing to increase HTS access. With self-testing, individuals collect their own sample, perform a rapid HIV antibody test, and interpret their results in the absence of a provider. It offers increased convenience, privacy, and autonomy and can normalize regular testing. Existing research shows a high level of acceptability and demand for HIVST across a wide range of populations and settings, as well as good accuracy in the hands of lay users [14-19]. A study conducted in Malawi found that uptake of self-testing was high, especially among adolescents, notably among young women in the age range of 16 to 19 years [20]. However, the acceptability of self-testing and use of this testing strategy among AGYW have not been well documented in other parts of sub-Saharan Africa. Therefore, this study provides an opportunity to expand the knowledge base of how HIVST may contribute as an additional option for youth to know their status. Offering HIVST as a testing option in this study will help assess acceptability and uptake of HIVST among AGYW. In light of WHO's recommendation for scaling up HIVST and call for additional evidence on ways to operationalize this technology [6], the Government of Kenya's inclusion of HIVST in their 2015 HTS guidelines [21] and national rollout is timely [22]. The lessons learned from this component of the study will inform Kenya's Ministry of Health about some of the challenges of making self-test kits available for the general public, as well as for AGYW.

Financial Incentives for Uptake of HIV Prevention and Treatment Behaviors

The use of financial incentives to encourage desired behaviors has been explored in sub-Saharan Africa. Interventions such as conditional cash transfer that offer cash or goods to individuals or households on the condition that they meet prespecified conditions such as send their children to school or seek certain health services have shown promise [23-25]. However, unconditional cash transfers (UCTs), which are not tied to any prespecified behaviors have also been found to be effective as an HIV prevention strategy [26,27]. In our study, we offer a one-time UCT for a subset of participants (ie, those who do not link to care after the first randomization in the linkage to care sequential multiple assignment randomized trial [SMART] pilot) because adolescents who test positive may experience structural barriers (eg, transportation costs) in linking to care in a timely manner. Linkage is a one-time event, and we assume that newly diagnosed HIV-positive female youth will link to care within 2 weeks after the first randomization (standard referral vs standard referral and short message service [SMS]). The 2-week time frame for linkage to care is defined by the national government; those identified as HIV-infected should be started on treatment during this period. In the study, we will track whether the participants have linked during this 2-week time frame and will analyze time to linkage to HIV care and treatment services.

SMS for Engagement and Retention in Care

Offering linkage to care after a positive HIV test is critical for risk reduction and lifesaving ART. Of Kenyans in the age range of 15 to 65 years self-reported as positive, 79.4% enrolled in care services within 90 days of diagnosis [28]. Previous studies in Uganda and South Africa showed 90% uptake of HTS and linkage among adults, but adolescents were not included; effective strategies need to be identified for adolescents, in particular females, as barriers likely differ. Evidence of SMS effectiveness for supporting linkage to and retention in HIV care exists for adults [29,30]; we will incorporate SMS elements in our study to assess impact for female youth.

Kenya is exploring a new electronic tracking system using SMS text messaging to facilitate linkage to and retention in care and adherence to antiretrovirals for people living with HIV (PLH), as well as to relay prevention messages for high-risk HIV negatives. This national platform envisions use of mobile phones via the SMS platform for communication among facilities, health care workers, and patients to track and support linkage, adherence to treatment, retention, and prevention interventions for improved outcomes. Data generated by this research in the use of an SMS to engage participants (while maintaining their privacy and confidentiality) will inform this planned national platform and guide improvements of the system.

Safeguards for protecting confidentiality of questionnaires and other data will be strictly enforced. We will ensure confidentiality with mobile phone usage by confirming user identity through using an agreed upon code to ensure that the phone user is the study participant before sending an SMS or unstructured supplementary service data messages, as well as airtime reimbursement and digital cash transfers.

Methods

The GIRLS Study will evaluate the prevention-treatment continuum interventions to increase uptake of HIV testing, linkage to and retention in care, and prevention among AGYW (see Figure 1). We will compare two *seek* recruitment strategies; three *test* strategies, including a self-testing option; and pilot adaptive *linkage* to care interventions among at-risk AGYW in the age range of 15 to 24 years in Homa Bay County, western Kenya. For participants newly diagnosed with HIV, we will pilot linkage to care interventions to know the best way to support AGYW so that they receive the care and treatment they need to stay healthy. Additionally, we will evaluate a primary prevention messaging intervention to support identified HIV-negative AGYW in reducing HIV risk and adhering to recommended HIV retesting frequency. Exit interviews offered to participants in the HIV-positive and -negative cohorts will explore barriers and facilitators to seeking HIV care services or HIV prevention services, respectively.

Participants

Participants will be recruited from Homa Bay County, Nyanza region, western Kenya from three subcounties: Homa Bay, Mbita, and Ndhiwa. Recruitment began in the last week of May 2017 and is planned to reach 1200 female youth over an accrual period of up to 12 months, followed by 1 year of follow-up. Eligibility criteria include (1) female in the age range of 15 to 24 years, (2) able to understand spoken English or Kiswahili or Dholuo, (3) resides in Homa Bay County, (4) not previously diagnosed as HIV positive, and (5) willing to provide their informed consent if aged ≥18 years or if in the age range of 15 to 17 years and not an emancipated minor, has a parent or guardian willing to provide consent, in addition to the minor's assent.

All study methodology has been approved by both the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (#P491/07/2015) and Yale University's Human Investigation Committee (#1512016985).

To improve the health and well-being of AGYW, it is vital to understand which testing services female youth prefer and whether they prefer receiving services at home, in the community outside the health facilities, or in the health facilities. This study focuses on aims 1 and 2; study methodology is described in further detail below.

Recruitment Strategies (Aim 1)

Home-based and community-based recruitment strategies will be utilized to determine which strategy identifies the highest number of previously undiagnosed HIV infected and at-risk AGYW. In the home-based strategy, research assistants provide information about the GIRLS Study and enroll participants in their homes. In the community-based strategy, temporary structures such as tents are set up, and participants are enrolled during mobile health clinic events. We will stratify the sample by the three study subcounties: Homa Bay, Mbita, and Ndhiwa. Mapping of catchment areas surrounding health facilities in the three subcounties was used to establish relationships with referral clinics. We will select a random starting point that is within walking distance (about 5 km) of the catchment area of the referral health facility (see Figure 2). In each stratum, the number of participants to be recruited will be proportional to the number of AGYW in the age range of 15 to 24 years living in the respective study catchment area. Participants will be recruited through two recruitment approaches (home-based or mobile health clinic event). Both recruitment strategies will run concurrently until the desired sample size is reached. If needed for sample size attainment, we will expand the sampling area to a 6 to 10 km circumference of the referral clinic.

Figure 1. Study design.

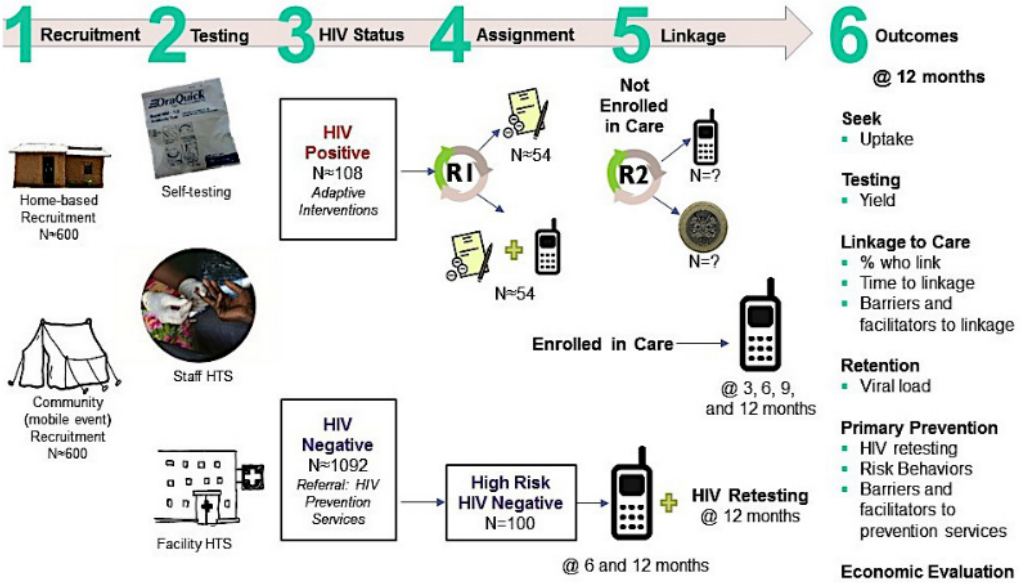
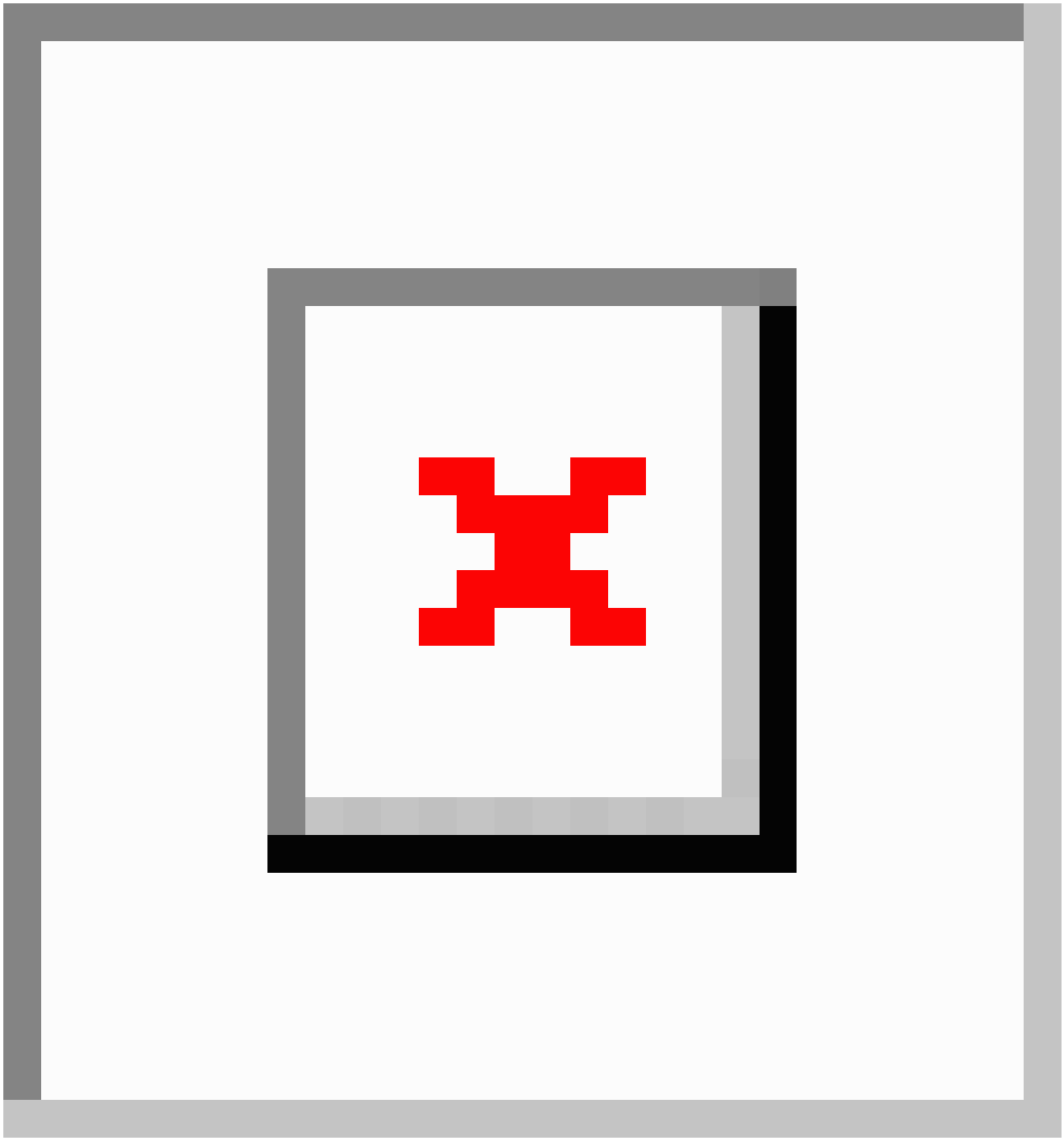


Figure 2. Sampling method.



HIV Testing Strategies (Aim 1)

Whether recruited in the home or at the mobile health clinic event, all participants will be offered three HIV testing options: (1) oral fluid-based HIV self-testing, (2) staff-aided testing per Government of Kenya testing guidelines, or (3) referral for standard facility-based HTS (see Figure 1). After completing the testing modality of their choice, participants will receive an SMS survey within 2 weeks to learn about their testing experience. After completing the survey, all participants will receive airtime reimbursement of KSh 100 (approximately US $1). For those who choose self-testing, participant will take a photo of the test result on a study phone (provided by the study), which will be collected by a study staff after the participant informs the study staff of test completion. During a follow-up visit, the study staff will also perform confirmatory testing for all participants with a positive or indeterminate result, as well as a proportion of participants with a negative self-testing result. The study staff will also collect the used self-test kit and conduct a brief interview on participant experience with self-testing and interpretation of results. Participants who choose referral to the health facility will be tested by the facility staff and testing completion confirmed by study staff from health records. In this way, the primary outcome of an HIV test conduction and result will be achieved as part of the *test* element of the study.

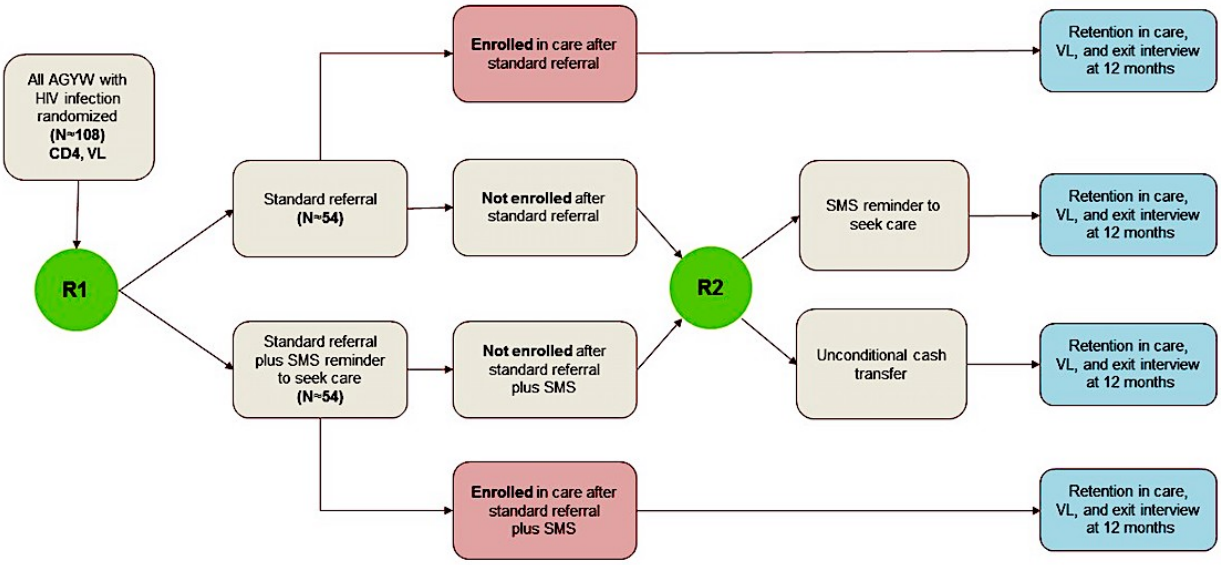
Adaptive Linkage to Care Pilot for AGYW Living With HIV (Aim 2)

All participants who are HIV positive per the Government of Kenya testing guidelines [31] will be invited to enroll in the SMART pilot to compare adaptive linkage to care interventions. Viral loads will be collected before enrollment in the linkage pilot. Additional criterion for participation in the cohort is a willingness to receive SMS texts to link to HIV care and treatment services. Participants will be given a study phone to ensure that lack of phone access is not a barrier to enrollment in the cohort. Participants enrolled in the pilot will undergo sequential multiple assignment randomization (SMART design; see Figure 3), with provision of the subsequent intervention based on participant response to the initial intervention [32]. The initial randomization is to standard referral (counseling and a referral note) or standard referral plus SMS. Some participants may seek HIV care after receiving the standard referral or standard referral plus SMS. Those who do not link to care within 2 weeks after the initial intervention will then be randomized to receive either an SMS text message with linkage encouragement or a one-time financial incentive equivalent to average transport cost to the health facility.

Randomization

We will utilize an approach called permuted blocks randomization for participant assignment to the SMART trial linkage to care intervention. Permuted block randomization has several advantages, one of which is promoting equal distribution of participants in each group. Block randomization is designed to ensure sample size balance across study conditions over time and supports allocation concealment. However, block randomization does not attempt to adaptively balance study conditions on prognostic covariates. A list of random allocations will be generated in randomly ordered permuted blocks of either 2, 4, 6, 8, or 12 allocations. The allocation list will be stored in a password-protected file that will only be accessible to the study statistician, data manager, and project manager.

Figure 3. Sequential multiple assignment randomized trial (SMART) design to compare adaptive interventions.



The field study coordinator will provide a list of study identification numbers of participants needing allocation. The study statistician or data manager will record the unique study identification number and the date of the assignment on the allocation list and relay the assignment to the field study coordinator. Alternatively, if we find that this is not efficient during implementation of our study, we will pursue other methods such as using sequentially numbered, sealed envelopes containing participant allocation that may be prepared beforehand [33].

We anticipate approximately 108 AGYW living with HIV to be identified and randomly assigned to either standard referral or standard referral plus SMS at the first randomization. Participants not linked to care after the first randomization will be rerandomized to receive either an SMS text message or financial incentive.

AGYW Successfully Linked to Care

Participants who successfully link to care, defined as date of first appointment at a comprehensive care clinic, will receive motivational SMSs with adherence to medication and care messages and an SMS survey at intervals of 3 months for 12 months. Participants will receive KSh 100 (approximately US $1) every time they complete the SMS surveys. At 12 months, we will follow up with those participants who tested positive and enrolled in care to measure HIV viral load to determine whether they were linked, retained in care, and adherent to treatment. We will also conduct an interview at 12 months to determine barriers and facilitators for linkage to HIV care and treatment. At this final study visit, participants will receive KSh 400 (approximately US $4) as reimbursement for their time and transportation costs.

Prevention Intervention for HIV Negative Cohort (Aim 2)

Beyond identifying PLH and linking them to care, primary HIV prevention efforts are also essential. Our study will evaluate a primary prevention messaging intervention to support identified high-risk HIV-negative young women in reducing HIV risk and adhering to HIV retesting recommendations. A *high risk*

determination is made if the participant is sexually active and meets one or more of the following: (1) sexual partner is HIV positive or of unknown HIV status, (2) reports 3 or more sexual partners in the last month, or (3) reports that her sexual partner has multiple sexual partners. Participants will be given study phones to ensure that lack of phone access is not a barrier to enrollment in the cohort. The messaging intervention will be a health promotion message. A follow-up survey will collect information on HIV risk behaviors, condom use, and assess HIV retesting behaviors and intentions. Participants enrolled in the HIV-negative cohort will receive airtime reimbursement of KSh 100 (approximately US $1) every time they complete SMS surveys (at 6 and 12 months). At 12 months, participants in the prevention intervention will be retested for HIV and will also complete a face-to-face interview on barriers and facilitators to accessing HIV prevention services. They will receive KSh 400 (approximately US $4) as reimbursement for their time and transportation costs.

Study intervention descriptions are outlined in Textbox 1. For the logic model, see Multimedia Appendix 1.

Data Collection

Computer-Assisted Personal Interviewing

Cross-sectional sociodemographic, HIV prevention, health services access, and other behavioral data will be collected at baseline from all females using a staff-administered CAPI. The CAPI data will contribute to better understanding of specific behavioral risks, HIV testing, and prevention intervention exposure for female youth enrolled in the study. Participants who select the self-testing option will complete an additional CAPI survey that will capture their experience with self-testing and interpretation of the results. Participants enrolled in the HIV-positive and -negative cohorts will undergo CAPI interviews to identify barriers and facilitators to seeking HIV care and treatment or prevention services, respectively.

Textbox 1. Study intervention descriptions.

All female youth (N=1200)

- Human immunodeficiency virus testing services (HTS) via home-based or mobile health clinic event–based recruitment strategies
- HIV testing approaches that females can choose from include (1) oral fluid HIV self-testing at their convenience, (2) staff-aided testing at home or mobile site, or (3) a referral to a health care facility where HIV testing will be done by a health care provider (standard facility-based HTS)
- Behavioral survey at baseline visit
- SMS (short message service) HIV test experience satisfaction survey
- Staff-administered questionnaire about self-testing for females who choose self-testing option

HIV-positive cohort (N≈108)

- Point-of-care cluster of differentiation 4 cell count at baseline
- Viral load testing using dried blood spot at 0 and 12 months
- *Referral for care and treatment; Adaptive linkage to care interventions.* All HIV-positive participants (N≈108) will be randomized to receive standard referral (N≈54) or standard referral plus SMS text message (N≈54) to link to HIV care and treatment services; those who do not link to care within 2 weeks will be rerandomized to an SMS text message or an unconditional cash transfer. We will confirm linkage by self-report via phone call and verified by medical record review
- Antiretroviral therapy adherence and treatment SMS reminders, combined with health status surveys at 3, 6, 9, and 12 months aligned to school holidays for those in school, when the participants would have access to phones
- Face-to-face interview on barriers and facilitators to seeking HIV care services after receiving a positive diagnosis at 12 months

HIV-negative cohort (N=100)

All HIV-negative females will receive the following: risk assessment counseling, condoms, and referral for other prevention services (partner and family testing, pre-exposure prophylaxis, other family planning (contraception) methods, sexually transmitted infection screening and treatment, drug use counseling and other mental health services, social and nutritional support, legal services, sexual and gender based violence services, and others that might be identified during the interview or risk assessment with participants

A subset of randomly selected high-risk (risk score ≥2 as defined by eligibility criteria for high risk) HIV-negative females (N=100) will receive:

- An SMS text message at 6 and 12 months with a health promotion message
- SMS survey to collect HIV risk behaviors, condom use, and willingness to retest for HIV at 6 and 12 months
- HIV test at 12 months
- Face-to-face interview on barriers and facilitators to accessing HIV prevention services at 12 months

SMS Surveys

The SMS surveys will capture the following information: (1) HIV testing option and test experience, (2) successful linkage, (3) sexual risk behaviors, (4) retention in care, (5) adherence barriers and facilitators, (6) willingness to retest (for subset of HIV negatives), and (7) status disclosure.

Power Analysis

Power calculations are based on the yield of newly diagnosed HIV infected across recruitment strategies and testing options offered to female youth (aim 1). Therefore, we did not approach this power analysis from the perspective of calculating a sample size needed to detect a particular effect size with at least 80% power. Rather, because this part of the study (aim 1) is not a clinical trial but an exploration of preferences and yield of recruitment and participant-selected testing strategies, we started with the large, feasible sample size and determined the size of effects that could be detected with at least 80% power when comparing recruitment strategies and HIV testing approaches using version 12 of the Power Analysis and Sample Size Software program [34] for logistic regression.

The expected percentage of AGYW testing positive is based on our MP3 Youth pilot study conducted in the same region [12]. In that study, 55 of 636 female youth not previously diagnosed were found to have HIV infection (data not yet published). Thus, we expect about 9% of all tested females in this study to have HIV infection not previously diagnosed. With this estimate of the expected percentage of girls with newly diagnosed HIV infection, we asked how small of an increase in the odds of newly diagnosed HIV infection could be detected with 80% power when community-based recruitment is compared with home-based recruitment. If approximately 600 youth are recruited by each strategy, power is 80% to detect an odds ratio (OR) of 1.67; in other words, a modest increase from 9% to 14% newly diagnosed with HIV infection. When comparing testing approaches and assuming an equal proportion of girls prefers each approach and testing approach does not interact with recruitment strategy, power is 80% to detect an OR of 1.85. If there is an interaction between recruitment strategy and testing approach when comparing testing approaches within a recruitment strategy (ie, estimating simple main effects), power is 80% to detect an OR of 2.32.

These calculations show that our sample size (N=1200) can detect modest differences in the yield of newly diagnosed HIV infection across both recruitment strategies and three testing approaches. Among the approximately 108 female youth we expect to be newly diagnosed with HIV infection, about 20.4% (22/108) are expected to successfully initiate HIV care at a health facility after standard referral plus a single SMS text message. The remaining 79.6% (86/108) who are not linked to care after the initial SMS text message will be randomly assigned to either SMS text messages or to an UCT. Assuming at least 60% (52/86) are linked to care at some point during follow-up, survival analysis employing Cox regression will be able to detect a hazard ratio of 2.2, describing the impact of treatment condition (SMS vs UCT) on the occurrence and timing of successful linkage to care at a health facility with 80% power.

Outcome Measures

For the analysis plan, see Multimedia Appendix 2.

The key outcomes we detail below are broken out by study aims and based on the HIV prevention and treatment continuum that organizes our outcomes of interest by recruitment strategies, testing, linkage, retention, and primary prevention.

The primary end point for comparisons of recruitment and testing strategies (aim 1) is newly diagnosed HIV infection. Additional outcomes of interest for aim 1 are outlined in Figure 4.

We will determine which HIV testing approaches are most preferred among all female youth and among high-risk female youth. We will also determine which recruitment and HIV testing approaches yield the highest rates of newly diagnosed HIV infection. Multinomial logistic regression will be used to understand which testing approaches are most preferred or used by female youth. Preference for HIV testing at a health facility will be the reference category for the dependent variable. A model with only an intercept will be used to estimate the proportion of girls preferring each testing approach and to test for pairwise differences in preferences (eg, does a higher proportion of girls prefer staff-aided rather than self-testing?). In addition to overall preferences, we will consider age, risk behaviors, and HIV testing history as predictors of preferences by adding participant characteristics to the multinomial logistic regression analysis. Type of testing selected by participants, including refusal to test, will be regressed on predictors to estimate how characteristics of female youth impact HIV testing preferences. Model coefficients will describe the change in odds of preferring other types of testing relative to the reference category (facility-based testing).

Logistic regression analysis will be used to determine which recruitment and HIV testing approaches yield the highest proportion of newly diagnosed HIV infection. HIV testing result (negative vs positive) will be regressed on variables indicating recruitment strategy (home vs mobile health clinic event) and type of HIV testing (oral self-testing, staff-aided, or facility-based). With facility-based testing following community-based (mobile event) recruitment as a reference category, we will estimate how home-based recruitment and other testing approaches change the odds of a positive test result. The interaction between recruitment strategy and HIV testing approach will be tested to determine whether the yield of each testing approach is conditional on recruitment strategy. If a significant interaction effect is found, simple main effects of testing approach within each recruitment strategy and simple main effects of recruitment strategy within each testing approach will be estimated. In addition to comparing yield by recruitment strategies and testing approaches, we will consider interaction effects with youth characteristics such as age, risk behaviors, and HIV testing history and type of testing. Similar logistic regression analyses will examine differences in the odds of completing all confirmatory testing by recruitment strategy and approach to testing.

Home-based and community-based recruitment strategies will also be compared to determine which strategy is more effective in reaching higher risk female youth. Rates of acceptance of screening among potential participants offered screening and rates of enrollment among eligible participants will be compared by recruitment strategy using logistic regression. Risk will be characterized by number and serostatus of sex partners, concurrency, condom use, and patterns of HIV testing by the participant and any sex partners.

Outcomes of interest for aim 2 are outlined in Figure 5.

Figure 4. Aim 1 outcome measures.

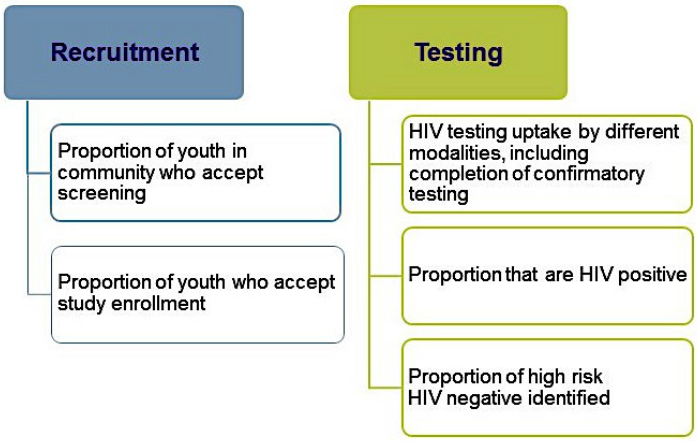
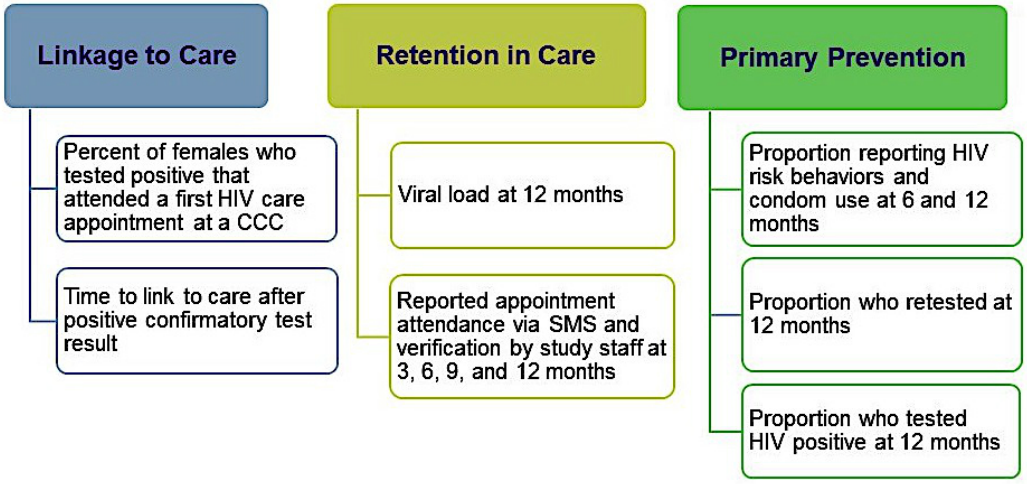


Figure 5. Aim 2 outcome measures.



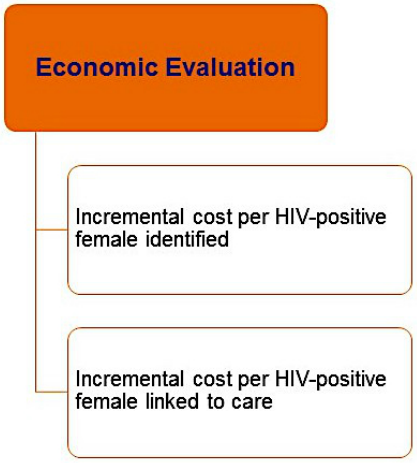
Descriptive statistics and survival plots will be used to characterize occurrence and timing of linkage among AGYW responding to the initial SMS text message and AGYW in each augmented treatment condition. Survival analysis [35,36] will determine which approach to augmenting linkage—SMS or economic incentive—is more effective in linking female youth newly diagnosed with HIV to care sooner. Using the Cox proportional hazards model, difference in the likelihood and timing of linkage between treatment conditions will be quantified with an interval estimate of the hazard ratio. Median time to linkage also will be estimated and compared across treatment conditions.

For the prevention intervention, we will assess risk behaviors, condom use, additional HIV testing, linkage to prevention, and any new HIV diagnoses over the year since study enrollment. Retesting, prevention service use, and new HIV will be examined in relation to recruitment strategy, testing approach at enrollment, and participant risk behavior and other characteristics. Key outcomes of interest for aim 3 economic evaluation to determine the comparative cost effectiveness of the seek, testing, and linkage interventions are outlined in Figure 6.

To determine costs, we will conduct a microcosting of the cost per HIV-infected person identified under each *seek* and *test* strategy. This will be followed by an incremental cost-effectiveness analysis of the linkage to care interventions among the HIV-infected and a cost analysis of the SMS intervention among HIV-uninfected AGYW. These costs will include all costs required to deliver each intervention (eg, home visits, staff time, supplies, and monitoring). Data will primarily utilize a microcosting methodology that uses project expenditure and management records, employing structured costing spreadsheets that record each resource, category (eg, personnel and supplies), quantity (eg, hours), and unit costs. The cost data for the self-test group will include costs of obtaining a confirmatory test for those with positive self-testing results. The cost data will be stratified by HIV testing venue (home-based, community-based (mobile), or referral facility). With these cost data, we will calculate and compare the cost per HIV-infected person identified in each HIV testing strategy. We will also evaluate the costs of the linkage interventions per individual successfully linked to care. The results of the economic evaluation will allow us to identify the most efficient, affordable way to seek high-risk young women and test them. For the linkage interventions, we will utilize the cost data as well as the effectiveness results to compute the incremental

cost-effectiveness ratio (ICER) for the novel linkage intervention that is used.

Figure 6. Aim 3 outcome measures.



The ICER will reveal whether the costs of achieving the incremental gains from additional linkage interventions suggest whether it is cost-effective or not. These results will provide novel data on the cost-effectiveness of linkage to care interventions for high-risk females in sub-Saharan Africa.

Results

We are currently in the recruitment phase of our study and anticipate accrual to be completed by summer 2018, and final study visits to be completed by 2019. We expect to enroll 1200 participants overall, with a random selection of 100 high-risk HIV-negative AGYW for the SMS prevention intervention (HIV-negative cohort) and approximately 108 AGYW who are living with HIV for the SMART design pilot of adaptive linkage to care interventions (HIV-positive cohort). Findings will determine the preferred recruitment strategy and testing option that finds the highest number of previously undiagnosed AGYW living with HIV and at-risk female youth. We anticipate that the linkage to care interventions for AGYW living with HIV and the prevention intervention for high-risk female youth will be feasible and acceptable to implement.

Discussion

To reach the 90-90-90 targets set by the Joint United Nations Programme on HIV and AIDS, innovative strategies are needed to reach adolescent girls and young women, a priority population at significant risk for HIV infection. Increasing knowledge of HIV status is the entryway into care and prevention services. Despite the need to increase knowledge of HIV status in this priority population, access, coverage, and uptake remain poor [1-3]. Data show that we are getting closer to, but still not reaching, the most vulnerable populations at a coverage level that will curb the HIV epidemic. Our findings will inform best practices to increase young women's uptake of HIV prevention, testing, and linkage to HIV treatment services in a high-HIV-burden African setting. As this study will be conducted within the framework of implementation science, data generated will help determine which study elements can be scaled up to a national level and will directly inform and support Kenya's HIV epidemic control. Study components include using mobile health clinic events (outreach) and home-based delivery of HTS, self-testing as an innovative strategy for expanding testing among youth, UCTs, and utilizing an SMS for engagement and retention in care. This study will provide additional insights to push programming closer to achieving 90-90-90 for adolescent girls and young women.

A study limitation is the small sample size of the SMART design pilot to compare adaptive interventions for AGYW living with HIV. Strengths of the study include the longitudinal cohorts (ie, HIV-positive and -negative cohorts), which will allow estimation of potential intervention impact over time in this important population.

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Authors' Contributions

This is a multi-principal investigator (PI) leadership study and AEK, II, and KA are the PIs. AEK, II, KA, NC, JB, HT, and CMC drafted the manuscript. CMC performed the sample size calculation. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Logic model.

[PDF File (Adobe PDF File), 307KB - resprot_v6i12e179_app1.pdf]

Multimedia Appendix 2

Evaluation plan.

[PDF File (Adobe PDF File), 305KB - resprot_v6i12e179_app2.pdf]

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Abbreviations

AGYW: adolescent girls and young women
ART: antiretroviral therapy
CAPI: computer-assisted personal interviewing
HIVST: HIV self-testing
HTS: HIV testing services

ICER: incremental cost effectiveness ratio
IRDO: Impact Research and Development Organization
OR: odds ratio
PLH: people living with HIV
SMART: Sequential Multiple Assignment Randomized Trial
SMS: short message service
UCT: unconditional cash transfer
WHO: World Health Organization

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Protocol

An Intervention Delivered by App Instant Messaging to Increase Acceptability and Use of Effective Contraception Among Young Women in Bolivia: Protocol of a Randomized Controlled Trial

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Abstract

Background: Unintended pregnancy is associated with numerous poorer health outcomes for both women and their children. Fulfilling unmet need for contraception is essential in avoiding unintended pregnancies, yet millions of women in low- and middle-income countries continue to face obstacles in realizing their fertility desires. In Bolivia, family planning progress has improved in recent decades but lags behind other countries in the region. Unmet need for contraception among women aged 15 to 19 years is estimated to be 38%, with the adolescent fertility rate at 70 per 1000 women. Mobile phones are an established and popular mode in which to deliver health behavior support. The London School of Hygiene & Tropical Medicine and the Centro de Investigación, Educación y Servicios in Bolivia have partnered to develop and evaluate a contraceptive behavioral intervention for Bolivian young women delivered by mobile phone. The intervention was developed guided by behavioral science and consists of short instant messages sent through an app over 4 months.

Objective: The objective of this study is to evaluate the effect of the intervention on young women's use of and attitudes toward the most effective contraceptive methods.

Methods: We will allocate 1310 women aged 16 to 24 years with an unmet need for contraception in a 1:1 ratio to receive the intervention messages or the control messages about trial participation. The messages are sent through the Tú decides app, which contains standard family planning information. Coprimary outcomes are use and acceptability of at least one effective contraceptive method, both measured at 4 months.

Results: Recruitment commenced on March 1, 2017 and was completed on July 29, 2017. We estimate that the follow-up period will end in January 2018.

Conclusions: This trial will evaluate the effect of the intervention on young women's use of and attitudes toward the (nonpermanent) effective contraception methods available in Bolivia.

Trial Registration: ClinicalTrials.gov NCT02905526; https://clinicaltrials.gov/ct2/show/NCT02905526 (Archived by WebCite at http://www.webcitation.org/6vT0yIFfN)

(JMIR Res Protoc 2017;6(12):e252) doi:10.2196/resprot.8679

KEYWORDS

behavior change; Bolivia; young adult; adolescent; contraception behavior; smartphone; cell phone; reproductive health

Introduction

The desire to limit and space childbirth has increased in recent decades, yet many women continue to face obstacles in avoiding unintended pregnancies [1]. Unintended pregnancy is associated with numerous poorer health outcomes for both women and their children [2]. Women with unintended pregnancies are more likely to experience depression and anxiety [3-11], and to initiate prenatal care later [5,11-15] and less frequently [5,12,15]. Unintended pregnancies also increase the risk of low birth weight and preterm birth [16,17]. With young women in particular, unintended pregnancy can delay or prevent educational and career achievements, which can affect future financial security [2]. Where safe abortion is restricted, unintended pregnancies can increase the occurrence of unsafe abortions [18,19]. Satisfying unmet need for contraception is essential in avoiding unintended pregnancy, which requires an understanding of the reasons for nonuse in particular contexts [20].

Bolivia is classified as a lower middle-income country. While the country has experienced recent economic growth, in 2015 around 39% of people were living below the national poverty line [21]. Income inequality is high [21], with substantial inequality between indigenous and nonindigenous populations [22]. Compared with other countries in the region, in Bolivia, progress in family planning has lagged behind [23]. Effective contraception methods are those with a less than 10% typical-use failure rate at 12 months [24-26]; the (nonpermanent) effective methods available in Bolivia are oral contraceptive pills, intrauterine devices, injectables, implants, and the patch. Despite the availability of these methods, the 2008 Bolivian Demographic and Health Survey estimated unmet need among women aged 15 to 19 years to be 38% [27,28]. World Bank indicators for 2015 report the adolescent fertility rate to be 70 per 1000 women aged 15 to 19 years [21]. Abortion is illegal in Bolivia except in cases of rape, incest, and danger to the health of the woman [29]. While there are no official figures on induced abortion, research suggests that around 100 illegal abortions are carried out per day [27], the majority of which are likely to be unsafe due to the legal restrictions on abortion in the country. A survey in 2008 found that, among unmarried sexually active women aged 15 to 19 years, 84% reported wanting to avoid a pregnancy in the next 2 years, but only 49% reported using any contraceptive method [28]. The main reasons given for not using contraception were not being married (52%) (sex before marriage is stigmatized in Bolivia) or having infrequent sex (55%) [28].

Mobile phones are now an established and popular mode in which to deliver health interventions [30-41]. An advantage of using mobile phones to deliver health support is that content can be received at a time of the recipient's choosing, which may be particularly important with sensitive topics such as sexual and reproductive health. Mobile phone interventions can be delivered through a variety of ways: through voice messages, text messages, mobile apps, instant messages that include videos and images, or bidirectional teleconsultation with health care professionals via text message or a live voice call, to name just a few. While there is some evidence from high-income countries that mobile phone-based interventions can increase contraceptive use [42-44] and knowledge [45], none of the trials evaluating these interventions had a low risk of bias [46]. To the best of our knowledge, only 1 trial has been conducted in a nonhigh-income country (Cambodia); this trial found that postabortion voice messaging with telephone counselling support increased effective contraceptive use at 4 months [47]. Since 2007, mobile phone ownership in Bolivia has increased sharply, with 92 mobile phone subscriptions per 100 people in 2015 [48], which is likely to be higher among younger people.

The London School of Hygiene & Tropical Medicine (LSHTM) and the Centro de Investigación, Educación y Servicios (CIES), a Member Association of the International Planned Parenthood Federation (IPPF), are collaborating to evaluate a contraception intervention delivered by mobile phone for young women in Bolivia. The intervention is informed by integrated behavioral model [49], consists of short mobile phone app instant messages, and is delivered over 4 months through CIES's Tú decides app. The intervention messages provide accurate information about contraception and include 10 behavior change methods [50]. It was developed through collaboration between LSHTM, CIES, and young people in La Paz and El Alto, Bolivia, with the support of the IPPF Western Hemisphere Region. The collaboration involved various activities aimed at understanding young people's knowledge of, attitudes toward, and barriers faced in using contraception and preferences for intervention delivery. Guided by behavioral science [51], the intervention was produced through an iterative process of writing, testing with the target group, and refining.

We present the protocol for the evaluation of the intervention by randomized controlled trial. The aim of the trial is to establish whether the intervention increases young Bolivian women's use and acceptability of effective contraceptive methods.

Methods

Study Design

This study is a parallel-group, individually randomized superiority trial with a 1:1 allocation ratio evaluating the effect of an intervention delivered by mobile app. Participants randomly allocated to the intervention arm will have access to the app and will receive the intervention instant messages. Participants randomly allocated to the control arm will have access to the app and receive control instant messages about trial participation.

Eligibility Criteria

Women aged 16 to 24 years who own a personal Android mobile phone and live in La Paz or El Alto, and who report an unmet need for contraception (ie, are sexually active, are not using effective contraception, and want to avoid a pregnancy), can provide informed consent, and can read Spanish will be eligible to take part. Participants must also be willing to receive messages about contraception on their mobile phone.

Recruitment and Setting

To achieve a diverse sample, we will promote the trial through a variety of routes: CIES's service delivery points in La Paz

and El Alto, the CIES website, flyers distributed through CIES's youth network, and social media sites. Potential participants will be provided the link to the enrollment pages of the secure online trial database and randomization system, where they can read the participant information sheet (Multimedia Appendix 1) and provide informed consent (Multimedia Appendix 2). (The information sheet and consent form will be provided to potential participants in Spanish. The English versions are included here for the purposes of publication.) If they do not have adequate Internet connectivity, youth network volunteers will provide this. Participants will also have the option of completing the paper-based version of the consent form.

To maximize the chance of recruiting to target, LSHTM conducted a pretrial training in La Paz to train local staff on all recruitment procedures. The training included discussions about the practicalities of recruitment with a view to developing the most appropriate strategies. CIES conducted a similar training with their youth volunteers, who will promote the trial.

We will report the number of people assessed for eligibility, the number excluded before randomization, and the number of participants randomly allocated to the intervention, who completed follow-up, and who were analyzed (Figure 1).

Intervention

In addition to providing accurate information about contraception (including the dual protection that condoms offer), the intervention messages target beliefs identified in the development phase that influence contraceptive use (eg, specific misconceptions about the side effects and health risks of contraception) and aim to support young women in believing that they can influence their reproductive health. The messages contain the following behavior change methods, adapted for delivery by mobile phone [50]: belief selection, facilitation, anticipated regret, guided practice, verbal persuasion, tailoring, cultural similarity, arguments, shifting perspective, and goal setting. The Tú decides app itself contains standard family planning information and no behavior change methods.

Participants allocated to the intervention group will receive 0 to 3 messages per day (a total of 183 messages) for 120 days. Included in the 183 messages that intervention recipients receive are 7 control messages about the importance of their participation and reminding them to contact the project coordinator if they change their number.

The message sets start with 6 days of messages with general information about the study, such as information about what they will receive over the next 120 days, how to stop the messages, who to contact if they change their number, how to keep the messages private, and information about who to call if they feel unsafe as a result of someone reading the messages.

On days 119 and 120, the intervention includes 4 messages: 1 that indicates that the messages have ended, 1 that provides a link to the database to complete the follow-up questionnaire, 1 that gives reassurance that the information they provide is confidential, and a final message stating that their participation is helping to determine the best ways to provide reproductive health services in Bolivia.

Details regarding the development and a description of the intervention will be reported in a forthcoming publication.

Control

Participants allocated to the control group will have access to the same Tú decides app pages as the intervention group. Control participants will also receive 16 messages about trial participation over 120 days. The first 4 days include 6 messages that introduce the study, as well as providing information about what they will receive over the next 120 days, how to stop the messages, and who to contact if they change their number. They then receive 2 messages a month for 3 months: 1 about the importance of their participation and 1 reminding them to contact the project coordinator if they change their number. On day 105, they will receive 1 message about the importance of their participation. On day 120, participants will receive 3 messages: 1 that provides information on how to complete the follow-up questionnaire, 1 that gives reassurance that the information they provide is confidential, and a final message stating that their participation is helping to determine the best ways to provide reproductive health services in Bolivia.

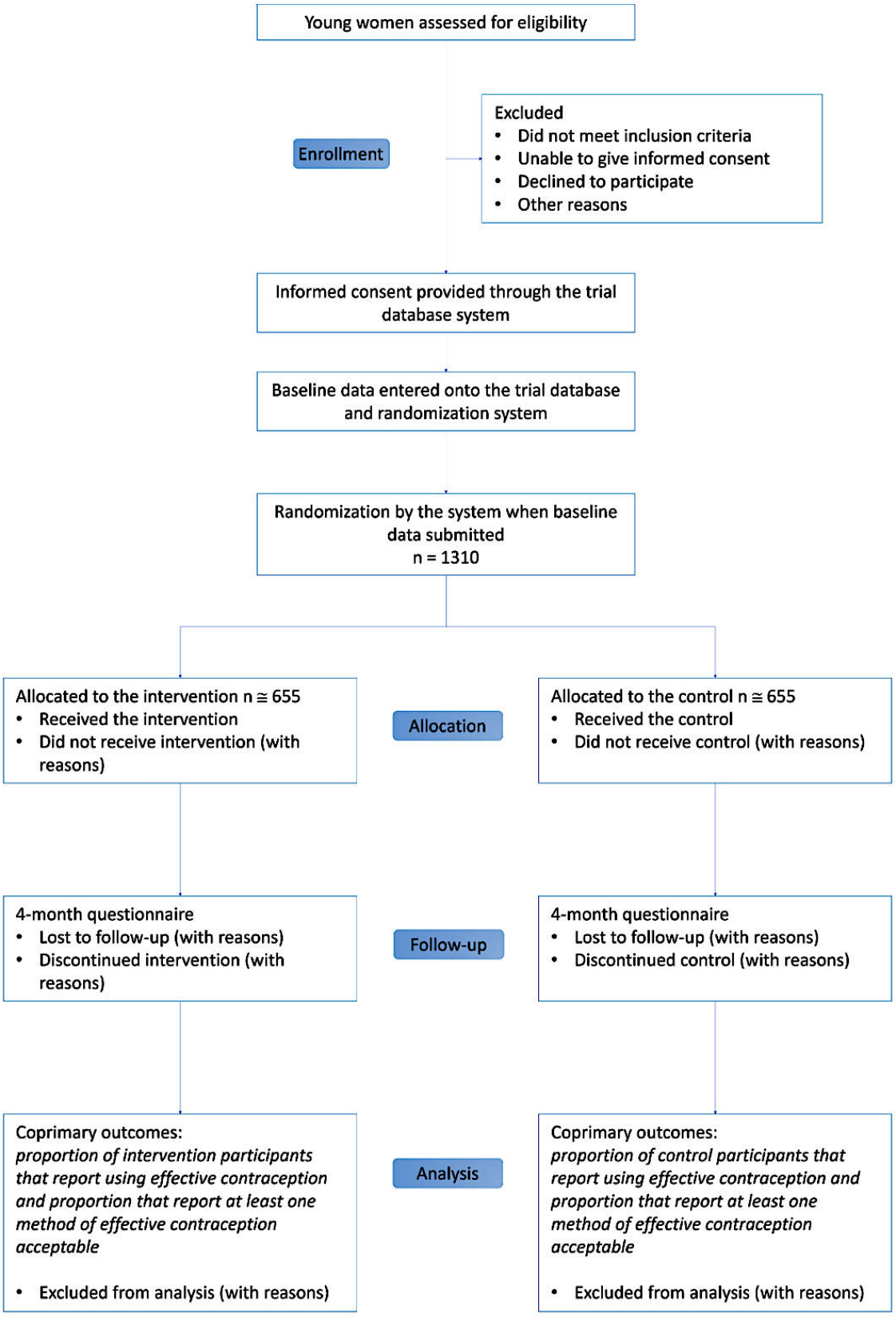
All participants will receive usual care and will be free to seek any other support, whether existing or new.

Outcomes

Primary Outcomes

The coprimary outcomes are self-reported current use of effective contraception and the proportion of participants reporting that at least one method of effective contraception is acceptable at 4 months after randomization. Because a validated measure of acceptability appropriate for this context did not exist, we constructed the primary outcome measure based on guidelines for measuring integrated behavioral model constructs [49,52,53] and tested its face validity with the target group. The acceptability of each method is measured by the following stems: "Using the [method]...causes infertility,...causes unwanted side effects,...is easy,...is a good way to prevent pregnancy" and "I would recommend the [method] to a friend." Intrauterine device and implant acceptability is measured by an additional stem: "The [method] insertion would not be a problem for me." The response options for each scale are "strongly disagree," "disagree," "not sure," "agree," "strongly agree," and "I do not know what the [method] is." A method is acceptable if participants report "agree" or "strongly agree" for all scales except for the "...causes infertility" and "...causes unwanted side effects" stems, for which "disagree" or "strongly disagree" denotes acceptability (items 1-27 in Multimedia Appendix 3 and items 4-30 in Multimedia Appendix 4).

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



Secondary Outcomes

Secondary outcomes are, for each contraception method, the proportion reporting that each effective contraception method is acceptable (acceptability of individual methods); the proportion reporting use of effective contraception at any time during the 4 months (discontinuation); the proportion reporting attending a sexual health service during the 4 months (service uptake); the proportion reporting that they became pregnant and they did not want to become pregnant during the study

(unintended pregnancy); and the proportion reporting having an abortion during the study (induced abortion).

Process Outcomes

The process outcomes are knowledge of effective contraception; perceived norms and personal agency in relation to using contraception and communicating with partners about contraception; intention to use effective contraception; and intervention dose received.

Data Collection

We will collect data at baseline and 4 months postrandomization using questionnaires. The questionnaires were written in English, translated into Spanish by a native speaker from Bolivia, and then tested for face validity with the target group. We asked 21 young women to comment on the length of the questionnaires, the comprehensibility of the questions, the meaning of the scales, and suggestions for improvement. All data will be entered onto the trial database system, which is on LSHTM's secure server. At both time points, participants can fill out a paper-based version of the questionnaire at the recruitment site, provide the data over the phone with research staff, or enter data directly onto the online system, according to their preference. If participants provide their questionnaire data by paper or over the telephone, research staff will enter these data onto the system.

Baseline Data Collected

At baseline we will measure the acceptability of effective contraception (a coprimary outcome) and collect the following personal and demographic data via the baseline questionnaire: full name; mobile phone number; email address; date of birth; marital status; number of children; ethnicity; occupation; highest education level completed; residence; current method of contraception; and how they found out about the study (Multimedia Appendix 3).

Follow-Up Data Collected

At 4 months, we will measure the primary, secondary, and process outcomes and collect the following data via the follow-up questionnaire: if participants report using an effective method, where they obtained it; current pregnancy intention; whether they knew someone else who took part in the study and, if so, whether they read each other's messages (contamination); whether they have experienced physical violence since being in the study; and whether anything good or bad happened as a result of receiving the messages (Multimedia Appendix 4). We are collecting data on physical violence because the intervention involves a sensitive topic and is delivered in a context where intimate partner violence is a public health concern. If participants do not complete the questionnaire themselves, local research staff will contact them to collect their data. For participants who report use of effective contraception on the follow-up questionnaire, local research staff will attempt to locate the service records to objectively verify use.

Methods to Maximize Follow-Up Response

The pretrial training also included training in follow-up procedures. It emphasized the importance of ensuring that participants understand that participation involves completing a 4-month questionnaire and potentially receiving daily messages about contraception for 4 months. The control messages, also sent to participants allocated to the intervention, are an effort to keep participants engaged. Staff will contact nonresponders up to 3 times for their follow-up data. Follow-up will end 6 months after the last participant has been randomized or after staff has attempted to contact all nonresponders 3 times, whichever comes first. See Figure 2 for the schedule of enrollment, interventions, and assessments.

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

		STUDY PERIOD						
		Enrollment	Allocation	Postallocation				Closeout
	TIMEPOINT	*0*	*0*	*Month 1*	*Month 2*	*Month 3*	*Month 4*	*6 months after last participant randomized*
ENROLLMENT	Eligibility screen	√						
	Informed consent	√						
	Baseline data completion	√						
	Baseline data entry	√						
	Allocation		√					
INTERVENTIONS	Contraceptive app instant messages (0-3 messages per day for 120 days)		—	—	—	—	→	
	App instant messages not about contraception (16 messages over 120 days)		—	—	—	—	→	
ASSESSMENTS	Baseline data: primary outcome, personal and demographic data	√						
	Follow-up data: primary, secondary, and process outcomes*						√	√

*Plus: if participants report using an effective method, where they obtained it; current pregnancy intention; whether they knew someone else that took part in the study and if so, if they read each other's messages (contamination); if they have experienced physical violence since being in the study and if anything good or bad happened as a result of receiving the messages

Allocation and Protection Against Bias

Randomization will occur immediately after baseline data are submitted on the trial database and randomization system. The allocation sequence is generated by the remote computer-based randomization software, ensuring that investigators are unaware of allocation before participants are randomized. Due to the nature of the intervention, participants will be aware of the allocation soon after they start receiving the messages. Local research staff collecting outcome data will not be made aware of allocation unless this is revealed to them by the participant. Researchers who analyze the data will be masked to treatment allocation.

Intervention Delivery

After participant baseline data have been entered, a confirmation of enrollment screen will provide instructions on how to install the app. When participants install the app, they will be prompted to enter the mobile phone number they entered on the baseline questionnaire. The trial database and randomization system will then send the allocation to the local app platform. Participants will then have access to the app and receive either the control or intervention messages, according to their allocation. Within the app, participants can choose when they want to receive the messages, and they can also stop the messages. Participants will receive the first message the day after they install the app.

Sample Size

A trial evaluating a postabortion mobile phone intervention using voice messages and counsellor support found that 18% more women in the intervention arm than in the control arm were using effective contraception at 4 months (64% vs 46%, relative risk 1.39, 95% CI 1.17-1.66) [47]. Assuming that Smith and colleagues' trial observed a larger increase in contraceptive uptake, as it involved women who had just had an abortion, we powered our trial to detect a smaller absolute difference of 10% uptake in effective contraception at 4 months.

The proportion of women aged 16 to 24 years in a partnership living in La Paz or El Alto using effective contraception is estimated to be around 44% [54]. A total of 1048 participants will allow us to have 90% power to detect a 10% increase in effective contraception, assuming 44% use in the control group (ie, 44% in the control vs 54% in the intervention, corresponding to an odds ratio of 1.49). Allowing for 20% loss to follow-up, we will randomly allocate 1310 people.

Data Management

We did not convene a data monitoring and ethics committee, as the intervention provides support and is unlikely to produce adverse effects. We have convened a trial steering committee, and they have agreed to take on the monitoring of ethical aspects of the trial. The trial sponsor may audit the trial according to their own risk assessment and schedule.

Personal details entered onto the trial database and randomization system will be stored on LSHTM's secure server. Personally identifiable information exported from the database will be stored separately from anonymized research data. Participant mobile phone numbers, but no other personal details, will be stored in the local platform that sends the messages through the app. Any signed paper consent forms and questionnaires will be kept in a data enclave at CIES. All data arising from the study will be kept confidential and accessible only to researchers directly involved in it. Personally identifiable data will not be kept longer than necessary and will be deleted within 3 months following study completion. We will retain primary research data for 10 years following study completion.

Ethical Approval

The trial was granted ethical approval by LSHTM Interventions Research Ethics Committee on May 16, 2016 and by La Comisión de Ética de la Investigación del Comité Nacional de Bioética on September 20, 2016. The trial is registered by ClinicalTrials.gov (NCT02905526).

Protocol Amendments

Any important changes to the protocol will be submitted to the LSHTM Interventions Research Ethics Committee as an amendment. Trial documentation will be updated accordingly and will be implemented once the Committee has approved the changes. LSHTM will communicate any changes relevant to local research staff.

Dissemination

The research results will be cowritten by LSHTM and CIES and submitted for publication in peer-reviewed academic journals. We will adhere to the International Committee of Medical Journal Editors authorship criteria. We will disseminate findings to all the study stakeholders and policy makers in Bolivia.

Analyses

General Statistical Considerations

The analysis of the data will follow the plan specified below. There will be no interim analyses and therefore no stopping rules. We will analyze participant data according to the arm that they were allocated to and will include only participants with complete outcome data in the primary analysis (a complete-case analysis). All statistical tests will be 2-sided. We will report all effect estimates with a 95% confidence interval and associated *P* value. Statistical significance will be considered at the 5% level, but interpreted with caution considering the 2 primary outcomes. We will use the latest version of Stata (StataCorp LLC) for analyses.

Loss to Follow-Up

To investigate whether loss to follow-up differs by arm, we will report this descriptively and use a chi-square test. We will use logistic regression to compare baseline characteristics of participants who completed 4-month follow-up against participants who did not. We will report predictors of loss to follow-up and investigate whether the effect of these differs by arm by testing for an interaction.

Assumptions About Missing Data

As we are not aware of similar trials, it is not possible to investigate the pattern of missing data. The complete-case analysis assumes that missing data for participants who did not complete follow-up are similar to data from participants who

completed follow-up, conditionally on baseline covariates included in the analysis model (ie, that data are missing at random) [55]. If participants who complete follow-up are more likely to use effective contraception and to find an effective method acceptable compared with those who are lost to follow-up, the observed proportion may overestimate use and acceptability [55].

Missing Covariates

The database requires all items on the baseline questionnaire to be submitted in order to proceed to the random allocation. Therefore, there will be no missing baseline covariates.

Principal Analyses

Descriptive Analysis

We will report a flow diagram of trial participation, as recommended in the Consolidated Standards of Reporting Trials (CONSORT) guidelines [56]. We will report the baseline characteristics by treatment arm. We will also explore the baseline factors associated with retention (see above).

Analysis of the Primary Outcome

Both coprimary outcomes are binary, and we will compare the crude proportion who report using effective contraception in each group and the crude proportion who report that at least one method is acceptable in each group. We will estimate the difference between the groups using logistic regression and will report the odds ratio along with the 95% confidence interval and *P* value for evidence against the absence of intervention effect from the model. The primary analysis regression will be adjusted for baseline covariates likely to be associated with the outcome in order to improve the efficiency of the analysis and avoid chance imbalances [57]. The prespecified covariates that we will adjust for are age (16-19 years/20-24 years), number of children (0/≥1), highest education level completed (university/other), and acceptability of effective contraception at baseline (at least one method acceptable/no methods acceptable). Primary outcomes will be analyzed individually, and no formal multiplicity correction will be applied, but interpretation will take into account the multiple tests if only 1 of the 2 outcomes reaches the 5% significance level. We will also report the crude odds ratio between arms.

Analysis of the Secondary Outcomes

The analysis of the secondary outcomes will be the similar to the analysis of the primary outcome. We will estimate the difference between the groups using logistic regression, and report odds ratios with 95% confidence intervals and *P* values. All regressions will be adjusted for the prespecified covariates as above (although, with the acceptability of individual methods, the outcome at baseline will replace acceptability of effective contraception).

Analysis of the Process Outcomes

The process outcomes perceived norms, personal agency, and intention comprise ordinal scales. We will analyze each scale individually using ordered logistic regression to estimate proportional odds ratios. For knowledge, each correct answer will receive 1 point. The points will be summed and an overall score will be produced. We will use linear regression to test for a difference in mean scores between the arms.

To assess the "dose" of the intervention that the intervention participants received, we will analyze the number of messages that participants reported to have read (all, most, some, none) and whether they stopped the messages. We will report this descriptively.

Additional Analyses

Sensitivity Analyses

We will conduct sensitivity analyses regarding the missing data. In the first sensitivity analysis, we will consider that data are not missing at random; that participants lost to follow-up did not find at least one method acceptable; and that participants lost to follow-up were not using an effective method of contraception. In the second, we will adjust for the main baseline predictors of missingness. Both sensitivity analyses will be adjusted for the prespecified covariates as above.

Subgroup Analysis

Recognizing that the trial is not powered to detect effect differences in subgroups, we will conduct exploratory subgroup analyses for the coprimary outcomes to determine whether the intervention effect varies by baseline characteristics. The prespecified subgroups are age (split at the median); marital status (married/not married); number of children (0/≥1); geographic location (El Alto/La Paz); occupation (in education/other); and highest education level completed (university/other). Within the prespecified subgroups, we will assess heterogeneity of treatment effect with a test for interaction [58-62]. Interaction test *P* values will be presented but will be interpreted with caution, due to the exploratory nature, the multiple tests performed, and the low power of the interaction test. We will estimate odds ratios along with 95% CIs for each subgroup without *P* values. As this is an exploratory analysis of potentially influential characteristics that are not justified a priori, we will not hypothesize effect directions.

Contamination

To assess the potential for contamination, we will report the proportion of control group participants who read another participant's messages and the proportion of intervention participants whose messages were read by another participant.

Analysis of Pooled Trial Data

We are conducting trials of a similar intervention in 2 other countries. If the results of the other trials are available, we will conduct the principal analyses on the pooled dataset.

The datasets used and analyzed during this study are available from the corresponding author on reasonable request.

Participants' Rights and Safety

Participants will have the right to withdraw at any time during their involvement, without having to give a reason. Participants can withdraw by contacting the project coordinator. Acting on a participant's request to withdraw from the trial, we will change the participant's status to "withdrawn" and exclude the person from the list of participants who are due for follow-up.

Participants' participation and personal identifiable data will remain confidential and research data will be anonymized.

In the formative work, we explored young people's views on confidentiality about receiving messages on their mobile phone. While the majority of participants did not report concerns regarding receiving messages about contraception on their mobile phone, it is possible that some participants will want to keep the messages confidential from certain people (eg, partner, parents) and that these people might view the messages. The messages remind participants that they can delete the messages and provide instructions on how to keep the messages private. We will provide participants with information on support services that they can contact if they feel unsafe as a consequence of the messages being read. We will review physical violence during participants' involvement in the trial reported on the follow-up questionnaire.

Results

Recruitment commenced on March 1, 2017 and was completed on July 29, 2017. The estimated completion date for the final participant recruited (final data collection date for the primary outcome) is January 2018.

Discussion

Among young women in La Paz and El Alto with an unmet need, the results of this trial will provide evidence for the effect of the intervention on their use of and attitudes toward effective contraception. The analysis of the secondary and process outcomes may provide evidence for the effect of the intervention on attitudes toward the individual effective methods, service use, unintended pregnancy, induced abortion, and the psychological processes that may have been altered by the intervention.

Because this trial is being conducted among young women with an unmet need for contraception in a context where information about contraception is low, it is reasonable to assume that enrolling in the trial will be popular. While this is an advantage with regard to meeting the recruitment target, it is possible that participants will tell their friends about the trial and that they will also enroll. While this is desired in a nontrial context, this could lead to contamination if the intervention messages are shared with control participants during the trial. To minimize this, participants will not be recruited through schools.

Because the intervention is being delivered through the Tú decides app, participants must own a personal Android mobile phone to take part in the trial. Although the intervention development work indicated that the majority of young people in Bolivia own a personal Android mobile phone, not everyone in the target group will. It may be that young people less likely to use and to find contraceptive methods acceptable are more likely to not own an Android phone, which would limit the generalizability of the findings. Smartphone ownership continues to increase rapidly, however, so it is likely that a greater proportion of young people from different socioeconomic communities will be able to receive the intervention in the future.

The trial will assess the effect of sending instant messages containing behavior change methods in addition to the app; it is not assessing the effect of the app itself. It is possible that the app, which provides standard family planning information, could have an effect on effective contraceptive use and acceptability of effective contraception. If the app itself is very effective, the added benefit of the instant messages will be lower. The results of the study will add to current research on mobile phones for intervention delivery and will determine whether mobile phones can be an important adjunct to sexual and reproductive health service provision in Bolivia.

Acknowledgments

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The trial is supported by the IPPF Innovation Programme. IPPF had some influence over the study design (SM and SH) but will have no involvement in the data collection or analysis.

Members of the trial steering committee at LSHTM are Dr James Lewis, Senior Lecturer, co-Deputy Director of the Centre for Evaluation, and Dr Rebecca French, Senior Lecturer of Sexual and Reproductive Health.

The guarantor at LSHTM is Patricia Henley, Quality & Governance Manager.

Authors' Contributions

OLM designed and managed the trial, developed the trial materials, and wrote the manuscript. VOC contributed to discussions and decisions regarding the design of the trial, assisted in the development of the trial material, and facilitated trial implementation. SM and SH contributed to discussions regarding the design of the trial. BL and PE provided advice regarding the statistical analysis. JLG took overall local responsibility for the trial. CF provided guidance regarding the trial design and implementation. All authors revised the work, approved the version to be published, and agree to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Trial information sheet.

[PDF File (Adobe PDF File), 197KB - resprot_v6i12e252_app1.pdf]

Multimedia Appendix 2

Trial consent form.

[PDF File (Adobe PDF File), 264KB - resprot_v6i12e252_app2.pdf]

Multimedia Appendix 3

Baseline questionnaire.

[PDF File (Adobe PDF File), 369KB - resprot_v6i12e252_app3.pdf]

Multimedia Appendix 4

Follow-up questionnaire.

[PDF File (Adobe PDF File), 488KB - resprot_v6i12e252_app4.pdf]

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Abbreviations

CIES: Centro de Investigación, Educación y Servicios
CONSORT: Consolidated Standards of Reporting Trials
IPPF: International Planned Parenthood Federation
LSHTM: London School of Hygiene & Tropical Medicine

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Protocol

Intervention to Match Young Black Men and Transwomen Who Have Sex With Men or Transwomen to HIV Testing Options (All About Me): Protocol for a Randomized Controlled Trial

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Abstract

Background: HIV testing is a critical component of HIV prevention and care. Interventions to increase HIV testing rates among young black men who have sex with men (MSM) and black transgender women (transwomen) are needed. Personalized recommendations for an individual's optimal HIV testing approach may increase testing.

Objective: This randomized trial tests the hypothesis that a personalized recommendation of an optimal HIV testing approach will increase HIV testing more than standard HIV testing information.

Methods: A randomized trial among 236 young black men and transwomen who have sex with men or transwomen is being conducted. Participants complete a computerized baseline assessment and are randomized to electronically receive a personalized HIV testing recommendation or standard HIV testing information. Follow-up surveys are conducted online at 3 and 6 months after baseline.

Results: The All About Me randomized trial was launched in June 2016. Enrollment is completed and 3-month retention is 92.4% (218/236) and has exceeded study target goals.

Conclusions: The All About Me intervention is an innovative approach to increase HIV testing by providing a personalized recommendation of a person's optimal HIV testing approach. If successful, optimizing this intervention for mobile devices will widen access to large numbers of individuals.

Trial Registration: ClinicalTrial.gov NCT02834572; https://clinicaltrials.gov/ct2/show/NCT02834572 (Archived by WebCite at http://www.webcitation.org/6vLJWOS1B)

(JMIR Res Protoc 2017;6(12):e254) doi:10.2196/resprot.8856

KEYWORDS

HIV testing, black men who have sex with men, transgender women, mobile technology, HIV prevention

Introduction

Men who have sex with men (MSM) comprised the largest proportion (67%) of new HIV diagnoses in the United States in 2015 [1]. Young black MSM are diagnosed with HIV at greatly disproportionate rates, comprising 50% of all new diagnoses among MSM aged 15 to 29 years [1]. The prevalence and incidence of HIV have repeatedly been demonstrated to be high among young black MSM [2-4]. Furthermore, high HIV prevalence and incidence rates have been reported among transgender women (transwomen), with black transwomen disproportionately affected [5,6].

A key component of HIV prevention for communities at risk is regular HIV testing. Persons unaware that they are HIV-infected cannot benefit from antiretroviral treatment and are more likely to transmit HIV to others due to lack of viral suppression [7]. Testing also provides gateways to HIV prevention strategies, such as pre-exposure prophylaxis (PrEP). The Centers for Disease Control and Prevention (CDC) recommends that MSM test for HIV at least annually and more frequently (every 3-6 months) if they have additional risk factors [8,9]. Although reports indicate that HIV testing has increased among young black MSM (eg, 65% testing in last 12 months in 2008 to 77% in 2011) [10], the need to further increase HIV testing, uptake of prevention strategies and linkage to care early in HIV infection continues for young black MSM and transwomen [5,11,12]. For example, in a cohort of black MSM and transwomen, only 28% of those queried in 2015 were aware of PrEP [13] and the CDC reports that young black MSM have significantly less favorable HIV care outcomes than do others; 66% of black MSM aged 20-24 years are linked to care within 1 month of diagnosis compared to 77% of white MSM in the same age group [14].

General strategies to increase HIV testing include community-based campaigns, opt-out policies at clinics, electronic medical record alerts, and offering testing in various outreach venues [15-19]. A limited number of HIV testing interventions among young black MSM and transwomen have been reported. One intervention that focused specifically on HIV testing among young black MSM found that a field outreach approach combined with motivational interviewing was associated with a higher uptake of HIV testing and returning for test results [20]. Of several peer-led interventions, a group-level, culturally congruent, theory-based behavior change intervention for older black MSM resulted in a significant increase in self-reported HIV testing [21].

Mobile technology and Web technology, as well as text messaging HIV prevention interventions, have been developed for young MSM, with some studies focused on HIV testing uptake as an outcome [22-28]. Distribution of self-test kits through social media promotions has also been examined as an approach to increase HIV testing [29,30]. Merchant et al [31] found that access to free self-tests resulted in the highest uptake of HIV testing, even among those for whom this was not their preferred testing approach.

To our knowledge, no interventions designed to increase HIV testing are oriented toward taking advantage of the variety of HIV testing approaches now available, including traditional clinic/doctor/community-based testing, self-testing [32], and couples HIV testing and counseling [33]. Multiple testing approaches provide the opportunity for a personalized intervention, which can enable user choice and increase levels of uptake as demonstrated with multiple technologies in the contraceptive field [34].

This randomized controlled trial was developed with the goal of increasing HIV testing among young black MSM and transwomen by providing a personalized recommendation for an individual's optimal HIV testing approach. The intervention is a brief survey completed by participants, which provides the data for an algorithm to make the personalized recommendation. The intervention integrates available HIV testing options, including HIV self-tests for those who may be unable or unwilling to visit a testing site; couples HIV testing and counseling, given data suggesting that a significant proportion of HIV transmission among MSM may be attributed to sex with main partners [35,36]; and traditional clinic-based testing for those most comfortable testing in such a setting. The intervention also takes advantage of the widespread use of the Internet and mobile devices by young black MSM and transwomen, including those who are otherwise hard to reach [37]. This approach has potential to reach large numbers of young black MSM and transwomen, especially those who are unlikely to attend public venues, are unable or unwilling to come to traditional testing sites, and are at risk but are less likely to have recently tested for HIV.

Methods

Design

A trial is being conducted among 236 young black MSM and transwomen randomized to receive either a personalized recommendation electronically (eg, on their computer or mobile screen) for an HIV testing approach (intervention) or standard HIV testing information (control). At 3 and 6 months, standardized online surveys assess outcomes and covariates. This randomized trial tests the hypothesis that the personalized recommendation increases HIV testing more than standard testing information.

Participants

The original study design limited enrollment to black MSM aged 18 to 29 years. Based on feedback from the study Community Consulting Group and their knowledge of HIV risk among black subpopulations in New York City, inclusion criteria were expanded to include those aged 16 and 17 years and transwomen. Thus, participants are eligible if they (1) are a male at birth; (2) self-identify as black, African American, Caribbean black, African black, or multiethnic black; (3) are able to read and respond in English; (4) are aged between 16 and 29 years; (5) are not known to be HIV-infected; (6) report insertive or receptive anal intercourse with a man or transwoman in the last 12 months; (7) reside within the New York City metropolitan area; (8) are willing to participate in a study for 6 months; (9) have a working email address and phone number to receive texts, calls, or emails for follow-up data collection; and (10) provide informed consent or assent for the study. Participants

are ineligible if they are enrolled in any other HIV-related research study involving HIV testing, have been a participant in an HIV vaccine trial, or are currently taking PrEP.

Recruitment occurs via online advertising, face-to-face outreach, and referrals by study participants. For online recruitment, persons who click on an ad and are deemed eligible from a brief eligibility assessment on the study website are asked to complete a short online contact card. For face-to-face recruitment, potentially eligible individuals are told about the study and given a brief eligibility assessment. Those who are deemed eligible are asked to provide a phone number or email address for study staff follow-up. If screening for eligibility is not possible, staff collect contact information so the person can be screened over the telephone. Participants can refer up to three people for the study and receive US $10 for each person who attends a baseline visit. Staff use the contact information from interested and preliminarily eligible persons to email, text, or call to schedule a study visit.

Study Procedures

After giving informed consent, participants are asked to provide extensive contact information to assist with study retention. Participants are then introduced to the All About Me computer-based platform with short videos describing the study (Figures 1 and 2; Multimedia Appendix 1: What is All About Me?).

The platform is comprised of four sections: (1) staff-only section for entering participant ID number and randomization assignment; (2) a quantitative baseline assessment; (3) information about each HIV testing method (each represented with a GIF; Figure 3), including how the tests are conducted (blood, oral sample) and availability of counseling and support; and (4) the intervention or control conditions (described subsequently).

Figure 1. All About Me platform introductory page (persons shown in photographs are models and are not actual study participants).

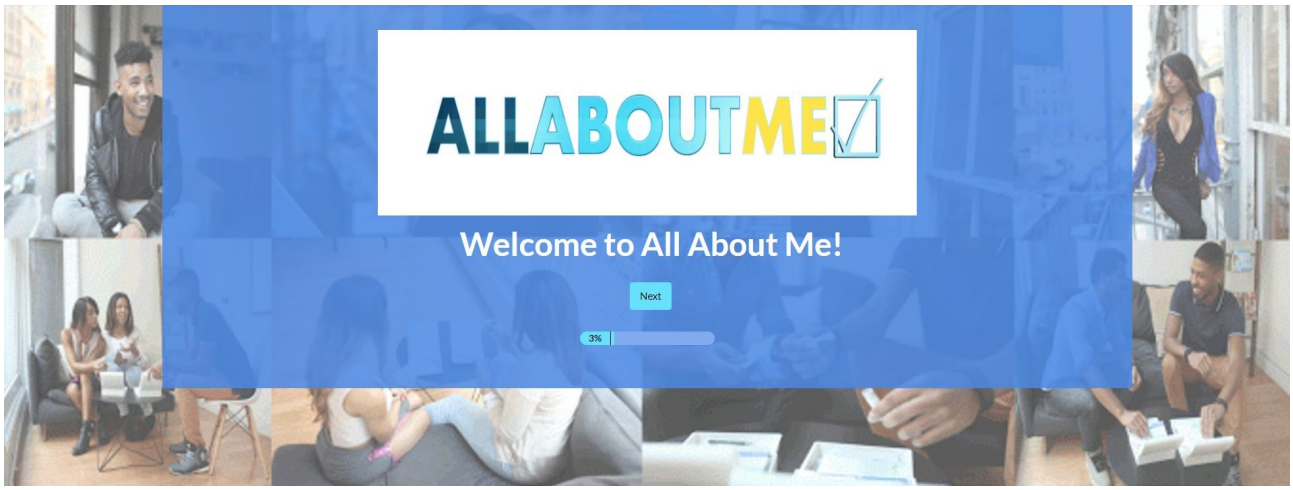


Figure 2. Still from video describing All About Me trial.

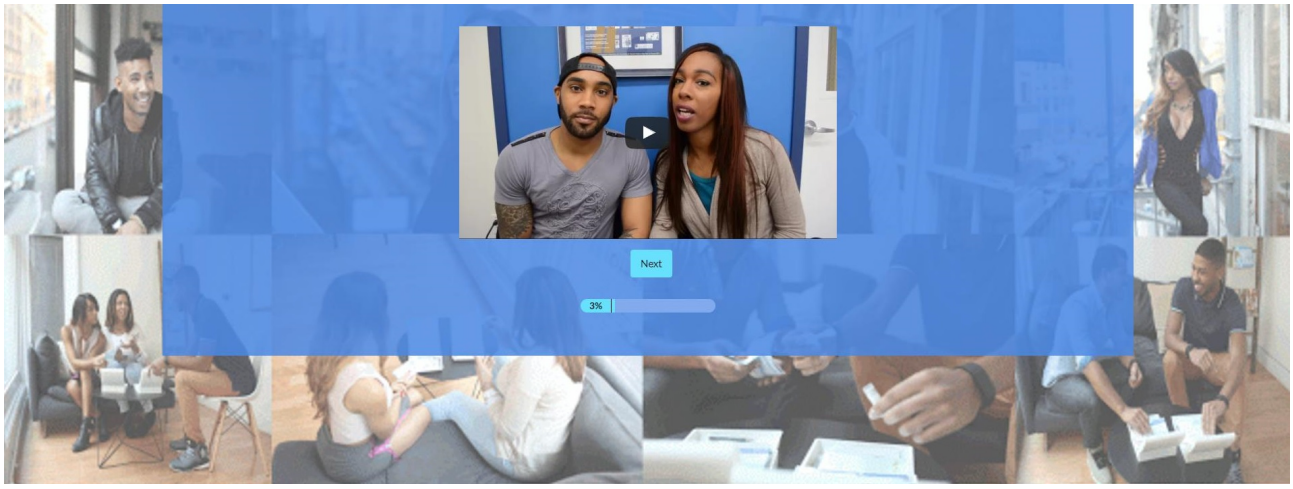


Figure 3. Stills from GIFs describing HIV testing approaches.

Still from clinic-based testing GIF

Still from couples HIV testing and counseling GIF

Still from self-test GIF

The baseline assessment covers demographics; HIV testing history, including use of self-testing and couples HIV testing and counseling; and sexual risk behaviors and substance use in the prior 3 months. Questions about sexual behaviors in the prior 3 months include the number of anal or vaginal sex partners, insertive and receptive anal sex, condom use, and HIV status of partners. Questions about use of substances in the prior 3 months include marijuana, stimulants (powder cocaine, crack cocaine, methamphetamine), prescription drugs, poppers, erectile dysfunction drugs, and club drugs [38]. Presence of depressive symptoms is measured with the Patient Health Questionnaire 2 (PHQ-2) [39]. HIV stigma is measured with a scale of eight items, such as "If you talk too much about HIV, people will think that you have HIV" with a four-point response scale of strongly disagree to strongly agree (α=.88) [40]. Participants receive US $25 cash for completion of the baseline visit.

Randomization

Participants are randomized in a 1:1 ratio into one of the two study arms. Randomly ordered block sizes of four and six stratified by age (16-23 and 24-29 years) are generated by the study data analyst (VN) using Sealed Envelope Ltd [41]. Assignments are placed in sequentially numbered, opaque, sealed envelopes. After informed consent, the next envelope is opened and the staff member enters the participant's study ID number and the assignment into the All About Me study platform. Neither staff nor participants are blinded to study arm assignment.

Follow-Up Surveys

For assessment of primary and secondary outcomes as well as covariates, participants are sent a link to 3- and 6-month follow-up surveys by email. The quantitative assessment includes the same questions as in the baseline survey, excluding some demographics. After the final survey at 6 months, all participants are offered the intervention algorithm to provide them with a personalized HIV testing approach. If a participant reports testing HIV positive in one of the follow-up surveys, the participant remains in the study and staff contacts the participant to provide resources for linkage to care and social services, as needed.

Incentives

To provide the participants with a choice of gift cards from a range of companies, we contract with a promotion code redemption site to distribute a US $25 e-gift card for completion of the 3-month survey and a US $30 e-gift card for completion of the 6-month survey.

Intervention Development

The intervention is modeled after a successful computer-based assessment to improve contraceptive method choice and continuation of use among women at urban publicly funded family planning centers [42,43]. To inform the development of

the intervention, a formative mixed method research phase of in-depth interviews and quantitative surveys was conducted, framed broadly within social cognitive theory [44,45] and several midrange theories, including the theory of planned behavior [46], stigma theory [47], social identity theory [48], and social norms theory [45]. In-depth interviews identified barriers and facilitators to HIV testing and knowledge about HIV testing approaches (self-testing, couples HIV testing and counseling, or clinic-based testing) among young black MSM and transwomen with a particular focus on the potential influence of sociodemographic, psychosocial, mental health, and sociostructural factors on HIV testing uptake, and assessed participant perspectives on the intervention that may enhance its effectiveness in increasing HIV testing [49].

The computerized algorithm that provides a personalized recommendation of the optimal HIV testing approach for individuals was based on the findings from a quantitative survey described previously [38]. The survey collected data on intentions to test by self-test, couples HIV testing and counseling, and at a clinic or other provider, as well as awareness and comfort levels with specific testing modalities, sociostructural factors, behavioral risk, peer norms, social support, and stigma [38]. Stepwise selection multivariable modeling identified variables statistically independently associated with intention to test by each of three specific HIV testing methods (Table 1; reported previously in [38]). In the intervention section of the All About Me platform, three probabilities of intention to test from this algorithm are calculated for each participant, one for each testing method. We developed decision rules that use these probabilities for calculating that participant's personalized HIV testing approach. Specifically, the testing approach with the highest probability for an individual is the recommended testing approach. If the probability for all three testing approaches is less than .45 (suggesting that none of the methods are strongly indicated) then testing at a clinic or other provider is recommended. If the probabilities for two approaches are within .05 of each other, then the recommendation is to test by either method.

Forty-two case studies with varied combinations of factors associated with testing were presented to the research team members who were not involved in the quantitative survey analysis to compare their recommendation to the computer algorithm. For example, one case was a young black MSM with a high school education and who has health insurance. He is comfortable testing at home with a friend or partner. He has a low level of social support and HIV testing self-efficacy. He cites stigma/fear as a reason not to test. Using the algorithm and the decision rules, this individual would receive a recommendation of self-testing. There were no cases in which the algorithm recommendation was determined to be an unacceptable recommendation by the team, even when taking into account case study psychosocial (eg, social support) and structural issues (eg, incarceration history).

Once the initial intervention interface was developed, feedback was obtained from the study Community Consulting Group and two focus groups of young black MSM and transwomen. A second Community Consulting Group meeting and two additional focus groups were held to demonstrate the intervention and to obtain feedback on the graphics and usability of the online intervention. For the final step in the intervention development, a small pilot study was conducted with 10 young black MSM and transwomen to obtain data on the usability of the online intervention. The participants tested the intervention at the study site and had a debriefing interview with trained study staff to describe the acceptability, clarity, and utility of intervention (eg, experience with the study platform, attractiveness of the graphics and layout, culturally appropriate language, clear HIV testing information, ease of use). Final changes to the intervention were completed based on pilot results.

Table 1. Stepwise selection multivariable analysis for intention to test by specific testing approaches, All About Me Study (N=169).

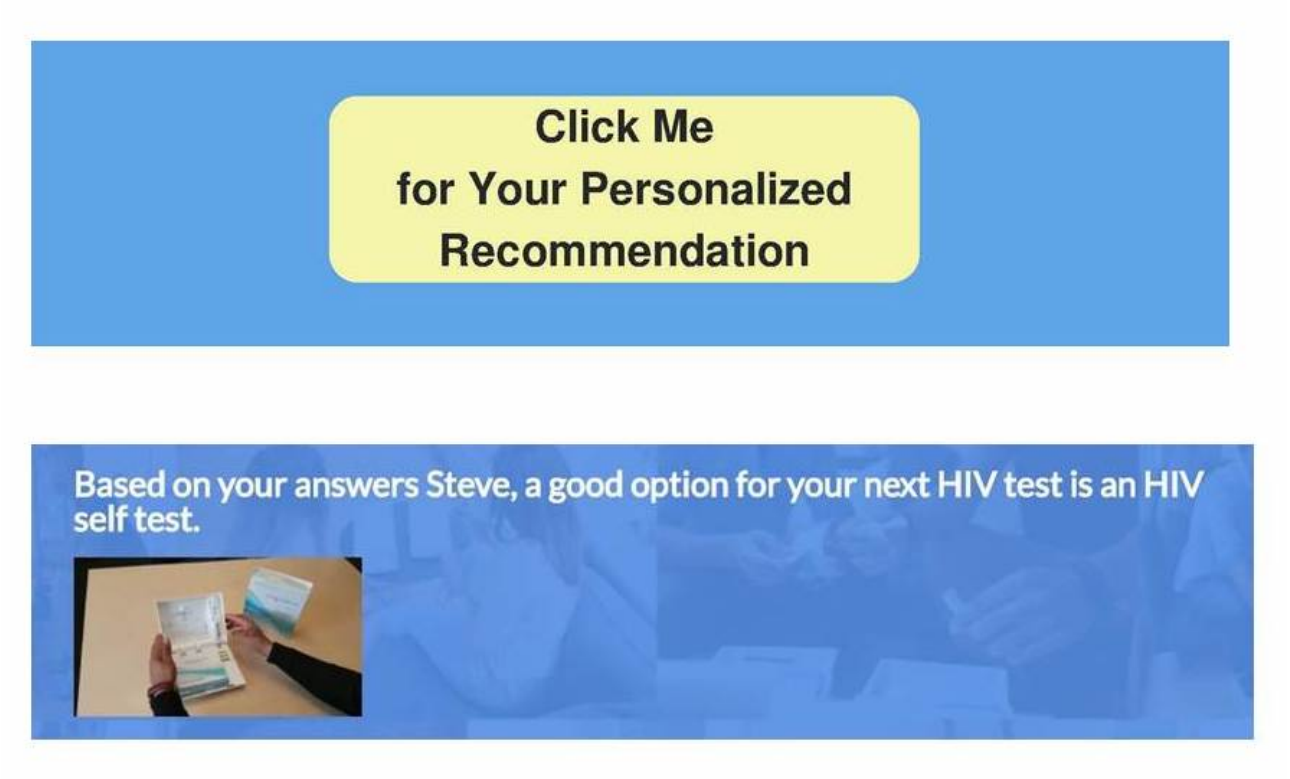
Variables	Intention to test by..., aOR (95% CI)[a]		
	Self-test[b]	Clinic or other provider[c]	Couples HIV testing and counseling[b]
Comfort in testing by a friend or partner at home	2.4 (1.1-5.3)		
Stigma or fear as a reason not to test	8.6 (2.5-29.7)		
Social support (per point higher)	0.5 (0.3-0.7)	2.0 (1.3-2.9)	
Health insurance	0.2 (0.1-0.5)		
Self-efficacy for HIV testing (per point higher)		2.9 (1.5-5.6)	
Lifetime history of incarceration		0.4 (0.2-0.9)	
Some college/associate's degree vs high school grad or less			0.8 (0.4-1.7)
Bachelor's degree or higher vs high school grad or less			0.3 (0.1-0.7)
Have a primary partner			1.8 (1.0-3.5)

[a]aOR: adjusted odds ratio.

[b]Self-test and couples HIV testing and counseling outcomes: very likely / somewhat likely versus somewhat unlikely / very unlikely.

[c]Clinic outcome: very likely versus somewhat likely / somewhat unlikely / very unlikely.

Figure 4. Personalized HIV testing approach.



Intervention and Control Conditions

Intervention Arm

Participants assigned to the intervention arm answer questions to assess factors required to complete the algorithm (Table 1: educational level, health insurance, incarceration history, primary partner, stigma or fear as a reason not to test, HIV testing self-efficacy scale, comfort testing with a friend or partner at home, social support scale). They then receive the results of the HIV testing algorithm, presented as their personalized HIV testing approach (Figure 4).

Participants recommended to clinic-based testing are presented with a widget [50] to find an HIV testing site. The widget can be sent to their phone via email or text. Participants recommended to the self-testing approach are given one of three options to receive a free self-test kit: (1) buy the kit and bring the receipt to the study site for reimbursement, (2) receive a code by text or email to order a test kit online to be mailed to them from OraSure, or (3) receive a coupon by text or email to pick up a self-test kit at the study site. Participants recommended to couples HIV testing and counseling are given a listing of free HIV testing sites that offer couples HIV testing and counseling. The list can also be sent to their phone by email.

Control Arm

Control participants are provided with information about ways to test by each testing approach but without a recommended approach. Thus, they are presented with all the following: a widget to find an HIV testing site that can be sent to their phone via email or text, information on how to obtain a self-test kit, and a list of free HIV testing sites that offer couples HIV testing and counseling that can also be sent to their phone by email.

To reduce the potential bias of the cost of self-test kits as a factor in future HIV testing, when an intervention participant is recommended a HIV self-test kit and offered a free kit, the next control participant in the same age strata is also offered a free self-test kit.

Outcomes

The primary outcome is self-reported occurrence of HIV testing during 6 months of follow-up. Secondary outcomes include use of HIV self-testing and couples HIV testing and counseling and, for intervention participants, testing methods used compared to algorithm-recommended methods.

Statistical Analysis

Analysis of outcomes will be conducted on an intention-to-treat basis. Descriptive analyses will identify outliers (including potential erroneous values), need for variable transformations to enable statistical comparison, and baseline comparability of treatment arms. To account for potential biases resulting from those who discontinue participation, dropouts will be compared to completers by intervention and control group assignment with respect to baseline behavior and other characteristics to test whether differential dropout could influence results. Sensitivity analyses in which dropouts are considered failures will also be done.

Contingency tables (with odds ratios, relative risks, and exact tests) or means/medians (with *t* tests or rank tests) will be used to compare baseline characteristics among study arms. For each time point considered, the binary outcome of primary interest will be compared between the intervention and control arms using contingency tables with odds ratios, relative risks, and exact tests. Pooled analyses of multiple time points will be done using generalized estimation equations with logit link and the

person as a cluster. If time to event is indicated, then Kaplan-Meir, proportional hazards, or discrete logistic regression analogs will be used. Comparisons will be adjusted for other covariates as needed using linear/logistic regression or proportional hazards models, as appropriate. Analyses will be stratified by specific covariates to test for modifying effects on the intervention, when needed. Similar approaches will be used to compare dropout and missing longitudinal data between intervention arms, and if these differ between study arms, a sensitivity analysis approach will be used to adjust for potential impact of this on comparisons of the study outcomes.

Sample Size

Hypothesis testing is two-sided with α=.05. We have enrolled 236 participants (118 per arm) and we estimate 15% attrition at 6 months and thus 100 participants per arm. With a range of testing uptake of 20% to 50% in the control arm, we have 80% power to detect an increase of at least 23% (ie, from 20% to 43% or 50% to 83%) in HIV testing uptake in the intervention arm [51].

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) has been convened, comprised of experts in HIV testing related to our priority population of black MSM and transwomen. All members are independent of the trial and funding agency. The DSMB determines safe and effective conduct of the trial and recommends conclusion of the trial if significant risks develop or if the trial is unlikely to finish successfully. Monitoring calls occur every 6 months and evaluation is conducted of the progress of the trial, including periodic assessments of participant recruitment, accrual and retention, participant risk versus benefit, and other factors that may affect study outcomes. Monitoring may also consider factors external to the study when interpreting the data, such as scientific developments that may have an impact on the safety of the participants or ethical issues related to the study.

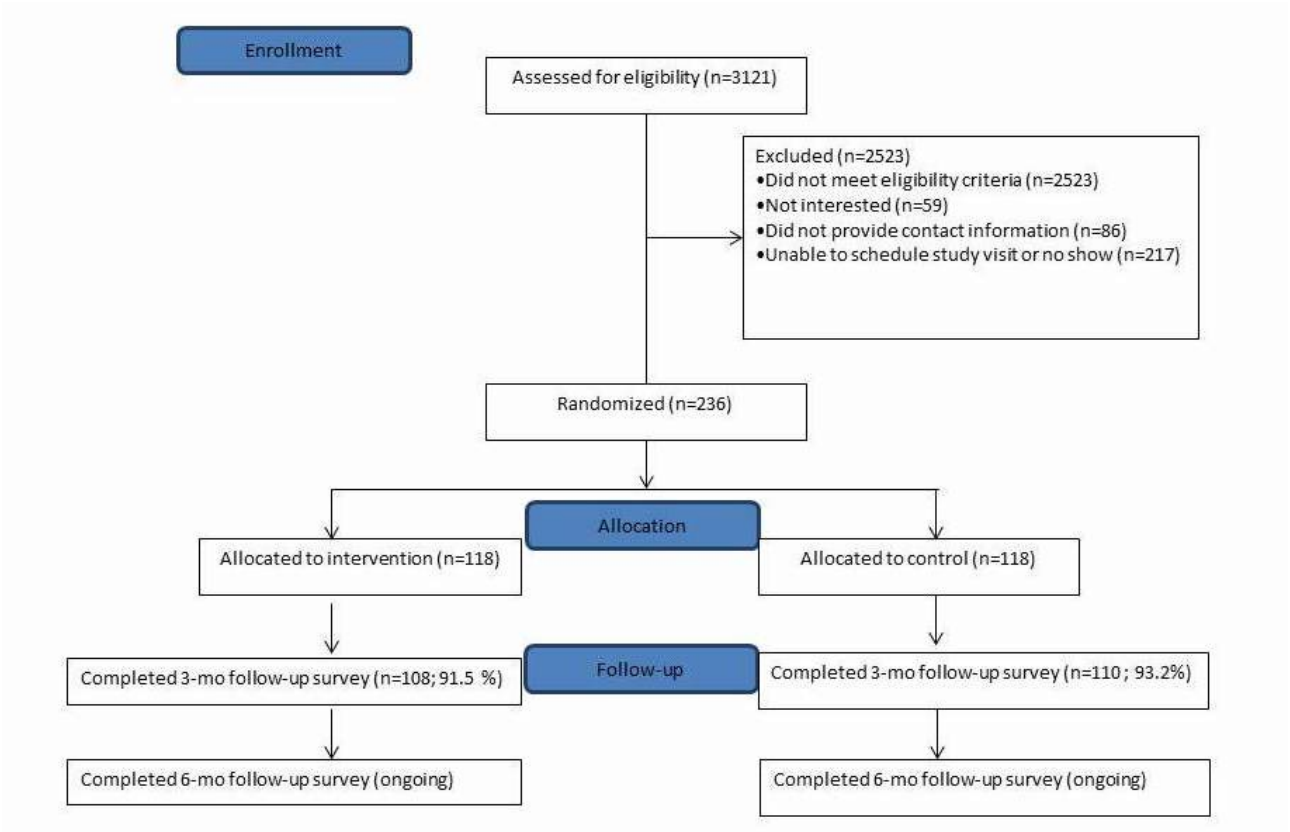
Institutional Review Board Approval

The study was approved and is reviewed annually by the Institutional Review Boards of the New York Blood Center, Public Health Solutions, and Binghamton University. A Certificate of Confidentiality was obtained from the funder.

Results

The trial was initiated in June 2016. Enrollment and randomization of 236 participants were completed in February 2017 with 118 participants randomized to the intervention arm and 118 to the control arm (Figure 5). Retention for follow-up surveys has been high. The visit windows for the 3-month surveys are now closed, with a retention rate of 92.4% (218/236). Six-month surveys are ongoing and the current retention among those with closed visit windows is 93.0% (107/115).

Figure 5. CONSORT flow diagram.



Discussion

The HIV epidemic among young black MSM and transwomen in the United States is an urgent public health problem. HIV diagnosis is essential for care and treatment and to reduce HIV transmission; regular HIV testing is critical for HIV prevention among persons at risk.

To this end, an option such as self-testing may increase HIV testing among young black MSM and transwomen by allowing them to test privately, at their convenience, alleviating the burden of having to access traditional testing venues, which carry potential stigma and confidentiality concerns. At the same time, for some, self-testing may not be appropriate (eg, lack of privacy at home, need for social support), thus warranting testing at an HIV testing site with a counselor. Alternatively, couples HIV testing and counseling by a trained counselor could provide the opportunity to test and receive test results with a partner, a potential source of social support.

In this study design, there are some limitations. We considered a longer follow-up period to address the issue of sustainability, but a mobile device intervention will likely have more immediate effects. The primary outcome is self-reported. It would have been difficult to verify HIV testing given the wide range of testing options and venues available.

The All About Me intervention provides an innovative approach that ties these options together and gives individuals a personalized recommendation of their likely optimal HIV testing approach, supported by evidence from the contraceptive field that personalized recommendations increase uptake, coverage, and adherence [42,43]. To access HIV prevention and care, increasing HIV testing as a gateway behavior is crucial. The All About Me intervention optimized for mobile devices and integrated into HIV prevention and care programs provides an opportunity to access large numbers of individuals, especially those who may be less likely to have recently tested and may not otherwise be reached.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

What is All About Me?

[MP4 File (MP4 Video), 82MB - resprot_v6i12e254_app1.mp4]

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Abbreviations

CDC: Centers for Disease Control and Prevention
DSMB: Data Safety Monitoring Board
MSM: men who have sex with men
PHQ-2: Patient Health Questionnaire 2
PrEP: pre-exposure prophylaxis

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Protocol

Clinic Versus Online Social Network–Delivered Lifestyle Interventions: Protocol for the Get Social Noninferiority Randomized Controlled Trial

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Abstract

Background: Online social networks may be a promising modality to deliver lifestyle interventions by reducing cost and burden. Although online social networks have been integrated as one component of multimodality lifestyle interventions, no randomized trials to date have compared a lifestyle intervention delivered entirely via online social network with a traditional clinic-delivered intervention.

Objective: This paper describes the design and methods of a noninferiority randomized controlled trial, testing (1) whether a lifestyle intervention delivered entirely through an online social network would produce weight loss that would not be appreciably worse than that induced by a traditional clinic-based lifestyle intervention among overweight and obese adults and (2) whether the former would do so at a lower cost.

Methods: Adults with body mass index (BMI) between 27 and 45 kg/m^2 (N=328) will be recruited from the communities in central Massachusetts. These overweight or obese adults will be randomized to two conditions: a lifestyle intervention delivered entirely via the online social network Twitter (Get Social condition) and an in-person group-based lifestyle intervention (Traditional condition) among overweight and obese adults. Measures will be obtained at baseline, 6 months, and 12 months after randomization. The primary noninferiority outcome is percentage weight loss at 12 months. Secondary noninferiority outcomes include dietary intake and moderate intensity physical activity at 12 months. Our secondary aim is to compare the conditions on cost. Exploratory outcomes include treatment retention, acceptability, and burden. Finally, we will explore predictors of weight loss in the online social network condition.

Results: The final wave of data collection is expected to conclude in June 2019. Data analysis will take place in the months following and is expected to be complete in September 2019.

Conclusions: Findings will extend the literature by revealing whether delivering a lifestyle intervention via an online social network is an effective alternative to the traditional modality of clinic visits, given the former might be more scalable and feasible to implement in settings that cannot support clinic-based models.

Trial Registration: ClinicalTrials.gov NCT02646618; https://clinicaltrials.gov/ct2/show/NCT02646618 (Archived by WebCite at http://www.webcitation.org/6v20waTFW)

(JMIR Res Protoc 2017;6(12):e243) doi:10.2196/resprot.8068

KEYWORDS

methods; randomized controlled trial; life style; obesity; weight loss; social support

Introduction

Lifestyle interventions have had established efficacy for over a decade but are not widely disseminated largely due to high cost and burden to patients and providers [1]. Online social networks provide an alternative way to interact with, educate, and counsel patients and may be less expensive because clinic visits are the main source of cost and burden in traditional lifestyle interventions [2-5]. Another advantage of online social networks is their capacity to reach large segments of the population without geographical barriers [6]. The majority of US adults who access the Web (79%) have at least one social network account and 56% have accounts on multiple platforms [7]. Data from the Pew Research Center indicates that Twitter is one of the most ethnically diverse online social network platforms; among adult Internet users, 21% of whites, 25% of Latinos, and 27% of blacks report using Twitter [8]. Additionally, many online social network users use these platforms to seek health information and connect with users with similar health concerns [9]. Thus, online social networks represent a promising modality to deliver lifestyle interventions and reach larger populations as well as vulnerable and underserved subgroups.

A growing number of studies have explored using online social networks, such as Facebook [10-12], Twitter [2,13,14], or study-specific online social networks [15,16], as a primary modality to deliver lifestyle interventions. A systematic review of 5 completed studies found weight loss ranging from −0.63 to −5.0 kg over 8 to 24 weeks [4]. A randomized feasibility trial of obese adults (N=70) found that a 6-month Facebook-delivered weight loss intervention was associated with similar weight loss compared with a group conference call-delivered intervention (5.8 kg vs 6.3 kg over 6 months) [10]; however, nonsignificance cannot be assumed to mean noninferiority because the study was not powered to test noninferiority. A series of pilot studies using private Twitter groups to deliver a lifestyle intervention found that this approach was feasible and acceptable, with a mean weight loss of 2.5 kg (3.0%) in 12 weeks [2]. If an online social network–delivered lifestyle intervention resulted in weight loss that was not appreciably worse than the traditional clinic-delivered model, it would provide an option for settings in which clinic-based interventions are not feasible.

The purpose of this paper is to describe the design and methods of a noninferiority randomized controlled trial (RCT) comparing a lifestyle intervention delivered entirely via an online social network with a traditional in-person clinic-based lifestyle intervention among overweight and obese adults. Intervention strategies in both study conditions are based on the Diabetes Prevention Program (DPP), which is considered the gold standard in evidence-based behavioral weight loss programs [17-19] and has been replicated and adapted numerous times [20]. Furthermore, the translational potential and effectiveness of the DPP have been evaluated across several studies. A systematic review and meta-analysis of 28 US-based studies that tested DPP-based interventions in real-world settings indicated an average of 4% weight loss at 12 months [20]. Intervention attendance varied, with the number of core DPP sessions offered positively correlating with the number of core sessions attended, and low attrition rates (10%-16%) were observed among studies that implemented the DPP using online or digital versatile disc (DVD) formats [20]. We hypothesize that the social network-delivered intervention will not be appreciably worse than the traditional clinic-delivered intervention in weight loss at 12 months. Secondary noninferiority outcomes are changes in dietary intake and physical activity from baseline to 12 months. We also hypothesize that the social network–delivered intervention will cost less per participant to implement than the clinic-based intervention. Exploratory outcomes include treatment retention, acceptability, and burden. We hypothesize that the online social network condition will have better retention and acceptability, with lower participant and clinician burden. We will also explore predictors of weight loss in the online social network condition. We hypothesize that greater engagement, younger age, higher sociability, neuroticism, openness, and greater social network use will be associated with greater weight loss in the online social network condition.

Methods

Study Design

This study is a noninferiority RCT comparing a lifestyle intervention delivered entirely via the online social network Twitter (Get Social condition) with an in-person group-based lifestyle intervention (Traditional condition) among overweight and obese adults. The use of the noninferiority design provides enough statistical power to establish that one modality is not appreciably worse than another [21].

Study Population

A total of 328 overweight or obese adults will be randomized to the two conditions. To be eligible for participation, participants must meet the following inclusion criteria: (1) a body mass index (BMI) between 27.0 and 45.0 kg/m^2, (2) aged between 18 and 65 years, (3) written clearance from their primary care providers, (4) possession of a smartphone, (5) an active social media user (ie, currently have an online social network account and log in at least 4 days/week), and (6) an interest in losing weight. Participants with a personal Twitter account will be asked to set up a separate Twitter account to use for participating in the study. Twitter allows users to have multiple accounts, and linked accounts can be toggled back and forth with a click on the Twitter app.

Individuals who meet any of the following criteria will be excluded from study participation: (1) plans to move during study, (2) pregnant, lactating, or plans to become pregnant during the study, (3) taking medication that influences weight, (4) participating in a formal weight loss program (eg, Weight Watchers), (5) lost 5% or more weight in the past 3 months, (6) bariatric surgery or plans to undergo surgery during the study

period, (7) a medical condition that precludes dietary or physical activity changes, (8) type 1 diabetes reported by the participant or their primary care provider or uncontrolled type 2 diabetes determined by the participant's primary care provider in a medical clearance letter, (9) currently smoking more than 3 cigarettes per day, and (10) preference for one condition over the other. Participants who do not complete baseline measures, do not agree to be randomized, and do not participate in a study orientation webinar will also be excluded.

Participant Recruitment

Study participants will be recruited from the local Central Massachusetts area in 9 waves of 36 to 37 participants. Participants will be recruited from the community, including online recruitment sources such as Craigslist, Twitter, postings in local Facebook groups (eg, local parent groups), the University of Massachusetts Medical School and UMass Memorial Health Care employee and student intranet, online newsletters, print newspapers, mass emails, and flyers in local community locations. We will also recruit participants through paid ads on Google, Facebook, and Twitter. Some recruitment efforts will specifically target males and racial/ethnic minorities, given that previous weight loss intervention trials underrepresent these groups [22]. Targeted recruitment efforts include recruiting participants from Facebook groups that have a high rate of male or racial/ethnic minority presence, recruiting participants from local businesses that have a high racial/ethnic minority population or that serve male clientele, and engaging a community leader to serve as a consultant on the study to aid in racial/ethnic minority recruitment efforts. Interested participants will email or call study staff to complete a telephone screening call, which will consist of a review of information about the study and an eligibility assessment. Eligible participants will be scheduled for a 1.5-hour baseline visit, which will include a review of written informed consent, physical measurements, a baseline survey, and the first of three computer-based 24-hour dietary recalls. Participants will be asked to provide the name of their primary care provider so he/she can be contacted for medical clearance. Participants will be asked to complete a randomization agreement that first explains randomization and asks participants specific questions about their understanding of each condition. Finally, participants will complete two additional computer-based dietary recalls at home over the following week. Participants will be provided US $30 after completing the baseline assessment.

Study Orientation Webinar

Before randomization and after completing the baseline assessment, participants will attend a 1-hour orientation webinar, adapted from the model used successfully in two other previous completed weight loss trials [23,24]. During the webinar, a study staff member will describe all aspects of the study, what it means to participate in research, what it means to be randomized, the importance of follow-up data to the integrity of the study, and what study participation entails. Attendees will have the opportunity to ask questions and to discuss the pros and cons of participation.

Randomization

Each wave of participants will be randomized 1:1 to the two study conditions in randomly permuted blocks of sizes 4 and 6 using the ralloc program in Stata (Stata Corp) [25]. Randomization will be stratified by gender (male vs female) and baseline BMI (27.0-34.9 kg/m^2 vs 35.0-45.0 kg/m^2).

Orientation Visits

Get Social Condition

Twitter was selected as the online social media platform for intervention delivery for several reasons. First, using a commercial platform saves the cost of developing a separate platform. Second, only 24% of the population uses Twitter, so most participants will not be users, unlike Facebook on which 79% of the population has a Facebook account [7]. To the extent that users utilize one of their personal social media accounts for the study, the intervention material will compete with the rest of the users' newsfeed, which could affect treatment receipt even among highly motivated users. In terms of having a separate account for the study, Facebook discourages single users having multiple accounts and has features that make it difficult to do so (eg, cannot use the same name or phone number on two accounts). Twitter makes it easy for users to have two accounts, and once accounts are linked, users can just click a button on the Twitter app to move from account to account without logging out of one and into the other. Finally, Twitter has very simple privacy settings (either all private or all public) which helps quell privacy concerns that arise in the context of complex, often changing privacy settings.

Participants randomized to the Get Social condition will attend individual and group orientation visits before the intervention. Given that all participants are locally recruited and could be randomized to either the Get Social or Traditional condition, we opted for in-person orientation visits to ensure that participants understand how to use the technology, though conducting the orientation visit via webinar may be a preferred method for future effectiveness trials.

At the individual orientation visit, participants will learn how to set up and use a private Twitter account. Twitter's privacy setting protects one's tweets from being viewed by anyone except those approved by the user. All participants and the dietitian use the "protected" privacy setting so that all interactions are only viewable to each other, thus creating a private group on Twitter. Participants are informed that their followers can see their username, Twitter handle, and profile picture. They will be urged to select aliases and avatars to represent themselves in the biographical section of their account to protect their anonymity. At start-up, participants will be asked to hold off on following nonstudy accounts so that their newsfeed is exclusively for the group. However, as the program posts become less frequent in the later phases of the intervention, they will be given suggestions for evidence-based healthy lifestyle feeds to follow to grow their social network. Participants will be advised not to post anything they feel uncomfortable posting and to remain on topic. Participants who wish to have a private exchange with a dietitian or a fellow participant will be instructed to use the Twitter direct message

feature, which allows private one-on-one communication between users. Participants will also be oriented to the study blog and instructed to log in with all devices they use regularly so that their time spent on the blog can be tracked for the cost analyses. The study blog will contain papers that dietitian posts occasionally, with a link to provide more information on a topic.

At the group orientation, participants will follow the dietitian and all other participants in their group on Twitter will receive instruction on ways to participate and practice tweeting. They will receive instruction on how to get the most out of the intervention, including guidelines to read the daily posts by the dietitian, to read and reply to each other's posts, to post about their progress and challenges, and to ask the dietitian or group any questions that come to mind. They will also learn about the DPP lifestyle intervention, program goals for weight loss and physical activity, and how to use MyFitnessPal for dietary and exercise self-monitoring. A mobile app for tracking is necessary in the Get Social condition because dietitians will not have physical contact with participants to exchange paper records. Instead, they can access participants' data by logging into their account. Protocols for the individual and orientation visits were developed based on a series of pilot studies [2].

Traditional Condition

Participants in the Traditional condition will attend a group orientation visit. At this visit, participants will learn about the DPP lifestyle intervention [26] program goals for weight loss and physical activity, as well as how to use MyFitnessPal for dietary and exercise self-monitoring. To avoid an imbalance across conditions in terms of mobile app versus paper-and-pencil tracking, participants in the Traditional condition will also be encouraged to use MyFitnessPal to track their diet and activity. However, participants preferring paper-and-pencil tracking or use of a different app will be allowed to use these instead.

Study Conditions

Participants in both study conditions will receive a 12-month lifestyle intervention based on the DPP. The DPP includes instruction in self-monitoring of food intake, nutrition, exercise, and behavioral modification [26]. The DPP was chosen for this study, given the ample efficacy data for weight loss and disease prevention [27-31]. Three dietitians who received training in both conditions will be randomly assigned to one condition each wave, alternating between conditions. By the end of the study, each dietitian will have led the same number of groups for the online social network and in-person modalities.

Get Social Condition

Participants randomized to the Get Social condition will receive 12 months of lifestyle counseling via a private Twitter group. For months 1 to 2 of the intervention, the dietitian account will post twice daily, for months 3 to 6 the dietitian account will post once daily, and for months 7 to 12, the dietitian account will post 4 times weekly. The frequency and spacing of these interactions correspond to the frequency and spacing of in-person visits that occur in the DPP.

Each DPP session was distilled into a collection of 14 tweets that met all visit objectives [32,33]. Tweets are of the following types: text only; a combination of text and an image of an excerpt of the original materials; a combination of text and an image that reflects the content of the text, polls, and text; and a link to a study blog post or other online resource that elaborates on the topic. The latter are used for more complex topics. The study blog was created with free blogging software, and blog posts were created in the format and length that is commonly seen in patient-oriented blogs (eg, 800 words with images). Content tweets will come from the dietitian's feed. To reduce interventionist burden, the tweets are automated and prescheduled to appear at 5 AM and 4 PM twice daily on weekdays and 5 AM once daily on weekends. The dietitian then logs in twice daily to field responses to the automated posts, answers and poses questions, tweets "check ins" to participants who have not engaged recently, replies to participants, "likes" participants' replies and posts, and replies to private direct messages.

Every Friday morning post will ask participants to reply to report their weight change from the previous week. This approximates the "weigh-ins" that occur in the Traditional condition, while protecting their privacy by focusing on change in weight from the previous week (eg, +1 lb and −1 lb) rather than absolute weight. To encourage participants to check their Twitter feed, participants will be informed of the various ways they can receive notifications (eg, emails and pop-ups) and will be encouraged to set notifications of their preference. They will be advised to log in daily to read the counselor's posts and to engage with the group. Each week, a newsletter will be emailed to participants to encourage participants to engage with the group and to highlight some of the newsfeed from that week in case any participants miss the content when it is posted.

Traditional Condition

Participants randomized to the Traditional condition will receive 12 months of lifestyle counseling via clinic-based group meetings lasting 90 min per session. Participants will receive the Core of the DPP Lifestyle Intervention Core intervention for 6 months, followed by monthly group meetings for another 6 months (total of 22 sessions) [26]. For months 1 to 4, groups will meet weekly; for months 5 to 6, groups will meet biweekly; and for months 7 to 12, groups will meet monthly. Before each session, the dietitian will privately weigh each participant. Participants who miss groups will be emailed the session content.

Follow-up Assessments

At 6 and 12 months, participants will complete an in-person study visit. Follow-up assessments include physical measurements, a follow-up survey, and the first of 3 computer-based 24-hour dietary recalls. Two additional computer-based dietary recalls will be completed randomly at home over the following week. Participants will receive US $40 after completing the 6-month follow-up assessment and US $60 after completing the 12-month assessment.

Measures

Primary Noninferiority Outcome: Percentage Weight Loss

Trained personnel will measure participants' height and weight using a digital scale and stadiometer with the participant wearing light clothing and no shoes; measurements will be taken to 2/10th of the nearest inch or pound. Percentage weight loss at 6 and 12 months will be calculated by subtracting follow-up weight from baseline weight divided by baseline weight.

Secondary Noninferiority Outcomes: Energy Intake and Physical Activity

To assess energy intake, participants will complete three 24-hour diet recall interviews over 2 weeks surrounding baseline, 6-, and 12-month in-person study visit using the National Cancer Institute's (NCI) automated self-administered 24-hour dietary recall (ASA24) [34]. One recall will be done at the baseline assessment visit so that the participant can learn the program and be assisted if needed. The remaining two baseline recalls will be completed at home on randomly selected days (2 weekdays and 1 weekend day). The 6- and 12-month assessments will be completed in the same manner. Daily energy intake and other nutrients for each recall will be estimated using the United States Department of Agriculture's Food and Nutrient Database, and the average of the three recalls will be used at each study visit.

To assess physical activity, participants will complete the 74-item Arizona Activity Frequency Questionnaire [35] at baseline, 6, and 12 months. Output will be calculated in number of minutes per day of moderate or higher intensity activity. Questionnaire assessments will be completed online using REDCap. The online link will be sent to participants to complete at home, and it will take approximately 1 hour to complete.

Cost

We will systematically track costs associated with delivery of both intervention conditions, capturing information on the costs that would be required to implement each intervention in practice (ie, outside the research context), including administrative, interventionists, and participant costs [36-38]. Time and other costs related to tasks performed to develop the interventions or to carry out the research, such as recruitment and study assessments, will not be included, as our interest is in comparing how much it would cost to deliver each intervention in real-world settings.

Administrative Costs

We have created an online survey system that will be used to evaluate staff time and money spent on these activities. Staff will record how much time they spent on each task weekly and any monetary costs (eg, purchase of supplies and copying expenses). In the Get Social condition, administrative tasks include scheduling posts, software (Photoshop and Buffer) for modifying and posting tweets, orientation materials, and conducting the orientation visits. In the Traditional condition, administrative tasks include the purchase or printing of participant materials, sending materials to members who missed the group, orientation materials, and conducting the orientation visits. For staff and interventionist time, we will calculate costs based on actual staff salaries [39] and will conduct sensitivity analyses using national salary data.

Interventionist Costs

Interventionists will report time weekly on a spreadsheet and document each task completed and the time taken to perform each task. Get Social condition interventionist tasks include time spent on the following: reading and responding to participant posts, fielding direct messages from participants, answering questions/concerns or researching information to answer questions, emailing participants who do not post for 2 weeks, and reviewing participant diet diaries. In the Traditional condition, interventionist tasks include time spent on the following: travel for group meetings, leading the group meetings, emailing participants who do not attend the group meetings, answering questions/concerns or researching information to answer questions, and reviewing participant diet diaries. Interventionists will record time spent on each task daily. Estimates for the cost of interventionist time spent traveling round trip to group meetings will be calculated as 5 min/mile for a 5-mile radius from the research center and then 2 min/mile beyond 5 miles based on local traffic patterns around campus.

Participant Costs

Get Social condition participant tasks include the time spent on Twitter to participate in the intervention and time spent reading the study blog. On the weeks the Traditional condition has group meetings, we will contact participants in the Get Social condition via email requesting them to complete a self-report online survey. In these surveys, we will ask participants to report the time they spent on Twitter to participate in the intervention that week and then use these data to estimate total time across all weeks. Participants with iPhones will be asked to report the time spent on the Twitter app under battery usage settings. To assess the time a participant spent on the Twitter app specifically for intervention participation (rather than using the Twitter app for other reasons), we will ask participants whether they access the intervention feed using another device (such as a desktop or a laptop computer or a tablet), and what percentage of the time they spent using the Twitter app was to participate in the intervention, and adjust time estimates from the iPhone battery statistics on their responses. Participants with Android or Windows smartphones will be asked to self-report their time spent on Twitter. Time spent on the study blog will be tracked through Pardot, a company that provides analytics for customers' online marketing campaigns. We will download these data from Pardot every 6 months.

Although participants will register their devices on the blog at baseline, it is possible that participants will access the blog from nonregistered devices. Therefore, the weekly surveys will also ask participants to report how many of the articles that the coach tweeted in the past 7 days they read, and we will compare these self-reported data with data downloaded from Pardot. In the Traditional condition, participant tasks include travel to and from the group meetings from their home address (using the same approach as for interventionist travel costs) and time spent attending group meetings. Time at group meetings for each

participant will be based on the duration of each meeting recorded by the interventionist and attendance records. Participant time will be converted to costs using information about participant income [40]. In the absence of income data, we will use the median or average wages for adults in their state of residence (Massachusetts) [41]. We will conduct sensitivity analyses using national salary data. This approach allows us to estimate the cost of participating in the intervention for adults across the United States.

Exploratory Outcomes

Treatment Retention

We will track which participants drop out of treatment. We have a protocol for reengaging participants who are not actively participating in treatment. In the Get Social condition, staff tweet participants who have not engaged that week and ask them how they are doing. Following the second consecutive week with no visible online engagement, the coach will email the participant. If another week passes with no engagement on Twitter, the coach will call the participant. In the Traditional condition, staff will email the missed intervention materials to participants who miss the group session. Following the second consecutive missed group session, the coach will email the participant. If another group session is missed, the coach will call the participant. We will consider participants who have not engaged in treatment in 4 consecutive weeks and have not responded to our attempts to reengage, as well as participants who express wanting to withdraw from the intervention to have dropped out of treatment.

Acceptability and Burden

At 6 and 12 months, participants in both study conditions will rate the *acceptability* (easy, would be willing to do again, willing to continue, and comfort level) and *burden* (time-consuming and costly) of their treatment condition on 5-point Likert scales.

Predictors of Weight Loss in the Get Social Condition

We will explore predictors of weight loss in the online social network condition, including engagement, age, sociability, neuroticism, openness, and social network use.

Engagement

Engagement data on tweets by interventionists and participants will be downloaded weekly from Twitonomy, a Twitter analytics and monitoring tool. Information on "likes" for each tweet will be downloaded weekly via a script that captures the data from Twitter. We will calculate the number of original tweets, replies, and likes per participant. We will also sum these metrics for a total summary measure of engagement. At 6 and 12 months, we will also ask participants survey questions about lurking (reading without visibly interacting) [42] and calculate metrics of engagement that include lurking.

Age

Participants will report their age at eligibility screening.

Sociability, Neuroticism, and Openness

Participants will complete the Ten-Item Personality Inventory (TIPI) [43] at baseline. Sociability, neuroticism, and openness scale scores will be calculated for each participant.

Social Network Use

At baseline, participants report which online social networks they have accounts on and frequency of online social network use in the past 4 weeks (study survey). Online social network use is expected to be a predictor of weight loss in the Get Social condition because individuals who use online social networks more regularly may be more likely to lose weight than nonregular users as they are more accustomed to using these platforms and engaging online.

Contamination, Treatment Fidelity, and Participant Safety

Contamination

Contamination is defined as the use of other forms of online or in-person weight loss support in either condition during the study. Using the Pew Internet & American Life Project Poll [44] questions, we will evaluate and report the number of participants who received support for weight loss using online or in-person programs, blogs, pages, or connecting with participants.

Treatment Fidelity

We randomly selected one topic within each phase of the study (weeks 1-8, weeks 9-24, and weeks 25-52) for a total of 3 topics (10% of 22 topics). Each topic has the same objectives to meet in both conditions. In the Traditional condition, we have an independent reviewer listen to the recording of the selected group to ensure that each objective was met. In the Get Social condition, the topics span from 1 week to 4 weeks depending on the phase of the study (1 week in phase 1, 2 weeks in phase 2, and 4 weeks in phase 3). The respective weeks of the topic selected will be extracted from Twitter and reviewed by an independent reviewer to ensure each objective was met. Findings will be reported.

Participant Safety

Possible risks during the intervention include injury during exercise or breach of confidentiality. Participants who report conditions at baseline that could create a safety concern while receiving the intervention are excluded. To avoid possible risks, participants are instructed to avoid over exercising at intense levels that could lead to discomfort, pain, or injury. Participants reporting discomfort will be referred to their primary care providers. Participant data are stored in network secure data entry programs, and any data on paper are stored in a locked file cabinet. Adverse events that occur during the intervention are assessed, recorded, and followed up until resolved. Serious adverse events are communicated immediately to the data safety monitoring board and the institutional review board (IRB).

Power Calculation

We powered the study to be able to detect noninferiority [21] for the primary outcome and percentage weight loss at 12 months. In a noninferiority trial, the null hypothesis (H_0) is that the new treatment is inferior to the standard treatment, and the alternative hypothesis (H_A) is that the new treatment is not inferior to the standard treatment. "Not inferior to" is defined by the noninferiority margin, δ. Other noninferiority behavioral weight loss trials have utilized various noninferiority limits depending on the study population, primary outcome, and

timeline. One study examined BMI reduction among adolescents and set δ=0.12 based on a 0.21 reduction of BMI at 12 months [45], whereas another weight loss trial among adults set δ=at 1 kg at 3 months [46]. We set δ=2% as a relative margin to the 5% weight loss as clinically meaningful cut point [47] and because 2% is not so small a difference in average weight loss between study conditions that we would have to recruit a prohibitively large sample. This means that if the Get Social condition loses up to 2% less weight on average than the Traditional condition, we will consider the Get Social condition to be noninferior to the Traditional condition. Thus, adequate power for clinical noninferiority requires a sample size such that there is better than 90% probability that the lower limit of the CI lies above –δ, if the true effect size is zero or above. We estimated standard deviation (SD) of 5.5% based on a previous, fully powered randomized trial [48]. With alpha=.05 and δ=2%, we have 90% power to conclude that the Get Social condition is not inferior to the Traditional condition with 131 participants per arm. Accounting for 20% attrition, we will enroll 328 participants in total (164 per arm). We considered adjusting the sample for intraclass correlation, but previous research shows that weight loss does not cluster among members of weight loss treatment groups [49].

For secondary noninferiority outcomes, we used 90% power to calculate noninferiority margins given N=131 per arm, setting alpha=.05 and using observed SDs from the literature. For change in energy (kcal/day) intake at 12 months, the study is powered at 90% to detect that the Get Social condition is not inferior to the Traditional condition with a noninferiority margin of 182 kcal/day (SD=500 kcal/day) [48,50]. For change in moderate to vigorous intensity physical activity minutes per day at 12 months, the noninferiority margin is 9.2 min/day (SD=25 min/day). For percentage weight loss at 12 months, the noninferiority margin is 2.2% (SD=5.5%) [48].

With N=131 available per arm (N=262 total) and alpha=.05, we have 80% power to detect differences in mean cost per participant of 0.35 SDs. For example, if the SD for cost is US $100, then we have 80% power to detect differences in mean cost per participant of US $35. With N=131 available in the Get Social condition and alpha=0.05, we have 80% power to detect correlations of .243 between continuous predictors and 12-month percentage weight loss. For categorical variables, detectable differences in mean percentage weight loss depend on the proportion of the predictor in the sample. For a predictor with 50% prevalence (ie, n=65 and n=66 with vs without the characteristic), we have 80% power to detect differences of 0.49 SDs. For predictors with 33% prevalence, we can detect differences of 0.52 SDs. For predictors with 20% prevalence, we can detect differences of 0.62 SDs, and for predictors with 10% prevalence (ie, n=13 vs n=118), we can detect differences of 0.82 SDs. For estimated SD of 5.5% for 12-month percentage weight loss, this indicates differences of 2.7%, 2.9%, 3.4%, and 4.5% weight loss.

Power calculations for noninferiority analyses were conducted using PROC POWER in SAS 9.3 (SAS Institute, Cary, NC) [51,52] and power calculations for Aims 2 and 3 were conducted in Stata 13 (Stata Corp, College Station, TX).

Analysis Plan

Reporting and data analyses of this trial will follow the recommendation of the 2012 *JAMA* paper *Reporting of Noninferiority and Equivalence Randomized Trials Extension of the CONSORT 2010 Statement* [53]. Analyses will be intent-to-treat, meaning all randomized participants will be analyzed and in their originally randomized conditions.

Preliminary Analysis

Baseline participant characteristics will be examined by condition. If groups differ on any characteristics, these variables will be included as covariates in the primary analyses. Other preliminary analyses will include assessing patterns of missing data, dropout rates, distributional properties of dependent measures, and correlations among outcome measures. A series of sensitivity analyses will be performed to examine the extent of potential bias by assuming that the participants who dropped out are missing completely at random (ie, independent of the outcome), are responders to the intervention, or are nonresponders to the intervention. Multiple imputations to impute missing data will be used if more than 5% of data are missing [54].

Primary Noninferiority Outcome

We will model percentage weight loss at 12 months using a linear regression model framework, with percentage weight loss as the dependent variable and study condition as the independent variable. Test of the intervention condition indicator will provide a statistical test of the intervention effect and the estimated coefficient, along with the estimated confidence interval. This analytic approach aims to test whether the Get Social condition is not appreciably worse than (ie, not inferior to) the Traditional condition by our a priori inferiority margin of 2%. The effect size estimates will reveal clinical noninferiority of the Get Social condition if the CI lies completely above −Δ or clinical noninferiority of the Traditional condition if the CI lies completely below +Δ, that is, 2%.

Secondary Noninferiority Outcomes

Secondary noninferiority outcomes (dietary intake and physical activity at 12 months) will be examined using the same approach as described for the primary outcome. Linear multivariable regression models will be used to estimate change in daily caloric intake at 12 months; such models are reasonable, given the target sample size and that changes in these outcomes are approximately normally distributed [48,55]. We anticipate using log transformation to estimate change in physical activity variables, given that physical activity data tend to be skewed. The distribution of secondary outcomes will be explored graphically and inform the primary outcome analysis; analyses will be modified as needed through transformation of the data.

Cost

We will compare total intervention costs per participant and total intervention costs per pound lost by treatment condition. As Ritzwoller and colleagues recommend [37,40], we will conduct sensitivity analyses to estimate the range of costs after varying the inputs (eg, time spent on Twitter by participants, staff pay across settings, and based on qualifications and

training). We will also examine administrative, interventionist, and participant costs by treatment condition. Assuming a normal distribution of total costs per participant, we will first compute *t* tests comparing the average cost per participant across treatment conditions. We will test the null hypothesis of no difference between groups using a two-sided test and alpha=.05. If total cost per participant is not normally distributed, a nonparametric approach using the Mann-Whitney test for median comparisons will be used. If participant characteristics are found to differ according to treatment allocation/condition, multivariable linear regression models will be used to adjust for the potential confounding effects of these characteristics. Assuming a normal distribution of total costs per participant, multivariable linear regression models will be used. If not normal, we will identify appropriate transformations (eg, logarithm and square root) for the cost variable.

Exploratory Outcomes (Treatment Retention, Acceptability, and Burden)

We will compare treatment retention (percentage retained in treatment, ie, percentage who has not dropped out of treatment) and ratings of acceptability and burden (measured on 5-point Likert scales) across treatment conditions using chi-square tests.

Predictors of Weight Loss in the Get Social Condition (Exploratory)

Bivariate associations between each potential predictor of weight loss (eg, engagement, age, sociability, neuroticism, openness, and online social network use) and percentage weight loss at 12 months will be examined among participants in the Get Social condition using linear regression models. Multivariable predictors of percentage weight loss at 12 months will be estimated using linear regression models. Variables will be added to the model one at a time, in order of magnitude of the crude effect estimate (largest to smallest; $P<.05$) associated with the outcome. The final model will be selected based on consideration of effect estimates, 95% CIs, and Akaike information criterion.

Results

The first wave of the intervention began in August 2016. Recruitment will continue through May 2018, and we anticipate completing this study by July 2019. Results will be examined at that time.

Discussion

Online social networks hold great potential for delivering lifestyle weight loss interventions for overweight and obese adults. Delivering such interventions through online social networks overcomes many of the barriers of traditional intervention modalities and provides several distinct advantages. First, online social networks address common barriers to participation such as scheduling, transportation, weather, and childcare [2,4,5]. Second, using online social networks overcomes implementation barriers by eliminating the need and costs associated with obtaining physical space for visits, by not limiting patient pool due to daytime work schedules (eg, in-person intervention groups typically must be scheduled on weekday evenings or early mornings, limiting the number of time slots available to treat patients in a week), and by more efficiently using dietitian time. Third, online social networks are highly conducive to increased and immediate (ie, same day) feedback from peers and interventionists. Behavioral theory has long shown that the longer feedback is delayed, the less impact it has on behavior [56]. Fourth, the online social modality may be more conducive to participants building a sustainable social network to support their weight loss journey after the intervention ends. Despite this promise, a limited scientific literature has assessed the efficacy of lifestyle interventions delivered via social network. This study will be among the first to do so. Another strength of this study is the use of targeted recruitment efforts to recruit males and racial/ethnic minority participants. Males have been historically difficult to recruit in behavioral weight loss trials, and racial/ethnic minorities, especially males, are underrepresented in such studies. A review of 244 RCTs of behavioral weight loss interventions indicated that on average, 27% of study samples were male, and 1.8% of participants in US studies were racial/ethnic minority males [22]. Targeted recruitment methods such as the ones proposed in this study are needed to enhance gender and racial/ethnic diversity of study samples and generalizability of study findings.

Limitations of the methods described are as follows. First, it is possible that the time required to deliver intervention via online social networks is the same or more than that via the traditional modality. Being available daily, albeit for short periods of time, may be burdensome for interventionists in different ways than the traditional model. Second, participants in the study must be available to participate in either modality and thus may not represent people who are unable to attend frequent clinic visits, the very people who stand to benefit the most from the social network modality. If hypotheses are confirmed, the next step in this work should be to test the social network–delivered intervention in real-world settings and with patients who are unable to participate in the traditional modality or who strongly prefer an online intervention. Third, use of a social media platform that not all participants are familiar with introduces a learning curve that could be burdensome to some. Difficulties adopting a new technology could impact engagement to the extent that individuals do not prefer the interface, do not already have a habit of using it, or have difficulty understanding the interface (eg, among Twitter users, toggling to a different account might present a barrier to engagement to the extent they forget to switch to the new account). Future research should explore leveraging different commercial social media platforms in the context of behavioral intervention delivery.

Findings from this study may support an intervention delivery modality that is conducive to settings such as worksites, health plans, and clinics that serve large populations but have limited space, staffing, and resources for traditional in-person clinic-based behavioral interventions. If this trial is successful, approaches to dissemination and implementation should be explored as well as models that further reduce interventionist burden to explore how much costs could be reduced while retaining efficacy. Behavior change programming is conducive to delivery via connected technologies such as social media;

thus, if proven cost-effective and more convenient relative to traditional models, connected health models could greatly improve the impact of behavioral interventions of all kinds.

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Conflicts of Interest

None declared.

Authors' Contributions

SLP conceived of the study and research question. MLW drafted the manuscript. SLP, MEW, DEJ, ZM, JLO, SCL, JMG, and YM provided critical revisions for intellectual content. SLP, JLO, DEJ, JMG, and ZM participated in developing intervention materials and procedures. All authors read and approved the final manuscript.

Multimedia Appendix 1

Peer-review report from NIH for Grant 1 R01 DK103944-01A1.

[PDF File (Adobe PDF File), 200KB - resprot_v6i12e243_app1.pdf]

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Abbreviations

BMI: body mass index

DPP: Diabetes Prevention Program
DVD: digital versatile disc
NCI: National Cancer Institute
NHLBI: National Heart, Lung, and Blood Institute
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
SD: standard deviation
TIPI: Ten-Item Personality Inventory

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Protocol

Mobile Health Technology (mDiab) for the Prevention of Type 2 Diabetes: Protocol for a Randomized Controlled Trial

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Abstract

Background: The prevalence of type 2 diabetes is increasing in epidemic proportions in low- and middle-income countries. There is an urgent need for novel methods to tackle the increasing incidence of diabetes. The ubiquity of mobile phone use and access to Internet makes mobile health (mHealth) technology a viable tool to prevent and manage diabetes.

Objective: The objective of this randomized controlled trial is to implement and evaluate the feasibility, cost-effectiveness, and sustainability of a reality television–based lifestyle intervention program. This intervention program is delivered via a mobile phone app (mDiab) to approximately 1500 Android smartphone users who are adults at a high risk for type 2 diabetes from three cities in India, namely, Chennai, Bengaluru, and New Delhi.

Methods: The mDiab intervention would be delivered via a mobile phone app along with weekly coach calls for 12 weeks. Each participant will go through a maintenance phase of 6 to 8 months post intervention. Overall, there would be 3 testing time points in the study: baseline, post intervention, and the end of follow-up. The app will enable individuals to track their weight, physical activity, and diet alongside weekly video lessons on type 2 diabetes prevention.

Results: The study outcomes are weight loss (primary measure of effectiveness); improvement in cardiometabolic risk factors (ie, waist circumference, blood pressure, glucose, insulin, and lipids); and improvement in physical activity, quality of life, and dietary habits. Sustainability will be assessed through focus group discussions.

Conclusions: If successful, mDiab can be used as a model for translational and implementation research in the use of mHealth technology for diabetes prevention and may be further expanded for the prevention of other noncommunicable diseases such as hypertension and cardiovascular diseases.

Trial Registration: Clinical Trials Registry of India CTRI/2015/07/006011 http://ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=11841 (Archived by WebCite at http://www.webcitation.org/6urCS5kMB)

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KEYWORDS

prevention; diabetes mellitus, type 2; mHealth

Introduction

The International Diabetes Federation estimates the global prevalence of type 2 diabetes mellitus (T2DM) to rise to 642 million by 2040 from the current number of 415 million [1]. Three-fourths of this population lives in the low- and middle-income countries (LMICs) such as India [1-3]. Studies in different populations have shown that a large part of T2DM is attributed to factors such as obesity (both generalized and abdominal), sedentary lifestyle, and poor diet [4-7]. Anjana et al [8] assessed the population attributable risks in an urban Indian population and reported that by modifying just two factors, namely, diet and physical activity, up to 50% of new onset T2DM can be prevented.

Several randomized controlled trials (RCTs) carried out on primary prevention of T2DM have shown that lifestyle modification and metformin therapy can reduce the incidence of T2DM in people who are in the prediabetes stage, that is, those having impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), or both [9-16]. However, most of these trials were conducted face to face. This involves a lot of man power, cost, and time. The question arises whether similar results can be obtained using modern technology without the need for face-to-face interaction.

The World Health Organization (WHO) considers mobile health (mHealth) as a component of electronic health (eHealth). The definition of eHealth according to the WHO is “the use of information and communication technologies for health,” and mHealth is defined as “medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices” [17].

It is of interest to note that India stands second worldwide both in the prevalence of type 2 diabetes [1] as well as in the number of mobile phone users [18]. According to the statistics provided by the Telecom Regulatory Authority of India, the number of wireless telephone users in India increased from around 1034 million in April 2016 to around 1174 million in January 2017, that is, 100 million users added within a year [19]. Moreover, the Internet and Mobile Association of India (IAMAI) and Indian Market Research Bureau (IMRB) statistics have also shown that India has the second largest population using the Internet, of which a large number gain access to the Internet using their smartphones. The IAMAI and IMRB prediction for the mobile-based Internet users is that there would be 371 million users by June 2017 from 306 million in December 2016, which represents an increase of 21% in just 6 months [20]. This massive upswing and uptake of technology in the field of mobile technology renders mHealth as a liable opportunity to provide individual-level support beyond traditional clinic-based care technology [17,20-24].

With this background information, we took up a trial of primary prevention of diabetes based on mHealth. The aims of this trial are to understand the feasibility, cost-effectiveness, and sustainability of a reality television–based lifestyle intervention delivered via a mobile phone app along with the support of a health coach for 12 weeks and to evaluate its effect on weight loss, cardiometabolic risk factors, and behavioral and social variables, such as physical activity, quality of life (QOL), and adoption of healthier diet and lifestyle behaviors, in Android mobile phone users who are at a high risk of developing T2DM.

Methods

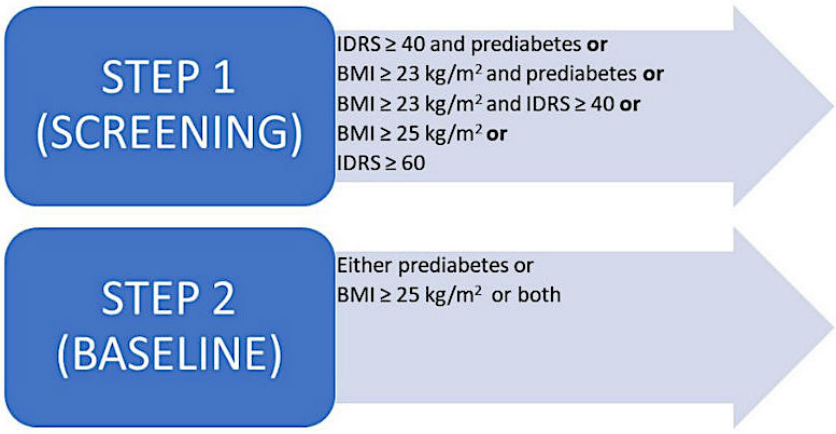
Study Design and Participants

This study is an RCT being conducted at three cities in India (Chennai, Bengaluru, and New Delhi) between 2016 and 2018. Android mobile phone users, between the age groups of 20 and 65 years, are screened for eligibility based on a combination of screening criteria detailed in Figure 1. The rationale for choosing Android users is based on the data published in 2016 that 97% of the mobile phone users in India use the Android operating system [25]. This figure rose from 90% in 2015 [25].

Eligibility Criteria

The screening criteria are designed to ensure that individuals at a high risk of developing diabetes are selected for the study. To select the high-risk group, a combination of the Indian Diabetes Risk Score (IDRS), body mass index (BMI), and capillary blood glucose (CBG) is used.

Figure 1. Eligibility criteria at screening and baseline. IDRS: Indian Diabetes Risk Score; BMI: body mass index.



IDRS is a simplified and validated tool that uses 4 parameters, namely, age, abdominal obesity, family history of diabetes, and physical activity [26,27]. It was shown that a high IDRS score increases with the risk of T2DM, metabolic syndrome, and cardiovascular disease [28]. Generally, an IDRS score of 40 indicates a moderate risk of developing diabetes and a score of 60 indicates a high risk. For the purpose of including a wide range of high-risk population, we classified an IDRS score of ≥40, along with either a BMI indicative of obesity or CBG indicative of prediabetes (IFG=100-125 mg/dL or IGT=110-199 mg/dL) to determine eligibility at screening. However, an IDRS score of ≥60 is considered as an independent criterion to determine eligibility. BMI is an important diagnostic marker for overweight and obesity [29]. We set a cut point of ≥23 kg/m^{2}to indicate overweight and obesity as defined by the WHO Asia Pacific guidelines [30], and this is used in combination with CBG, indicating prediabetes and/or and an IDRS ≥40. However, a BMI ≥25 kg/m^2 is considered as an independent criterion to determine eligibility. The CBG testing is used to identify an IFG of 100 to 125 mg/dL or an IGT of 110 to 199 mg/dL at screening using the WHO cut-offs [31]. The final eligibility criterion for entry into the trial is defined as either an IFG of 100 to 125 mg/dL and/or an IGT of 140 to 199 mg/dL through a 75-g oral glucose tolerance test and/or a BMI ≥25 kg/m^2, indicating obesity at baseline (Figure 1).

The exclusion criteria for the study are participants who are pregnant or breastfeeding, are involved in other wellness programs, whether they have been previously diagnosed with diabetes or have a history or evidence of heart disease or any other serious illness, are children or young people (ie, aged <20 years) or older adults (ie, aged >65 years), or have conditions (such as orthopedic conditions) that would impede participation in this study.

Recruitment

Recruitment is carried out through screening camps at clinic settings, corporates/worksites, residential colonies/gated housing complexes, educational institutions, religious or spiritual institutes, open public spaces, and direct referrals (such as participants referred by study staff and physicians) to cover the general population at large.

If an individual fulfilled 1 or more of the criteria enlisted in Step 1 (Figure 1), they are invited for baseline testing, and each participant is subjected to a panel of tests as detailed in Table 1 to ensure final eligibility into the study (Step 2 in Figure 1). At each site, approximately 3000 people are screened based on the screening criteria shown in Figure 1, and approximately 1000 individuals would be available for baseline testing. The main aim of the baseline visit is to ensure that the individuals screened do not have type 2 diabetes [31] or fall under any other exclusion criteria and that they have understood the requirements of the intervention study. A summary of measures that are conducted at each visit are detailed in Table 1 and Multimedia Appendix 1.

Table 1. Summary of study measures.

Measurements	Screening	Baseline	Post intervention	End of follow-up
Questionnaires				
Short questionnaire	✓			
Questionnaires measuring participants' health habits, diet behavior, quality of life, health-related costs, and physical activity/inactivity		✓	✓	✓
Anthropometry				
Weight (in kg)		✓	✓	✓
Height (in cm)		✓	✓	✓
Waist circumference (in cm)	✓	✓	✓	✓
Body fat (%)		✓	✓	✓
Blood pressure		✓	✓	✓
Indian Diabetes Risk Score	✓			
Biochemical parameters				
Capillary blood glucose	✓			
Venous fasting blood glucose		✓	✓	✓
Postglucose load (2 hours)		✓		✓
Fasting insulin assay		✓	✓	✓
HbA1c		✓	✓	✓
Lipid profile		✓	✓	✓

Randomization

A study staff not involved in the study randomizes the participants into the intervention and control group across sites by the random allocation sequence method using a random numbers table. The randomization grid, which contained only the study unique ID number and inclusion criteria variables, is filled at each site by the site coordinators and sent to the personnel at the central randomization site as per the weekly randomization schedule. The grids are sent back to the sites post randomization. Therefore, the study personnel randomizing the participants are blinded to the group allocation of the participants, whereas the study team and participants at each site are not.

Control Group

The control group participants receive usual care for patients with prediabetes or obesity at all the 3 study sites. They meet a nutritionist once after randomization and receive handouts reinforcing prevention of T2DM through increased physical activity and weight loss. All control group participants are offered access to the app at the end of the study.

The Mobile App Description

An mHealth app called *mDiab* is used by all intervention group participants. mDiab has 12 weeks of video lessons that were created based on the Diabetes Community Lifestyle Improvement Program (D-CLIP) lessons and experiences [16], which in turn were originally developed using the US Diabetes Prevention Program. The video lessons are in the form of a reality television show, where real actors role-play and enact the concepts of lifestyle behavior change. This inspires and motivates the participants viewing the video lessons in the app to change their lifestyles to improve their health. For example, for the video lesson on incorporating a healthy diet, the actors act out ways to help the participant understand the concept and share experiences on the challenges faced while adopting it in real life. They also help in overcoming the challenges by suggesting suitable solutions. Apart from the video lessons, the app also has goal setting, alerts, and small text modules, which are brief write-ups on the video lessons. There are also multiple-choice questions to help reinforce learning. The 12 weeks of video lessons cover various aspects of T2DM prevention, with the goal of reducing diabetes risk through weight loss of at least 5%. The contents of the video lessons are described in Table 2 and Multimedia Appendix 2. Overall, the app has 3 important components—the video lessons as described above, tracking of behaviors, and weekly calls by the health coaches.

Tracking

This feature of the app is meant to enable users to track their diet, physical activity, and weight. The calorie and fat goals provided are based on the D-CLIP study. The participants are encouraged to track their daily food intake. The food database is developed using the Dr Mohan's Diabetes Food Atlas [32] and National Institute of Nutrition's guidelines [33]. The activity tracker automatically counts the number of steps using the mobile phone's inbuilt accelerometer sensor. Additionally, the participant is encouraged to add any specific activity he/she likes to do. The weight tracker sets an initial weight loss goal of 5% and enables tracking. Every participant in the intervention group receives a weighing scale as an incentive to enable them to track their weight. The app sends out standardized reminders and motivational messages according to the progress of each user. Screenshots of the app's tracking features are shown in Figure 2 for better understanding.

Communication With the Health Coach

Health coaches in the mDiab program are trained nutritionists who call participants once a week to inform them about the objectives of the video lessons and their progress and finally email them with a progress report using the data tracked by the respective participant. The participants also have the opportunity to communicate with the health coaches in any case via a message tool inbuilt in the app, and the health coaches respond to the participants in 24 hours.

Procedures

Data Collection

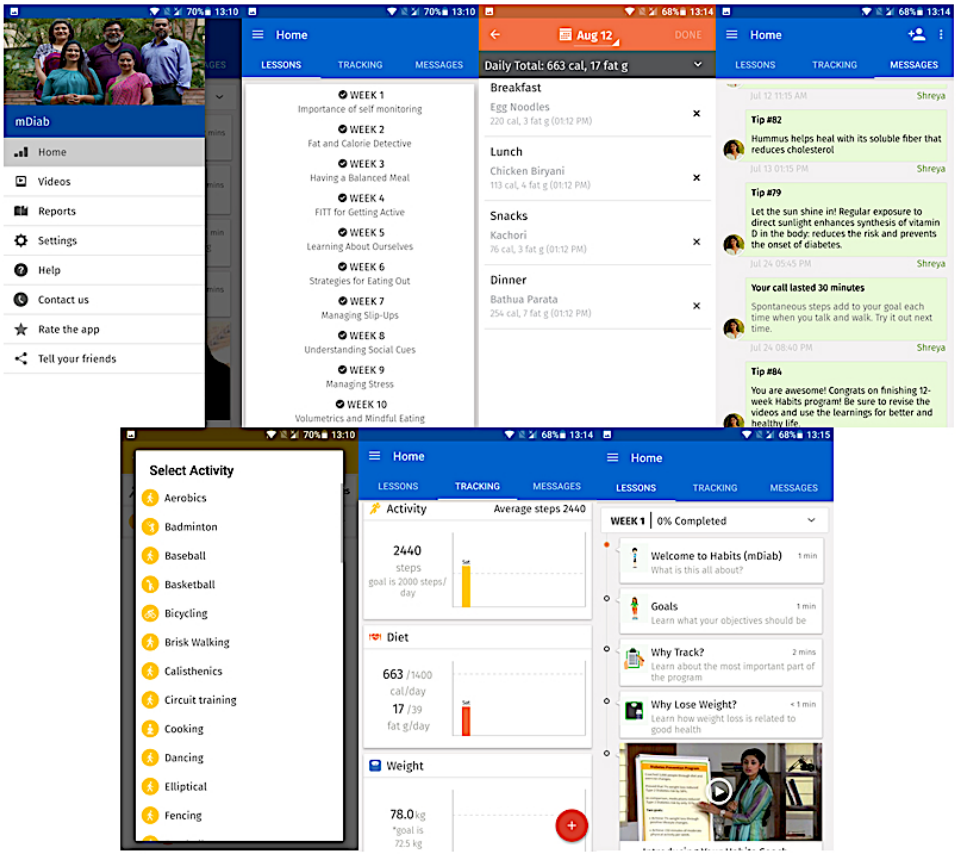
At screening, the participant's basic demographic details, IDRS, and CBG are measured. Post that, the study has a total of 3 testing time points including baseline, post intervention, and end of follow-up. All testing visits (except screening) occur after an overnight fast of at least 8 to 10 hours. The study participants are administered a questionnaire to record their sociodemographic data at baseline. Changes in diet and frequency of consumption of common foods are assessed using a 3-day diet recall, and short validated food frequency questionnaires are administered at all visits. Mobile phone usage and mHealth efficacy are also assessed at all visits. Physical activity and exercise behaviors are recorded using the short Madras Diabetes Research Foundation Physical Activity Questionnaire (MPAQ). MPAQ is a reproducible and validated instrument that captures data from multiple activity domains (including sedentary activity) over a period of a year from adults of both genders and varying ages from various walks of life, residing in India [34]. The participant's QOL is assessed using the WHOQOL-BREF instrument comprising 26 items [35]. It measures 4 broad domains: physical health, psychological health, social relationships, and environment. We also aim to assess the cost-effectiveness of using the mHealth intervention by assessing the incremental costs and benefits per quality-adjusted life-year (QALY). The cost-effectiveness of the mHealth intervention from an individual and collective perspective is compared with usual care by conducting incremental cost-effective analyses in which the net costs and net effectiveness of the mHealth intervention and the usual care are calculated and expressed as a ratio. All analyses are within the time frame of the trial. The direct medical and nonmedical costs/indirect costs associated with the mHealth intervention over 10 to 12 months are included in the cost-effectiveness [36]. Program adherence is measured by monitoring how well the participants used the various features of the app by responding to reminders and alerts. This is tracked using a Web-based dashboard. A 75-g glucose tolerance test [37] at 0 and 120 min along with blood tests for insulin, glycated hemoglobin (HbA1c), and lipids are conducted at baseline and at the annual follow-up visit.

Table 2. *mDiab* overview of video lessons.

Sessions (Weekly)	Objectives
Session 1: Importance of self-monitoring	Effective and daily tracking using the habits program
	The importance of breakfast as a wholesome and balanced meal, along with sample meal plans
	How one can be in charge of their health beyond all daily challenges, including overloaded work schedule, trials of family life, involved social life, and healthy lifestyle changes
	Plan one's day by planning the right time for eating
	Being true to oneself and achieving success
	Sleeping well for a healthy lifestyle
	Staying on track during the weekend
	Rewarding oneself
Session 2: Fat and calorie detective	Learning how fat and calories can affect health
	Learning where to find them in food
	Importance of portion sizes and measurement of food
	Being aware of fattening foods and hidden fats and switching to low-fat options to improve health and alleviate the risks of heart disease and diabetes
	Practicing being more aware and choosing food items consciously with lesser calories and fats, dwelling more into measuring foods
	Understanding that correlating the quantity of food eaten to its nutrient contribution (calories and fats) helps to remain within the fat and calorie limit for the day that is pre-determined by one's initial weight
	Using one's skills to ration portions and choose food items judiciously by evaluating the consolidated caloric intake for the day; trying to find a balance through food and exercise
	Incorporating physical activity into your lifestyle
Session 3: Having a balanced meal	Understanding the importance of taking a balanced meal and learning what it looks like
	Getting the relevance of the "My plate" concept
	Understanding what it is to eat from different food groups
	Learning the good side of everything, especially fats
	Understand the balance between calories in and calories out by tipping the calorie balance and understanding the food serving sizes
Session 4: Being active	Techniques to make physical activity fun
	The FITT principle to balance your activity
	Exercises—leg raises and back extensions
	Reviewing what was learnt and putting it to practice
	Understanding the serious threat of sedentary lifestyle and keeping a track of F—frequency, I—intensity, T—type of activity, and T—time
Session 5: Learning about ourselves	Keeping food and activity cues by simplifying them to one's core problems
	Learning how our environment causes us to be unhealthy
	Becoming aware of temptations that might steer one off course
	Steps to problem-solving
	Singling out areas in need of improvement and creating an action plan focusing on making these changes gradually
	Use tracking to one's advantage
Session 6: Strategies for eating out	The healthy side of eating out
	Learning how to control what you eat when not at home
	Ordering healthy

Sessions (Weekly)	Objectives
	Planning ahead when going out to eat with friends or family
Session 7: Managing slip-ups	Managing and dealing with slip-ups
	Identifying the reasons for a slip-up
	Identifying negative thoughts and learning how to manage them
	Stretching exercises and learning some seated stretching techniques
	Understanding common external triggers for mismanaging diet and exercise and dealing with them
Session 8: Understanding social cues	Understanding social cues and how they affect us
	Making lifestyle changes using social cues to one's advantage
	Being aware of your social interactions and how they affect you
	Learning to positively affect outcomes of unhealthy social cues
Session 9: Improving strength and flexibility	Improving strength and flexibility
	Strengthening one's exercise program and learning resistance training
	Standing up for your health
	Incorporating strength training into your activity routine
Session 10: Volumetrics and eating mindfully	Understanding the importance and concept of volumetrics and eating mindfully
	High volume, low calorie foods—learning to eat more food that has fewer calories
	Eating mindfully by perceiving your physical and mental state
	Thinking before eating and being aware how one eats
	Paying attention to size, smell, texture, taste, and its other qualities
	Enjoying one's meal to its fullest
Session 11: Stress management and staying motivated	Maintaining the momentum
	Recognizing positive lifestyle changes made so far
	Stress management
	Combating stress with planned activity or a healthy session of yoga
Session 12: Long-term heart health	Nurturing your heart into a healthy heart
	Understanding the importance of reducing risk of heart diseases by adopting positive lifestyle changes
	Understanding the importance of the new habits you have developed
	Using your skills to successfully keep the new habits you have created
	Keeping a schedule—tracking your new skill

Figure 2. mDiab app screenshots.



At the post-intervention visit (3rd-month visit), fasting glucose, insulin, HbA1c, and lipids are measured. Height is measured at baseline visit, and anthropometry (height, weight, waist circumference, and body fat) and clinical measures (blood pressure) are measured at baseline, post intervention, and end of follow-up visits.

Program Acceptability

Program acceptability is assessed through focus group discussions (FGDs) with the intervention group participants at the end of follow-up. We plan to organize 2 FGDs at each site consisting of at least eight participants each. Thus, a total of 6 FGDs will be conducted in the study. The participants will be encouraged to share their experience on the benefits and problems of the intervention, financial worth of the program, and suggestions, if any, for improvement. Participants who drop out will also be contacted to understand their reasons for dropping out and to obtain their feedback.

Sample Size Calculation

Our study randomizes 1500 individuals across 3 sites to receive either the mHealth diabetes prevention program or usual care with a 6-month maintenance period. Considering an obesity prevalence of 20% as reported in the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study [38,39] and with south Asians having a low BMI threshold compared with the rest of the population, 5% weight loss was determined as the primary outcome in the intervention group. On the basis of this assumption, a sample size of 588 individuals in each arm will be required to obtain a minimum of 3% difference in weight loss between groups with a power of 80% and a significance level of 5%. As this is a mobile phone–based intervention study, expecting a slightly higher dropout rate of 25%, 735 individuals in each group will need to be tested in the trial, resulting in a total of 1470, which has been rounded off to a total of 1500 individuals across 3 sites (500 per site).

All sample size and power calculations were done using the OpenEpi (The OpenEpi Project, Version 3, Atlanta, Georgia).

Ethics Approval

The study protocol was approved by the Institutional Ethics Committee at Madras Diabetes Research Foundation, All India Institute of Medical Sciences, and the Human Research Ethics Committee at Deakin University, Australia. Consent is obtained from all participants. At baseline testing, all participants were also given a plain language statement of the study.

Statistical Analysis

Quantitative analyses of the obtained data will be conducted in STATA (StataCorp, Version 15, College Station, Texas) and SPSS (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY). A probability of <0.05 will be considered statistically significant for all tests. Effectiveness of the intervention will be assessed by measuring the differences in the study arms in terms of the primary outcome, weight loss and secondary outcomes, behavioral and social variables, and cost-effectiveness. Continuous variables will be assessed for normality, and anomalous values will be categorized. All variables will undergo descriptive analyses. *t* tests will be used to compare between the 2 groups. Data will be presented before and after adjusting for confounders. Qualitative data include

analyses of the audiotaped transcripts from the FGDs. The transcripts will be de-identified, and textual data will be extracted from the same. Following this, key themes will be identified and reported.

Cost-Effectiveness

Two sets of outcomes are used to measure cost-effectiveness: cost-effectiveness analysis, which is the incremental cost per case of diabetes prevented, and cost-utility analysis, which is the incremental cost per QALY. The cost-effectiveness of the mHealth intervention is represented by the ratio of incremental cost to increment effectiveness. In addition, sensitivity analyses will be performed to examine effects of key parameters on cost-effectiveness ratios [36].

Discussion

Mobile phone technology has been shown to have wide acceptance across various age groups and socioeconomic groups. It offers several opportunities for self-management as well as prevention of T2DM [40-42]. The mDiab study looks at the effect of combining various mHealth technologies that could all act as an effective tool for diabetes prevention in high-risk Asian Indians. The intervention is unique in that it is backed by evidence provided by the D-CLIP study [43]. The D-CLIP study was an RCT that compared an intervention group, which received 16 weekly sessions on lifestyle behavior change, nutrition, and physical activity, followed by 8 weeks of maintenance classes, with a control group that received standard of care. Individuals in the intervention arm who remained at high risk, that is, those with an HbA1c of >5.6% after 4 or more months in the program, received metformin, in addition to the lifestyle program. The goals for the individuals were set as weight loss of at least 7% and 150 min or more of moderate physical activity. In the mDiab intervention, however, we lowered the weight loss goal based on the learnings from the D-CLIP study as most Indians are not overtly obese. The D-CLIP results showed an almost 50% risk reduction in the obese population, and the numbers needed to treat were 6.8, which means that if 7 “high-risk cases” are given the intervention, one case of diabetes can be prevented [43].

On the basis of the D-CLIP results, the need to scale up diabetes prevention in India was felt, and mobile technology was thought of as a tool to introduce the intervention. This was the basis for the mDiab trial. Very few studies have been carried out in India to test the efficacy of mHealth technology in diabetes prevention. Ramachandran et al [44] studied the effect of SMS text messaging (short message service, SMS) in a high-risk population and showed that it is possible to decrease the incidence of diabetes with almost 10% difference between the groups by using a structured SMS text messaging intervention. However, their population sample was limited to working Indian men only. In another study that evaluated the impact of mobile SMS text messages on self-reported diabetes awareness and prevention behaviors among cell phone users in India, it was observed that the intervention group showed 15% improvement in their dietary and physical activity behaviors compared with the control group [45].

Globally, many studies have shown significant improvements in glycemic control using mobile phone technology. Hussein et al [46] showed that continuous and individualized support and interaction with a diabetes educator and a clinician through SMS text messages could decrease the HbA1c by 1.16% in individuals with type 2 diabetes. Studies using SMS technology, based on knowledge, attitude, practice, and self-efficacy and motivation, have shown improvement in glycemic control [47,48]. Some studies have also looked at secondary prevention of diabetes by enforcing self-management of lifestyle behavior, insulin therapy, medications, and physician visits [49,50]. The study by Browne et al [51] reported that younger adults are more susceptible to using eHealth services for diabetes self-management. This may be because younger adults were tech-savvy and found using eHealth self-management supports time-saving. The Diabetes MILES (Management and Impact for Long-term Empowerment and Success)—Australia study [52] reported that telehealth and eHealth are promising areas for diabetes management, especially to reach out to wider population groups.

In the context of rapid adoption of mobile technology [18] and the fast rise of the T2DM epidemic in LMICs such as India [1-3], mDiab is an RCT testing the effectiveness, cost-effectiveness, and sustainability of a culturally tailored mHealth diabetes prevention program for Asian Indians. If successful, mDiab can be used as a model for translational and implementation research on the use of mHealth technology for diabetes prevention. Indeed, the mDiab experience can be further expanded to the prevention of other noncommunicable diseases such as hypertension and cardiovascular diseases.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Summary of study measures.

[PDF File (Adobe PDF File), 355KB - resprot_v6i12e242_app1.pdf]

Multimedia Appendix 2

"mDiab" overview of video lessons.

[PDF File (Adobe PDF File), 384KB - resprot_v6i12e242_app2.pdf]

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Abbreviations

BMI: body mass index
CBG: capillary blood glucose
D-CLIP: Diabetes Community Lifestyle Improvement Program
FGDs: focus group discussions
IAMAI: Internet and Mobile Association of India
ICMR-INDIAB: Indian Council of Medical Research-India Diabetes
IDRS: Indian Diabetes Risk Score
IFG: impaired fasting glucose
IGT: impaired glucose tolerance
IMRB: Indian Market Research Bureau
LMICs: low- and middle-income countries
mHealth: mobile health
MPAQ: Madras Diabetes Research Foundation Physical Activity Questionnaire
QALY: quality-adjusted life-year
QOL: quality of life
RCT: randomized controlled trial
SMS: short message service
T2DM: type 2 diabetes mellitus
WHO: World Health Organization

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Protocol

Direct to Public Peer Support and e-Therapy Program Versus Information to Aid Self-Management of Depression and Anxiety: Protocol for a Randomized Controlled Trial

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Abstract

Background: Regardless of geography or income, effective help for depression and anxiety only reaches a small proportion of those who might benefit from it. The scale of the problem suggests a role for effective, safe, anonymized public health–driven Web-based services such as Big White Wall (BWW), which offer immediate peer support at low cost.

Objective: Using Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) methodology, the aim of this study was to determine the population reach, effectiveness, cost-effectiveness, and barriers and drivers to implementation of BWW compared with Web-based information compiled by UK's National Health Service (NHS, NHS Choices Moodzone) in people with probable mild to moderate depression and anxiety disorder.

Methods: A pragmatic, parallel-group, single-blind randomized controlled trial (RCT) is being conducted using a fully automated trial website in which eligible participants are randomized to receive either 6 months access to BWW or signposted to the NHS Moodzone site. The recruitment of 2200 people to the study will be facilitated by a public health engagement campaign involving general marketing and social media, primary care clinical champions, health care staff, large employers, and third sector groups. People will refer themselves to the study and will be eligible if they are older than 16 years, have probable mild to moderate depression or anxiety disorders, and have access to the Internet.

Results: The primary outcome will be the Warwick-Edinburgh Mental Well-Being Scale at 6 weeks. We will also explore the reach, maintenance, cost-effectiveness, and barriers and drivers to implementation and possible mechanisms of actions using a range of qualitative and quantitative methods.

Conclusions: This will be the first fully digital trial of a direct to public online peer support program for common mental disorders. The potential advantages of adding this to current NHS mental health services and the challenges of designing a public health campaign and RCT of two digital interventions using a fully automated digital enrollment and data collection process are considered for people with depression and anxiety.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 12673428; http://www.controlled-trials.com/ISRCTN12673428/12673428 (Archived by WebCite at http://www.webcitation.org/6uw6ZJk5a)

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KEYWORDS

depression; anxiety; peer support; online; self-management

Introduction

Background

Unipolar depression and anxiety are the second and seventh leading causes of years lived with disability in the world among all health problems, respectively, according to the World Health Organization [1]. The 12-month point prevalence of unipolar depression, anxiety disorder, and mixed anxiety and depression is 15% in the United Kingdom [2] and ranges from 4% to 20% across 14 different developed and nondeveloped countries in the world [3]. There are a number of reasons why a population approach [4] to the management of depression and anxiety employing supported self-management is required: (1) the scale of the problem is too great both in terms of prevalence, recurrence rates, and access to be met through primary care and secondary care services alone, with only 33% of people receiving any treatment in the United Kingdom with broadly similar rates in developed countries in Europe and North America and half these rates in less developed countries [3,5]; (2) people may choose not to seek professional help for a number of reasons, including a preference for self-management, fear of stigma, fear or lack of motivation resulting from anxiety and depression, or as a result of having a previous bad experience of mental health care [6,7]; (3) people may be unsure where the boundary lies between their experience of stress on the one hand or clinical anxiety and depression on the other [6], sometimes preferring guidance before, or instead of, seeking medical care; (4) people may prefer to manage their problems themselves (personal empowerment) and at their own pace but seek guidance and support when they choose [8,9]; (5) to combat social isolation, people with depression and anxiety may sometimes prefer to develop a social network of people who are sympathetic to and understand what it is like to have depression, anxiety, or related mental health problems [10,11]; and (6) primary and secondary care services largely manage acute symptoms of anxiety and depression, focusing particularly on depression as a common cause of suicidal behavior and may not provide sufficient information and support for self-help to prevent recurrence [12]. Public health interventions to manage very common problems such as cigarette smoking, weight loss, and diabetes care have increasingly utilized the Internet to reach the public [13]. Provided safeguards are put in place to identify and transfer care to primary and secondary care services when appropriate (eg, high suicide risk), Internet programs offering a range of tailored information and support might address all or some of the six scenarios outlined above, among others.

Big White Wall (BWW) is a well-established digital service (website and apps) being accessed by approximately 13,000 people in the United Kingdom in the past year. Currently, BWW has been purchased by the armed forces, some universities, and 25% of clinical commissioning groups throughout England that provide free access to 98% of the users. Only 2% of the users are individuals who pay for the service through a £25 monthly subscription. It is also available or being piloted in the United States, Canada, Australia, and New Zealand.

BWW offers the following to people over the age of 16 years [14]: (1) Web-based assessment to assess common mental health problems and comorbid physical conditions; (2) moderated online peer support network: a community of peers, professionally staffed at all times, enabling safe, anonymous support through talking therapies and creative self-expression; (3) guided support: a range of self-managed and facilitated programs for individuals and groups for depression and anxiety and related issues such as sleep, smoking, and alcohol problems based on cognitive behavioral therapy (CBT) and social support principles; and (4) live therapy: a range of real-time therapies by instant text, audio, or video from a panel of approved BWW therapists offering CBT, interpersonal therapy, person-centered counseling, or integrative counseling.

On the basis of public health principles, BWW emphasizes a recovery model to improve well-being and is theoretically based on a social model of depression emphasizing autonomy, hopefulness, and support [14] (see [15] and [16] for reviews of the social model of depression). There are no waiting lists, eligibility criteria, or restricted opening hours (available 24/7). Specially trained counselors employed by BWW as *wall guides* facilitate interactions, ensuring that a culture of respect toward others, tolerance, mutual learning, and safety are maintained at all times. Mental well-being is seen as a systemic interplay of factors that contribute to an individual's engagement with themselves, their social networks and communities, and the society in which they live. Mental well-being is also seen as being intimately connected with physical health and general well-being.

BWW offers guided self-help based on CBT principles, with additional peer support—interventions that are recommended as face-to-face interventions for mild to moderate depression by the National Institute for Health and Care Excellence (NICE) in England and Wales [12]. However, the randomized controlled trial (RCT) evidence base for such interventions using a peer social support model requires more extensive testing. Currently, there is no RCT evidence that BWW is effective and only one large previous RCT of Internet peer support in 311 people with primary depression and anxiety [17]. This showed that both Internet peer support and Internet peer support plus guided self-treatment of depression (both of which BWW offers) versus information about depression and anxiety alone, improved depression and empowerment with additional benefits on quality of life (QOL) and self-esteem in the combined intervention [17,18]. The effects on empowerment were immediate, although improvement in QOL was only apparent at 6 months. Peer support was utilized more extensively than a formal course of CBT. Furthermore, the study found that weekly contact with the site was associated with greater improvements on ratings of social support and loneliness. However, it is not a test of the reach or effectiveness using the Reach, Effectiveness, Adoption, Implementation (including economics) and Maintenance (RE-AIM) methodology of a peer support program backed by a public health campaign, unlike this study.

Moreover, BWW is a complex intervention that operates differently to a psychological intervention in that people choose exactly when and how they utilize it rather than commit themselves to a course of treatment of a defined duration and frequency, which may be restricted by external issues such as clinician availability.

Peer support Internet interventions take less effort for service users than Internet-guided CBT [18]. The involvement is usually ongoing and unrelated to psychiatric crisis, for example, suicide or self-harm, unlike crisis lines such as Samaritans. In principle, relief from depression or anxiety can be achieved through BWW by improving the quality and consistency of support [19]. The effectiveness of BWW may be in keeping with the social model of depression and anxiety on which it was conceived. The onset of depression and anxiety is precipitated by the self-perception of a potential or actual lasting and severe threat to the person's well-being from a life event or a life difficulty in the absence of social support (isolation) or insufficient social support [20]. Relief from depression or anxiety is achieved by improved quality and consistency of support or life events that offer fresh starts or increased security. People with personality dysfunction may obtain less relief from depression and anxiety but still benefit [21].

Thus, a person with depression and anxiety has access through BWW to appropriate psychosocial support when they require it. They are given guidance and are enabled to choose to intervene in their own mental well-being (empowerment). This early intervention approach may preempt the need for later intervention if the person becomes worse. Although guided, people are encouraged to make their own decisions on how to use BWW so they retain their autonomy because perceived control is thought to improve outcome in depression and anxiety [15,16].

Alternatively, the National Health Service (NHS) has developed a free website providing information on mental health conditions and locally available resources called NHS Moodzone. It does not provide anonymized moderated peer support.

The RE-AIM (model [22]), which is designed to enhance the quality, speed, and public health impact of translational research in a defined population, will be used as a framework for the study. Here it will be used to compare free access to BWW versus free access to information about depression and anxiety from the NHS Choices Moodzone website for people who score above depression or anxiety caseness in one area of England serving inner city, urban and rural areas, and where there is no current institutional or commissioned access to BWW.

The overall aim was to utilize a strategy that is broadly similar to how BWW is usually implemented in a geographical area, with clinical champions from primary care and service users alongside publicity through local public health campaigns and commissioners.

Objectives

The objectives for this study (known as “the REBOOT study”) are bound within the RE-AIM framework:

Reach: To determine the number and representativeness of participants invited and eligible to receive BWW or the NHS Choices Moodzone website compared with the expected number of participants (based on estimates from census data in the study area).

Effectiveness: To determine the short-term clinical effectiveness of randomization to BWW versus the Moodzone website on well-being (primary outcome), depression symptoms, anxiety symptoms, social function, and QOL in one locality over 3 months.

Adoption (by services): To determine the number, percent, and representativeness of NHS primary care practices and organizations, secondary care mental health, community and acute trust, third sector, and social care organizations that referred people to either BWW or the Moodzone website.

Implementation: To explore the implementation of the BWW program, including barriers and drivers to reach, effectiveness and adoption, and an economic evaluation of its costs and cost-effectiveness from personal, social, and health care perspectives.

Maintenance: To determine (1) The maintenance of treatment effects on well-being, depressive symptoms, anxiety symptoms, QOL, and social function over 6 months and (2) The take-up by organizations and implementation (number, percentage of BWW across the East Midlands) after the trial has been completed.

We will also explore how the interventions may work by quantitatively examining moderators and mediators of outcome and conducting a qualitative analysis, and in the case of the BWW intervention, discourse analysis.

The discourse analysis aims to answer the following research questions:

- How social support is provided within peer support exchanges within BWW?
- What topics are discussed by trial participants when using BWW?

Methods and Analysis

Trial Design

A single-blind, pragmatic RCT will be conducted in the county of Nottinghamshire, United Kingdom using a fully automated bespoke study website. Eligible participants, recruited through self-referral methods such as social media, general practitioner (GP) advertisements, and general marketing will be allocated at random and without stratification to receive either 6 months free access to BWW or be signposted to the NHS Moodzone website. The primary outcome will be clinical effectiveness (mental well-being) of BWW versus Moodzone as measured by the 14-item Warwick-Edinburgh Well-being Scale [23,24] from baseline, 3 to 6 weeks. Maintenance of effect at 12 and 26 weeks will be secondary outcome measures.

This RCT forms part of the East Midlands Collaboration for Leadership in Applied Health Research and Care (CLAHRC-EM), an applied health care research center funded by the National Institute for Health Research (NIHR), the Universities of Nottingham and Leicester, and over 50 partners from health care, social care, and industry across the East Midlands. Funded across the United Kingdom, there are 13 CLAHRCs that focus on the clinical and cost-effectiveness of translational research that has been identified as priority areas by local services. Service delivery studies of this kind, therefore, require more than just the clinical outcomes that traditional RCTs might produce and present the need to explore cost-effectiveness, risk, adoption by services, reach, and the barriers and drivers to implementation.

Ethical approval has been granted by the Local Research Ethics Committee (REC 16/EM/0204), and final approval was received from the Health Research Authority.

Recruitment

To optimize recruitment to the trial as well as the regional uptake of BWW, a public health engagement campaign will run alongside participant recruitment via local services to maximize the opportunities for people without, as well as with current access to mental health services, to take part in the trial. Potential participants will all self-refer to the study website after accessing information about the study via two main routes: (1) general media and digital social media advertising and (2) recommendation from health care professionals and other support workers in NHS primary care, NHS secondary care, social care, and third sector and community services. Recruitment and adoption throughout the study will be closely monitored and recorded in order that networks and reach can be determined and analyzed.

Engagement Strategy

The public engagement strategy and recruitment to the study will run in parallel with each other. The engagement strategy will, for 1 month, publicize the study to NHS, local authority, and third sector organizations in Nottinghamshire a month before recruitment to the trial begins. The study will be integrated into the early intervention stream of the Clinical Commissioning Groups and Health and Well-being Board Mental Health Strategy for Nottinghamshire. A range of methods will be used to engage with potential study participants, including:

- Identification of primary care practices and other groups of health professionals, for example, health visitors and community pharmacists that are known to have an interest in mental health and a willingness to adopt new interventions early after their introduction in one part of the county before moving to other parts
- Introducing a local general media advertising campaign (eg, bus and tram adverts, newspapers, and radio), followed by a Facebook and social media campaign
- Presenting the study to interested community groups, targeting both the young (eg, further education colleges and universities) and old (eg, Age UK), vulnerable groups (eg, new parents living in disadvantaged areas, through Surestart), third sector mental health groups (eg, Mind branches in Nottinghamshire), and local organizations promoting self-help (eg, Self-Help Nottingham)
- Producing online and offline presentations and written materials
- Other novel approaches as they might arise in public health and primary care, for example, public health message with receipts in high footfall supermarkets or shopping centers

Patient and public involvement is central to the design and delivery of this study. A user consultant has been appointed to develop novel approaches and monitor, iterate, and evaluate the effectiveness of the different engagement methods, with an action-research type approach. The user consultant will develop a lived experience advisory panel to help shape the study process throughout. They will work with at least one GP knowledge broker (who will act as clinical champions for the study as a whole) in other areas where BWW has been implemented successfully; this role has been important linking with GP and other community health professionals and the early intervention stream. Regular checks will show which methods are best for broadening the reach of the study and BWW to a wider range of people and groups and especially those isolated.

On the basis of 6- to 12-month engagement strategies using a part-time engagement officer carried out by BWW in the West Midlands (Dudley, Wolverhampton, and Walsall; in total a similar size population to that of Nottinghamshire), 1950 participants (1.6% of the population) were recruited. We anticipate a similar rate of recruitment in Nottinghamshire, with approximately 2200 participants recruited to our study website over a 12-month recruitment period, and we will have the additional help of the user consultant and the public health campaign publicizing the study.

The learning achieved from the recruitment period will inform the best approaches to engage with the public in later stages of the study. A feedback conference will engage with study participants and other stakeholders groups (commissioners, Improving Access to Psychotherapy services, public health, etc)

to enable understanding of the wider validity and relevance of emerging findings. An effective public dissemination strategy, informed by our earlier learning, will communicate the findings of the research to a wide audience to help mobilize the new knowledge as part of the implementation strategy (see later section).

Sample and Eligibility

Potential participants from the county of Nottinghamshire will be able to self-refer, and their eligibility will be assessed by an automated digital program on the study website. The study website requests GP practice contact details in case the participant is ineligible for the study.

The inclusion criteria are as follows:

- Aged 16 years or over
- Resident in the County of Nottinghamshire
- Scores between 10 and 20 on the 9-item Personal Health Questionnaire (PHQ-9) [25] and/or 10 or more on the 7-item Generalized Anxiety Disorder (GAD-7) questionnaire [26], indicating probable caseness for depression and anxiety, respectively, but not a definite diagnosis of depression or anxiety disorder
- Access to the Internet through a computer, tablet, or smartphone (Windows, iPhone operating system [iOS, Apple Inc], and Android)
- Able and willing to give informed consent (through electronic consent)

The exclusion criteria are as follows:

- Scores 21 or more on the 9-item Personal Health Questionnaire (PHQ-9, severe depression)
- Scores 2 or 3 on PHQ-9 item "thoughts that you would be better off dead or of hurting yourself in some way."
- Scores below 10 on PHQ-9 and 7-item Generalized Anxiety Disorder (GAD-7) questionnaire
- BWW and Moodzone are only available in English. Therefore, the website will recommend to participants that if they do not feel that they are sufficiently proficient in the use of the English language, they need not take part. There will be no test of proficiency.

Participants who are ineligible for the trial because they score in the severe range on the PHQ-9 or signs of suicidality will be provided with an opportunity to request that the study team inform their GP, mental health care team, or carer of their current mood state. If they choose not to take this offer, the study team will follow this up on one occasion with an email to ask them again if they would like the team to inform their GP or care team. If they do not reply, the team will consider this confirmation that they do not wish us to act on their behalf.

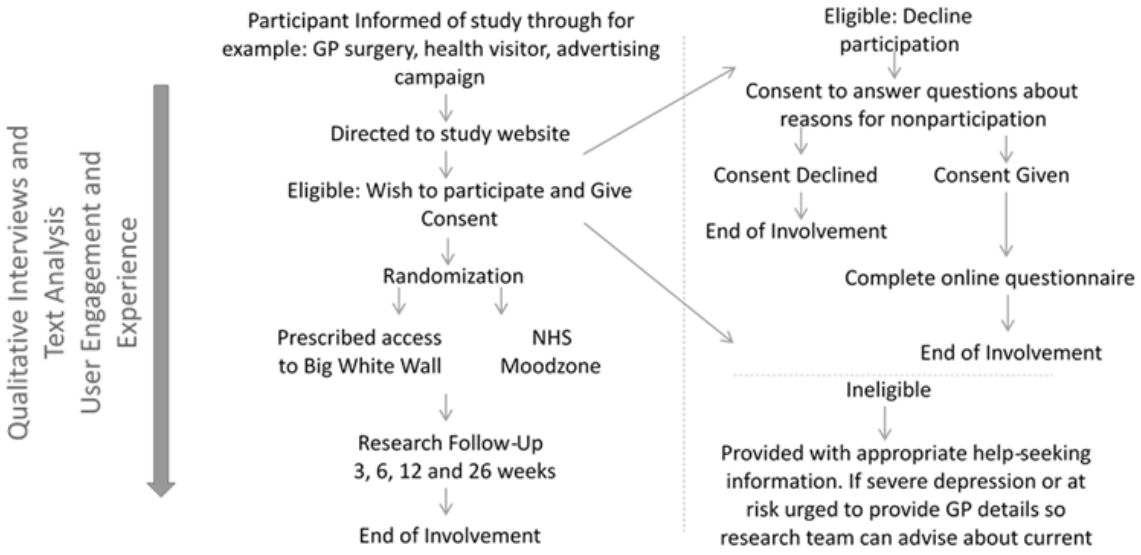
Participants that are under age will be given details of local children's mental health services. They will be informed that they may return to the study website if they turn 16 years within the recruitment period, should they still wish to participate.

Information for participants and the associated consent forms are provided electronically within the study website. Participants who wished to discuss the study could email and telephone the study team if they had any further questions before consenting to the study. An email confirming consent is sent to a participant once they have fully enrolled in the study.

Expected Duration of Participant Participation

Participation in the study will be for 6 months (see Figure 1 for participant journey through the study). Participants will receive electronic follow-up invitations at 3, 6, 12, and 26 weeks after randomization to be completed on the website. Participants may also be asked to take part in a short interview by phone or face-to-face to talk about their experiences of services and/or the study no later than 3 months from the ending of their participation.

Figure 1. Participants' journey through the study.



Interventions

Randomization: Arm 1—BWW

Participants allocated to receive 6 months free access to the BWW website will create a user profile using a pseudonym that will be linked to the trial identification that they are assigned within the study website. Participants will be able to access any part of the BWW site (apart from the option of personalized therapy or counseling sessions that have to be prescribed by a clinician [ie, is not offered direct to the general public], and for this reason it will not be accessible for participants in this study) and interact with other users within the boundaries of the site's house rules. [14]. Anonymized records of log-ins, time on site, interactions, and page categories will be recorded by BWW on behalf of the study team.

Randomization: Arm 2—Participants Allocated to Moodzone

Participants will be directed to the Moodzone area of the NHS Choices website, a free to access website providing information on mental health conditions and locally available resources. Participants will be able to access all of the available material on mental health, including depression and anxiety. The site contains reading material and suggestions about maintaining mental health and provides measures of depression and anxiety for visitors to use.

All participants will be asked about whether they have received or used any additional mental health resources during their time in the study. NHS Moodzone access is used as the control digital resource so that all the participants are offered some help for their problems with depression or anxiety, but the control group do not access moderated, anonymized peer social support.

Outcome Measures

Once consented, participants will be asked to complete self-rated questionnaires to measure well-being, depression, anxiety, work and social adjustment, QOL (for economic analysis), receipt of services (for economic analysis), social support, and personality dysfunction (see Table 1). These will be completed online (through the study website) in approximately 20 to 30 min, with the primary outcome data collected first. All data will be stored on the website and downloaded and anonymized by the clinical trials manager.

Primary Outcome Measure

- Change in self-rated well-being at from baseline to 3 and 6 weeks after baseline using the 14-item Warwick-Edinburgh Mental Well-Being Scale (WEMWBS)

Secondary Outcomes Measures

- Maintenance of well-being 12 and 26 weeks using the WEMWBS
- GAD-7 scale—completed as part of eligibility at baseline and then at 3, 6, 12, and 26 weeks as a brief measure of the severity of 7 symptoms of anxiety
- PHQ-9—completed as part of eligibility at baseline and then at 3, 6, 12, and 26 weeks as a measure of depression severity according to the *Diagnostic Statistical Manual, 4th edition* criteria [27]
- 12-item Medical Outcomes Study Short Form health survey version 2.0 (SF-12v2) [28]—a short and practical measure of health-related QOL derived from the longer SF36 that is obtained during interview
- Social support is measured using the 8-item Medical Outcomes Study Social Support Survey (MOS-SS) [29], and it is completed at baseline
- Social function on the 8-item Work and Social Adjustment Scale (WSAS) [30]—a simple measure of impact on function, which is attributable to a particular cause such as depression or anxiety. It is completed at baseline and then at 3, 6, 12, and 26 weeks

Mediators of the effectiveness of BWW compared with Moodzone on mental well-being might be the emotional and informational support subscales of the MOS-SS [29]. Data collected by BWW suggest that perceived social support might be an important mediator of outcome, particularly in people experiencing life events and loneliness.

Moderators of outcome at baseline might be the presence of life events in the previous 6 months, measured by the 12-item Brugha Inventory of Life Events [31], and the presence of anxiety alone at baseline. Personality dysfunction will be measured at baseline using the 8-item Standardised Assessment of Personality-Abbreviated Scale (SAPAS) [32]. There may be an interaction between the presence of life events at baseline and greater perceived emotional support from BWW at 3 months and on mental well-being at 6 months, whereas higher scores on the SAPAS may predict dropout and little difference between the treatment arms on mental well-being at 6 weeks.

Table 1. Timing and delivery of outcome measures.

Measure	Baseline	3 weeks	6 weeks	12 weeks	26 weeks
WEMWBS[a]	Website	Website	Website	Website	Website
PHQ-9[b]	Website	Website	Website	Website	Website
GAD-7[c]	Website	Website	Website	Website	Website
WSAS[d]	Website	Website	Website	Website	Website
MOS-SS[e]	Website	X[f]	X	X	X
SAPAS[g]	Website	X	X	X	X
Brugha Life[h]	Website	X	X	X	X
SF12-v2[i]	Website	X	X	X	Interview
CSRI[j]	Website	X	X	X	Interview

[a]WEMWBS: Warwick-Edinburgh Mental Well-Being Scale.

[b]PHQ-9: 9-item Personal Health Questionnaire.

[c]GAD-7: 7-item Generalized Anxiety Disorder Scale.

[d]WSAS: Work and Social Adjustment Scale.

[e]MOS-SS: 8-item Medical Outcomes Study Social Support Survey.

[f]X: Measures are not collected at this time point.

[g]SAPAS: Standardised Assessment of Personality-Abbreviated Scale.

[h]Brugha Life: 12-item Brugha Inventory of Life Events.

[i]SF-12v2: Medical Outcomes Study Short Form health survey version 2.0.

[j]CSRI: Client Service Receipt Inventory.

To explore the reach, adoption, and implementation arms of the RE-AIM framework, a number of process measures will be recorded as the study progresses:

- Live log of services, individuals, groups, and charities that are approached to engage with the study. The networks that surround these and how this may spread will be recorded and used to determine reach and adoption. A network of practice comprising all health care stakeholders will be established to explore implementation pathways.
- Reach will be further explored using Internet analytic software or to derive anonymous data around hit and bounce rates, pages visited, length of visit, type of geography, and simple demographics to the study website can be recorded, downloaded, and analyzed
- Implementation will be explored when highlighting the barriers and drivers to reach, effectiveness, and adoption assessed through qualitative work with the services, groups, and individuals engaged through recruitment, as well as an economic evaluation of its costs and cost-effectiveness from personal, social, and health care perspectives. In particular, we will explore how participants utilize BWW in relation to the literature on similar websites offering peer support and information for physical illness and literature on social and organizational aspects of depression and anxiety care.
- Working with the local Academic Health Science Network to record the take-up by organizations and implementation (number, percentage, and representativeness in East Midlands) of BWW across the East Midlands after the trial has been completed should it prove to be clinically and cost effective.

In terms of socioeconomic inequalities, we will record the following provided such detailed recording of information does not deter participation: postcode, age, gender, ethnicity marital status, highest level of education, and employment.

Sample Size and Justification

Given that the focus of BWW is on improving mental well-being rather than specifically depression or anxiety, a clinically important difference on the WEWBS was selected as the primary outcome. Data from BWW online support groups show clinically important differences in depression by 6 weeks, so the primary outcome will be a change in the WEWBS from baseline to 3 and 6 weeks. The minimal clinically important difference (MCID) for adults on the 14-item WEWBS with mild to moderate depression and anxiety is 3 points and WEWBS scores are normally distributed [24]. On the basis of data from a Web-based CBT intervention versus information from an RCT in a similar participant group with a similar design [33], and inflating the variance (to allow for contamination) at 6 weeks by almost 50%, we estimate the sample size required to detect a 3-point MCID between the BWW and Moodzone groups at 6 weeks to be 676 in total or 338 per treatment group using the analysis of covariance method with 90% power to show a difference at two-sided 5% significance level assuming zero correlation between pre- and posttreatment outcomes. In the previous study, the intervention and control groups were 42.20 (standard deviation [SD] 9.83) and 42.32 (SD 9.64), respectively, and by 6 weeks they were 44.46 (SD 8.1) and 41.92 (SD 9.18). In the power calculation, we have assumed that at baseline, each intervention group will have a mean baseline score of 42.20 (SD 9.83) and that this will increase to

44.46 (SD 12.0) in BWW and fall slightly to 41.46 (SD 12.0) in the Moodzone control group at 6 weeks. There are no data currently available using the WEWBS with BWW, but BWW online support groups show a drop in PHQ-9 score from 13.9 (SD 7.1) to 8.6 (SD 6.5) at 6 weeks—a change that is equal to an MCID of 5.0 points suggesting that BWW can produce clinically important differences in outcome.

The analysis will use multilevel modeling because of repeated measures in the same individuals. People directly participate in the study so there is no other form of clustering operating in this study. Our power calculation performed has already taken into consideration clustering because of repeated measures. Assuming a 50% loss to follow-up, a total of 1352 participants are required for the RCT [33,34] but typically BWW would be expected to enroll 2200 people in a county the size of Nottinghamshire if the uptake of BWW was consistent with the general pattern seen in similar parts of the country. Furthermore, in a study with a similar design [33], 3070 (63.52%, 3070/4833) participants who were enrolled into the study completed eligibility criteria on a website and were invited to take part. Taking a conservative approach, we would recruit approximately 1400 participants out of 2200 people meeting eligibility criteria and enrolling onto the study site. This would be sufficient to recruit an adequate sample size. Stata 14 (StataCorp LLC, USA) was used to perform power analysis [35].

Randomization and Monitoring

The treatment to which a participant is assigned will be determined by a computer-generated pseudorandom code using random permuted blocks of varying size by a randomization system embedded within the website. No stratification or minimization is required. The outcome will be single-blind with the clinical trials manager and research associates responsible for the collection, cleaning, and analysis of the data remaining blind to arm allocation until data collection has been completed. Cases of unblinding will be recorded electronically but will not be excluded. Unblinding will only be necessary upon completion of data collection.

Overall, trial monitoring and oversight will be carried out by the CLAHRC-EM Scientific Committee who will act as the trial steering committee and data monitoring committee. The CLAHRC-EM scientific committee is composed of independent experts in statistics, epidemiology, medicine, and patient and public involvement. They will be sent quarterly reports on the status of the study and have the power to recommend or implement changes to the protocol if necessary. They are also able to stop the study if it is deemed unsafe or is failing to recruit after all avenues to recruitment have been exhausted.

There is no planned assessment of safety within the study design, and unless participants report any intercurrent illness or adverse events directly to the study team, it is unlikely that these can be recorded systematically.

Statistical Analysis

Analysis of the primary and secondary outcome measure data will be carried out by the trial statistician, who will remain blind to arm allocation, using STATA 14.

In a RE-AIM study, all outcomes are considered to address important facets of a public health intervention. Therefore, we will examine reach (the percentage and representativeness) of participants entering the trial. Exploratory analysis will summarize outcome variables and participant background variables by treatment arms across follow-up time with mean (SD) for normally distributed data, median (interquartile range) for skewed variables, and frequency (percentage) for observed level of categorical variables. The analysis to examine the treatment effect will be performed on an intention-to-treat basis. As the primary outcome WEWBS score will be repeatedly measured at baseline, 3 weeks, and 6 weeks, multilevel modeling will be performed to quantify the treatment effect with participant as a level 2 unit and baseline measurement as a covariate using Stata 14. Missing values will be imputed using a multiple imputation approach under a missing at random assumption. Path analysis will be used to explore changes in perceived emotional social support and empowerment at 3 weeks as potential mediators for treatment effects on mental well-being at 6 weeks, alongside life events, loneliness, having a partner, gender, age, anxiety without depression, and personality dysfunction at baseline as possible moderators for treatment effect. Such information will provide important information to refine both the targeting and content of BWW to optimize its reach and effectiveness.

A detailed statistical analysis plan setting out full details of the proposed analyses will be finalized before the trial database is locked for final analysis. Stata 14 will be used to perform exploratory data analysis and multilevel modeling, Mplus software (Muthen & Muthen, USA) will be used to perform path analysis [36].

Adoption and Implementation

Adoption will be examined according to the prevalence of uptake and promotion of the study by primary care, secondary care, social care, and third sector organizations. Implementation will be examined in four ways: (1) a quantitative analysis of patterns of acute use of BWW from baseline to 6 weeks according to clinical and sociodemographic factors; (2) an economic evaluation; (3) long-term effects will also be explored using qualitative interviews and patterns of use of data from the websites. An analysis of barriers and drivers of participants, public and patient groups, and health professionals to reach, adoption, effectiveness, and maintenance of BWW using digitally recorded and thematically analyzed individual qualitative interviews; and (4) textual analysis of written comments made by participants and qualitative interviews to explore the process of self-management, peer support, and organization of care on BWW.

Health Economics

The study will be conducted from an NHS and societal perspective, which will include cost to the individual but will in addition to clinical outcomes measure the participant's own health status using the SF12-v2 during participant interviews [28]. Thus, the study results will be reported in terms of cost-effectiveness and cost-utility. A detailed resource profile will be established for the intervention versus usual care. The resource profile will include capital costs, for example, the

technology, licensing agreements, and assumptions around the length of life of the respective Internet technologies and participant costs in each arm (eg, time accessing the Internet). Economic data will be collected using the economic resource proforma (the Client Service Receipt Inventory [37]), which was piloted successfully in a previous study [38]. Economic data around service use will be collected at baseline, and further economic data, including any time lost from work or usual activities, will be collected during interviews with 200 participants at 12 and 26 weeks who consent to be interviewed. Medication costs will be obtained from the British National Formulary, primary care contacts assigned using community and hospital-based costs from NHS reference costs. Information collected from participants will include any time lost from work or usual activities. An incremental cost-effective ratio and cost-effectiveness acceptability curves will be produced for the BWW versus Moodzone sites. This use of this probabilistic analysis is recommended in NICE guidelines and is economically more useful than classical probability estimates of significance.

Qualitative Analysis

Qualitative interviewing and analysis will be used to determine the barriers and motivations for participant engagement in the study to inform and further develop the study's engagement strategy. We also intend to explore participants' experiences of taking part in the study to gain and understand the motivations for use of online peer support. For those in the BWW arm of the study, this will include patterns and levels of engagement (eg, active user vs "lurker"), negative experiences and beliefs about efficacy, and role in personal empowerment. For those in the Moodzone arm, we will interview participants about negative and positive experiences of receiving just information in relation to managing depression and anxiety. Qualitative interviews will be sought with a maximum variance sample based on sociodemographic factors, scores on baseline clinical measures, and whether or not they are using other health services. Participants will be contacted after they have been in the study for 6 weeks. We will also interview those who did not wish to participate or dropped out but indicated they wished to be contacted to leave feedback.

Participant Messages

All conversation threads over 6 months in which at least one message has been posted by a trial participant will be retrieved by BWW and sent securely and anonymously to the research team. These will include messages posted by nonstudy participants. However, these messages will not be analyzed; rather they are provided to understand the context of the messages posted by the study participants.

The data generated for this phase will be analyzed using content analysis [39]. This approach is frequently used to quantify theoretical concepts and qualitative data categories in the manifest content of large volumes of textual information and has been successfully employed in previous studies [40-42]. We will address the discourse analysis questions as follows:

How social support is provided within peer support exchanges within BWW?

We propose to employ the Social Support Behavior Code [43] as our guiding theoretical framework. This framework has been used extensively in the analysis of online forum communication (eg, [43]) and provides the means to identify and quantify the presence of five key categories of social support: information support, emotional support, network support, esteem support, and tangible assistance. Our analysis will record separately the number of requests for support as well as the provision of support, by category (above), within the dataset.

What topics are discussed by trial participants when using BWW?

We propose to use thematic analysis to address this research question using previous guidelines [44]. This approach allows the systematic analysis of textual data to identify and describe emergent themes based on patterns within the dataset.

Discussion

Only 33% of people with depression or anxiety receive any help from health services in England [5] and other developed countries in Europe and North America [3]. Public-facing websites, such as BWW, offering support and help may offer effective help delivered at scale to very large populations. Yet, the effectiveness of BWW has yet to be established, and our study will provide the first rigorous test of this.

The design of such a large automated study in one geographical area poses a number of methodological challenges, and our study design has a number of strengths as well as inevitable weaknesses.

Strengths

The pragmatic design of the trial means that our estimates of effectiveness and cost-effectiveness are likely to be generalizable to other areas of the United Kingdom and other high income populations as this is a direct to the public study that does not rely on health service infrastructure that varies from place to place.

The public health (RE-AIM) approach of the REBOOT study will help to raise awareness of the possibility of digital intervention with a large group of people with depression and anxiety who are not currently engaged with primary care or mental health services. It will also explore whether it provides additional help to those who are already engaged with these services in relation to immediate moderated anonymized support and digital approaches to socialization and recovery that might be more convenient and approachable than comparable face-to-face approaches. It will provide a great deal of information surrounding the reach and adoption of such a resource and the role it plays in their well-being. We will know the clinical, sociodemographic, and health care service use of participants and visitors to the site who complete baseline information but decide not to be randomized as well as those who utilize the interventions, and completers and dropouts from the study. We will also be able to explore through process evaluation moderators and mediators of mental well-being through both treatment arms and in more detail in the BWW treatment arm by detailed quantitative and qualitative analysis

of social messaging through BWW. Therefore, there is the opportunity through such process evaluation to improve the reach or effectiveness of digital interventions such as BWW and also to predict more clearly what the impact of BWW might be in an area outside Nottinghamshire if such services were commissioned [45]. The protocol is ambitious, but the feasibility of conducting a fully mobile randomized clinical trial for depression has been demonstrated recently with the randomization of 626 participants [46].

Limitations

Therefore, we have carefully coproduced the REBOOT study website with e-mental website developers such as M-Habitat [47] and the lived experience of the Lived Experience Advisory Panel of service users, who have also contributed to the public health campaign, to reflect the experience of people of different ages, gender, and sociodemographic background with personal experience of depression and anxiety. By doing so, we hope that the REBOOT public health campaign and study website will engage and connect with people who have depression and anxiety in the community so that they will enter the study and continue in follow-up. We have also considered issues of intrinsic reward (eg, altruism, motivational statements, and feedback on completion) and extrinsic reward (reminders through text, email, and entry of completers into competitions) to encourage completion of data on the website at each time point [48]. Issues around access to the Internet, ownership of devices, and having access and competence with information technology may also be barriers to the use of the interventions that will be explored through qualitative interviews.

A further complication in the digital study is the issue of contamination. People with depression or anxiety might access BWW or Moodzone independently, although in the county of Nottinghamshire the opportunity to enroll in BWW is limited to access through the Armed Forces as new personal subscription has been suspended for the duration of recruitment and follow-up in the REBOOT study. Only one randomization is possible from each web browser within a 30 day period. Participants may be able to deceive the randomization process through access from a different computer or web browser or by clearing the cookie installed to prevent multiple attempts. Internet protocol (IP) address was not used as a marker to prevent multiple randomizations in case several people might be sharing the same computer. There may also be potential leakage with people who live outside Nottinghamshire using work postcodes that are within the county. Furthermore, there are potential problems with contamination through digital users utilizing alternative sources of digital support and information rather than the study treatment allocated to them. For instance people might join Facebook and offer support to each other even though it is not anonymized, and there is no profession moderation or support. If any of these occurred to a significant extent, it may be difficult to show real improvements in clinical and cost-effectiveness. To understand these potential sources of contamination, we are asking all participants about use of other sites.

The design of studies to evaluate the reach, adoption, clinical-effectiveness, and cost-effectiveness of direct to the public digital health interventions for mental health problems are important, given the reach, popularity, and low cost of such approaches in a world that is increasingly digitally connected even in the poorest countries of the world. However, we are in the early stages of understanding how to optimally design such studies.

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BWW has provided funding in kind through the provision of 1100 six-month licenses for use by study participants. They have also given the team restricted access to the website for the purposes of study design, and a research manager from BWW has attended many of the team meetings in an advisory capacity as to the practical and marketing aspects of the study design. BWW has not provided incentives in any other form and has not influenced the study beyond that mentioned above.

The sponsor (Angela Shone, University of Nottingham) was consulted in the preparation of the study protocol for the purposes of obtaining ethical approval and any subsequent amendments. The CLAHRC-EM Scientific Committee provides overarching trial committee responsibilities.

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Conflicts of Interest

None declared.

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Abbreviations

BWW: Big White Wall
CBT: cognitive behavioral therapy
CLAHRC: Collaboration for Leadership and Applied Health Research and Care
CLAHRC-EM: Collaboration for Leadership and Applied Health Research and Care-East Midlands
CSRI: Client Service Receipt Inventory
GAD-7: 7-item Generalized Anxiety Disorder Scale
GP: general practitioner
IP: Internet protocol
MCID: minimally important clinical difference
MOS-SS: 8-item Medical Outcomes Study Social Support Survey
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
NIHR: National Institute for Health Research
PHQ-9: 9-item Personal Health Questionnaire
QOL: quality of life
RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance model
SAPAS: Standardized Assessment of Personality-Abbreviated Scale
SD: standard deviation
SF-12v2: Medical Outcomes Study Short Form health survey version 2.0
WEMWBS: Warwick-Edinburgh Mental Well-Being Scale
WSAS: Work and Social Adjustment Scale

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Protocol

The Effectiveness of Text Messaging for Detection and Management of Hypertension in Indigenous People in Canada: Protocol for a Randomized Controlled Trial

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Abstract

Background: Hypertension, the leading cause of morbidity and mortality, affects more than 1 billion people and is responsible globally for 10 million deaths annually. Hypertension can be controlled on a national level; in Canada, for example, awareness, treatment, and control improved dramatically from only 16% in 1990 to 66% currently. The ongoing development, dissemination, and implementation of Hypertension Canada's clinical practice guidelines is considered to be responsible, in part, for achieving these high levels of control and the associated improvements in cardiovascular outcomes. A gap still exists between the evidence and the implementation of hypertension guidelines in Indigenous communities in Canada, as well as in low- and middle-income countries (LMICs). The rapid rise in the ownership and use of mobile phones globally and the potential for texting (short message service, SMS) to improve health literacy and to link the health team together with the patient served as a rationale for the Dream-Global study in both Canada and Tanzania.

Objective: The primary objective of the Dream-Global study is to assess the effect of innovative technologies and changes in health services delivery on blood pressure (BP) control of Indigenous people in Canada and rural Tanzanians with hypertension using SMS messages and community BP measurement through task shifting with transfer of the measures electronically to the patient and the health care team members.

Methods: This prospective, randomized blinded allocation study enrolls both adults with uncontrolled hypertension (medicated or unmedicated) and those without hypertension but at high risk of developing this condition who participate in a BP screening study. Participants will be followed for at least 12 months.

Results: The primary efficacy endpoint in this study will be assessed by analysis of variance. Descriptive data will be given with the mean and standard deviation for continuous data and proportions for ordinal data. Exploratory subgroup analyses will include analysis by community, sex, mobile phone ownership at baseline, and age. The knowledge gained from the text messages will be assessed using a questionnaire at study completion, and results will be compared between the groups.

Conclusions: This study is expected to provide insights into the implementation of an innovative system of guidelines- and community-based treatment and follow-up for hypertension in Indigenous communities in Canada and in Tanzania, an example of an LMIC. These insights are expected to provide the information needed to plan scalable and sustainable interventions to control BP virtually anywhere in the world.

Trial Registration: Clinicaltrials.gov NCT02111226; https://clinicaltrials.gov/ct2/show/NCT02111226 (Archived by WebCite at http://www.webcitation.org/6v7IdYzZh)

(JMIR Res Protoc 2017;6(12):e244) doi:10.2196/resprot.7139

KEYWORDS

hypertension; health services, indigenous; chronic disease; disease management; telemedicine; text messaging

Introduction

Background and Rationale

Worldwide, hypertension is the leading cause of morbidity and mortality, affecting more than 1 billion people and responsible for 10 million deaths annually [1]. Hypertension increases the burden of disease globally through cardiovascular disease, kidney disease, and dementia [2-4]. For every 20-mm Hg increase in systolic blood pressure (BP) above 115 mm Hg, and every 10-mm Hg increase in diastolic BP above 75 mm Hg, there is a doubling in the risk of mortality from cardiovascular disease [5]. Placebo-controlled studies of BP lowering in people with hypertension demonstrate a 17% reduction in major cardiovascular events for every 5-mm Hg fall in systolic BP [6]. Hypertension can be controlled at the national level. For example, BP control improved dramatically in Canada from only 16% in 1990 to 66% at present [7,8]. The ongoing development, dissemination, and implementation of Hypertension Canada's clinical practice guidelines is considered to be responsible to a great extent for achieving these high levels of awareness, treatment, and control, which in turn are linked to improved cardiovascular outcomes [9]. However, although BP control and treatment have improved nationally, the improvements are not distributed equally at the regional level linked to disparities in the determinants of health.

In Tanzania and other low-income countries, hypertension control presents a significant challenge because of deficiencies in primary health care resources such as health care providers and antihypertensive medications. Tanzania, like many countries in sub-Saharan Africa, is experiencing an epidemiological transition from a disease burden of mostly communicable diseases and injuries to a disease burden increasingly dominated by noncommunicable diseases such as cardiovascular disease, diabetes, and cancer [10]. The approaching wave of chronic diseases that require monitoring and access to drugs is a threat to the health care system in Tanzania. At present, in Tanzania, the prevalence of hypertension is between 35% and 40% in adults, with awareness of hypertension only 20%, treatment 10%, and control approximately 5% [11]. Many of the determinants of health affecting Canada's Indigenous communities are shared by people in low- and middle-income countries (LMICs) [12]. Thus, interventions that work in LMICs may have a role in Indigenous communities and other similar populations.

In Canada, rates of hypertension in Indigenous populations are 20%, similar to the rest of the country [13]. Although data for treatment and control rates in Indigenous populations are lacking, higher cardiovascular disease rates suggest poorer control. A framework for discussion on how to improve the prevention, management, and control of hypertension from 2011 to 2020 describes this situation and calls for Indigenous populations to have similar rates of BP surveys and health indicators as the rest of the population [14]. Inequities in the social determinants of health—poverty, in particular—lead to poorer health outcomes in Indigenous communities than in the general Canadian population [15]. The social determinants particularly important for Indigenous health include income, education, employment, living conditions, adequate housing, and access to culturally competent health services. Indigenous health is also affected by the consequences of colonialism, including loss of language and ways of life and dispossession of traditional lands. This has led to food insecurity; environmental deprivation; and spiritual, emotional, and mental disconnectedness [16,17]. Compounding these issues are frequent experiences of social exclusion, discrimination, and racism [18,19]. All of these issues must be considered when undertaking a research project with Indigenous communities.

The DREAM3 (Diabetes Risk Evaluation and Management) study demonstrated that clinical practice guidelines could be implemented in Canada's First Nation's Communities leading to improved BP control. This community-based participatory randomized controlled research study in a Northern Canadian First Nations community was conducted in response to the community's goal of controlling BP in people with diabetes to prevent the progression of kidney disease [20]. The hypothesis tested was whether the implementation of a chronic care model implemented by the addition of a home and community care nurse to support the chronic care model could provide a more effective means of lowering BP than usual care. Our research showed that the implementation of the new model led to significantly better BP control [20]. Two years after the completion of the DREAM3 study, BP in the treatment arm remained controlled, and BP in the control arm had fallen equal to that of the treatment arm [21].

The DREAM3 program included many of the components of a sustainable chronic disease intervention initiative, which are as follows: (1) patient self-management and participatory care; (2) decision support tools and easy-to-use, evidence-based aids for providers; (3) clarity of delivery team roles with planned coordination; (4) clinical information system that can track the

progress of chronic disease management; (5) organization of health care delivery to accommodate the needs of chronic disease management; and (6) involvement of community-wide partnerships [22]. Furthermore, there was a focus on refreshing health education of skilled staff and educating new health care providers about new processes. The insights from the DREAM3 program have been integrated in the Dream-Global study, with an emphasis on changes in health services delivery supported by technology. Dream-Global incorporates patient self-management and participatory care by using texting (short message service, SMS) with BP readings, which provide the patient with the information they need to understand and participate in their own management. In the Dream-Global study, rather than increasing the burden of the home and community care nurses, task shifting was used to optimize the efficiency of the health care team and a dashboard was developed to track progress for each community. The SMS messages helped to link members of the interprofessional team, including the participant, the community health resource (CHR), the home and community nurse, and the participant's primary health care provider.

SMS text messaging has become more widespread in research since the Dream-Global protocol was developed. A recent meta-analysis has demonstrated that text messages increased adherence to drug therapy [23]. Most studies compare the use of SMS messages to usual care; the Dream-Global study is unique in comparing disease-specific active messages to passive messages alone and their impact on BP control.

The research program described in the Dream-Global protocol focuses on high BP prevention and control in First Nations communities in Canada and rural communities in Tanzania. It builds on our research as well as previous research on the efficacy and effectiveness of approaches to prevention and control of high BP. The program is designed to work within existing health systems and workflows [24]. The research program involves the active engagement of the participating communities. It is designed to be adaptive to the settings where the research is occurring; factors to be taken into consideration include social, economic, and cultural contexts; disparities in population health and disease burdens; existing health care models for chronic disease management; level of awareness of the importance of hypertension as a disease burden; and existence of national clinical practice guidelines designed to reduce the burden of hypertension. In Canada, Indigenous populations include First Nations, Métis, and Inuit people. The study recruited participants from six First Nations communities, all of whom lived on reserve. In Tanzania, this program is being implemented in rural communities in Hai district of the Kilimanjaro region. Due to differences in the structure and financing of the health care system in both countries, the protocols for each country vary in their design and implementation. The SMS intervention remains the same but in different languages (English in Canada and Swahili in Tanzania) [25].

The implementation of a complex intervention such as the Dream-Global program is strongly affected by cross-cultural relationships between local partners and outside researchers. Trickett and colleagues have argued that "culture pervades all aspects of community interventions" [26]. Strong community engagement and community-based participatory research (CBPR) are the necessary foundation for successful implementation of a pragmatic trial, particularly in diverse geographic and cultural contexts [24]. The CBPR approach developed for Dream-Global is designed to incorporate local knowledge in the research process by meaningfully engaging those affected by the issue under study in all aspects of the research. This research program is also informed by the Behavioral Change Wheel (BCW), an evidence-based theoretical model that explains the individual and system changes necessary to support hypertension management in low-resource settings [27]. The BCW model incorporates essential internal and external conditions necessary for behavioral change, including changes in supporting policies, mechanisms, and systems, and patients' capability, opportunity, and motivation [27]. The long-term goals of the Dream-Global research program are listed in Textbox 1. The program is designed to engage local decision makers and community leaders to involve multiple stakeholders from a variety of sectors, including the food industry, nursing, medical health, and public health, and to function smoothly with existing community programs. The components of the intervention will be robustly evaluated both individually and together to understand the relative contribution of each component and the synergies between them.

Objectives

In this paper, we outline the methods, tools, and processes of the Dream-Global research program. This research program was designed to integrate innovations in communications technology and health services delivery with the local realities of health care while taking into account each community's unique circumstances regarding geography, the social determinants of health, and the interplay between local, provincial, and federal health care systems.

This study includes the development of a community readiness to participate in research tool, a project to understand the sources of dietary sodium and how to reduce it in a remote community, the development of mobile health technology to incorporate BP measurement by nonmedical health workers, the transmission of the measurement to health care providers and patients, the development of guidelines-based culturally appropriate SMS messages for BP management, and the testing of these messages for BP lowering in a multicommunity randomized controlled trial in both Canada and Tanzania. The background information is provided here for both parts of the study, but for pragmatic reasons, the Tanzanian portion of the study was delayed and a fuller protocol is being prepared for separate publication.

Textbox 1. Dream-Global objectives.

- To ultimately reduce the prevalence of cardiovascular disease, including heart attack and stroke, as a consequence of blood pressure lowering
- To enable scale-up of larger programs at the local, regional, and national levels
- To develop a better understanding of key barriers at local and national levels that affect hypertension control and how they can be overcome
- To understand how innovations for hypertension control can be introduced and scaled up
- To improve hypertension control rates, particularly in vulnerable populations

Methods

Study Goals

The purpose of this study is to investigate the efficacy of an evidence-based system of SMS messages linked to accurately measured BP in the community. The individual BP measurements are taken by community health workers (CHWs). This innovation allows for transmission of accurate BP measurements from patients in isolated or underserviced populations to health care providers and, subsequently, improvement of patient knowledge about hypertension management. Participants in the Dream-Global study are randomized to receive either SMS messages that are both active and passive, compared with those receiving only passive messages. All messages are derived from the Hypertension Canada Clinical Practice Guidelines and are subsequently modified with community input to make them culturally sensitive and specific in both Canada and Tanzania [25]. The 12 active messages explain the importance of BP control, describe the rational for medical therapy, and, based on the BP reading, may instruct the participant to contact their health care provider for further BP follow-up. The 26 passive messages include health behaviors change advice for diet and exercise. Messages are sent twice weekly, on Monday and Thursday at 11 AM (to avoid holidays). The study is divided into five projects that involve the design, implementation, and then staging of the research program for the successful execution of a randomized controlled trial in both Canada and Tanzania.

Project 1 is to develop a readiness to participate tool. The tool entails a multidimensional checklist intended to assess community readiness for implementation of a research program for hypertension awareness, treatment, and control. The tool developed was piloted in both Canadian Indigenous and Tanzanian communities participating in the Dream-Global study with evaluation and feedback for validation [24].

Project 2 is a substudy to determine whether the sodium consumption of Indigenous people can be modified to help prevent hypertension. The goal was to plan and implement a food procurement policy for reducing sodium and fat intake from commercial food sources in an isolated Northern Indigenous community. This was approached by collating scientific evidence and existing policy recommendations, engaging community leaders and local food suppliers, and developing a policy approach for commercial food procurement practices. Evaluation includes process measures and examination of successes and barriers to implementation.

Project 3 entails the development of a closed loop app to transmit BP results taken by the CHR in Canada and the CHW in Tanzania to the health care provider and to the participant in a manner consistent with personal health privacy rules in each country.

Project 4 includes the development of a guidelines-based set of SMS messages in English that are culturally appropriate for Canadian First Nations communities and a set of SMS messages in Swahili that are culturally specific and appropriate for rural Tanzanian communities.

Project 5 will evaluate the impact of the active and passive messages together, compared with that of passive messages alone on BP control over 1 year through a prospective, pragmatic, randomized controlled trial in both Canada and Tanzania.

Blood Pressure Screening: Canada

In the Canadian Indigenous communities, the community nurse and CHR, a nonmedical health worker (analogous to CHWs in Tanzania), was trained in all aspects of the study, including BP measurement with the automated device, how to recruit, and how to consent participants. Consent was obtained from all participants, including the CHR, community nurse, and other members of the health care team and Band leadership who participated in surveys and interviews, as well as all participants for the BP measurement and lowering study.

Community leadership recommended that all interested individuals be allowed to participate as long as they are eligible. The study initially had focused on BP lowering, but to meet the community needs, a BP finding substudy was expanded to allow participants who were medically untreated but who screened below enrollment thresholds to participate. The screening BP was measured by trained Home and Community Care nurses or CHRs in community clinics using the BpTRU (BpTRU Medical Devices Ltd, Coquitlam, British Columbia, Canada), which takes six readings, omitting the first and averaging the final five. This BP reading, along with the participant's baseline demographics, was recorded on a data collection form, which was deidentified and faxed back to the study center. Participants for the BP lowering study had to have uncontrolled hypertension while being on or off medications. Uncontrolled hypertension was defined as 140/90 mm Hg or above, or 130/80 mm Hg or above for participants with diabetes. In this way, only people on medications and who had BP controlled to target were not eligible. By limiting subjects who were ineligible for ongoing BP monitoring and SMS messages, the study met the needs of the community. It was recognized that some subjects who appeared to have controlled BP at screening might turn out to

be uncontrolled and that some who appeared to be uncontrolled at screening might later turn out to be controlled.

Eligible participants were registered online. At registration, they were randomized electronically to receive active and passive SMS messages or passive only, and their names were then listed on the Dream-Global mobile app on the smartphone used by the Home and Community Care nurse or CHR in their community. BP was measured with the A&D UA-767PBT-C monitor (A&D Medical, San Jose, CA) to test that it was being transmitted properly; an SMS message to the participant's registered mobile phone, with the BP reading, was the confirmation of transmission. The Home and Community Care nurse and CHR were trained to take three BP readings with this device. The study server was programmed in such a manner that it waits for up to three readings and then sends their mean to the participant's own phone. Randomization through the study server ensured that participants and study personnel were blind to the allocation.

The baseline BP was defined as the mean of all readings from the A&D device in the first 2 months after randomization. If the average BP was uncontrolled during the first 2 months, the patient was identified as being in the BP lowering study; otherwise, they were followed up for BP screening. BP readings were stored on the central server, and deidentified data were transferred monthly to the data analysis center in Ottawa.

Blood Pressure Screening: Tanzania

A 6-week BP screening exercise in Tanzania was used as training to test the technology and the operationalization and feasibility of the protocol implementation in the participating rural communities in Kilimanjaro, Tanzania. CHWs were trained to utilize an Android smartphone with the study app. All eligible participating members were invited to participate in the BP screening study to measure community interest.

Canada-Specific Considerations

The Canadian arm of the project was carried out in six Indigenous communities located in three different geographic regions, including Ontario's Manitoulin Island, the James Bay Coast of Quebec, and the north shore of New Brunswick. Recruitment into the study began in the spring of 2013 and was completed by November 2015. The last patient exited the study at the end of 2016. Study participants were followed for a period of at least 1 year. Communities were selected through a semirandom method. Canadian Indigenous communities can be found on an interactive map maintained by the Government of Canada with profiles, including population information [28]. Potential communities included those with a population of at least 3000, existing 3G mobile phone service, stable governance, and a clinical champion to serve as a bridge between the Dream-Global study researchers and the community. Potential communities were listed and put into a random order. They were contacted one by one until it was felt that sufficient communities had been contacted to make the planned study enrollment. Communities were later assessed with the Intervention and Research Readiness Engagement and Assessment of Community Health Care (iRREACH) tool (see below) to determine their readiness for research and the necessary study adaptations required to meet their needs [24].

Following an invitation by the community to discuss the study, a visit was arranged with the Canadian study lead (ST) and study staff (NP) to introduce the Dream-Global research program. This was followed by another visit to determine research readiness with the iRREACH community research participation tool [24]. A Band or Tribal Council resolution was required to ensure that the study was endorsed by the community leadership. This was particularly important because the nonmedical worker, or CHR, was central to the functioning of the study. The CHR was not compensated by the study but rather by the community who felt that the study was of sufficient importance, including research capacity development to provide enough of the CHR's time to manage hypertension (typically 1 day per week).

The CHRs participating in the study in each community were identified by the community leadership. The CHR worked closely with a Home and Community Care nurse, and both were trained by the Dream-Global study staff to perform the BP measurements, to recruit, consent, and enroll study participants. The training took place over a period of 2 days and was conducted by one of the Dream-Global staff (NP). The training manual was developed with input from the communities and was designed to be culturally safe. As needed, weekly teleconferences were held between the CHRs, the Home and Community Care nurse, and the Dream-Global study team. These sessions were used to troubleshoot challenges with the technology, recruitment strategies, and BP management. The CHR or the Home and Community Care nurse were aware of the BP readings but were instructed not to act on them unless the readings were 180/100 mm Hg or higher or the participant appeared to be in distress. Every effort was made to get medical attention for the participant on an escalating scale based on the BP reading through the local health care system, even to the point of activating the local emergency medical system. Study staff were available at all times through their personal mobile phones via SMS texting or direct calls. Focus groups and key informant interviews were undertaken at the beginning and end of the study to understand the health team's response to the Dream-Global technology. Exit interviews were arranged for participants, including a knowledge test of the content of the SMS messages.

Pragmatic Aspects of the Randomized Controlled Trials

Pragmatic randomized controlled trials (RCTs) are designed to evaluate an intervention in real-life routine practice conditions in contrast to traditional explanatory RCTs that operate in optimal conditions [29]. When working with Indigenous community–based health research, including community engagement and community involvement in the design and study implementation, a pragmatic RCT supports data collection in a respectful and participatory way. It can determine whether the intervention is effective and works in a real-life setting. The Dream-Global study was designed to be a pragmatic study to meet the needs of the participating communities, to provide the ability to do a process evaluation to understand the ultimate

study results, and to increase the probability that evidence from the study could be used in clinical practice and policy [30].

Eligibility Criteria

Inclusion Criteria

Inclusion criteria were as follows: age 18 years or older and a diagnosis of hypertension for at least 12 weeks before screening. If already on drug therapy, continuation of the same dosing interval for 8 weeks before the screening for BP. Participants must be able and willing to provide written informed consent, possess a mobile phone capable of receiving SMS text messages, or, for those in Canada with no phone, willing to carry and learn to use a flip phone for the study duration.

Exclusion Criteria

People who meet the eligibility criteria for either of the above studies but have poorly controlled hypertension (BP>180/110 mm Hg), have an active malignant disease (except nonmelanoma skin cancer), are planning elective surgery during the study period (except for cataracts), are participating in another clinical trial, do not have a primary health care practitioner, are unable or unwilling to visit a health care provider, and/or are unable to read the SMS messages are ineligible for study participation. People on investigational drugs (in the 3 months before initial screening visit or during screening and treatment periods) or using SMS-related interventions (in the 12 weeks before screening or during screening and treatment periods) are also ineligible.

Local Health Provider Engagement and Support

In Canada, a continuing professional development information session was made available for local primary health care practitioners on the Dream-Global research program and hypertension clinical practice guidelines were updated. These sessions were held at least once for each region and took place on reserve or close to the reserve. In addition to the extensive training on the Tanzanian Standard Treatment Guidelines for Hypertension (2013) provided to the local health providers at the participating health centers, the research team in Tanzania collaborated with a local referral hospital to host an event on updated hypertension treatment guidelines and cardiovascular disease management.

Sample Size

For BP lowering, a reduction in systolic BP of 5 mm Hg is associated with a 14% reduction of stroke, a 9% reduction of coronary heart disease mortality, and a 7% reduction in total mortality; even reductions of 2 mm Hg are associated with significant benefits (−6%, −4%, and −3%, respectively) [28]. Thus, a significantly important difference could be as low as a 2-mm Hg change in systolic BP. In the DREAM3 study groups, systolic BP changed by mean 24.0 (SD 13.5) mm Hg and 17.0 (SD 18.6) mm Hg, with a between-groups difference of 7 mm Hg. Using the more conservative change in diastolic BP from that study, with mean 11.6 (SD 10.6) mm Hg versus 6.8 (SD 11) mm Hg in the control group (mean difference 4.8 mm Hg), provides an intraclass correlation coefficient for BPs between groups of 0.0133. This translates to an inflation factor of 1.1729 with 176 subjects per group for power of 97% to find the difference. Thus, a target was set for 360 participants to be recruited. The extra power was built in to allow for underrecruitment and a smaller difference in BPs between the groups.

The BP finding study is run as a pilot to determine the role of the Dream-Global program to identify the new onset of hypertension.

Blinding and Randomization

Participants were randomly allocated after enrollment using random number sequence with blocking of 2s and 4s for each community so that participants and study staff would not know which group participants had been enrolled. The randomization to receive active and passive or passive only text messages took place at the time of enrollment by the central server software. This information was available only to the database manager; participants, clinicians, and study staff had no knowledge of randomization.

Participant Flow

Canadian community members were invited to participate in the study through local advertisements and community engagement (town hall meetings and messages from the Band leadership). Referrals were also expected to come from all community health practitioners and Band leadership.

After enrollment, all BPs are measured with the A&D Bluetooth-enabled BP device by the CHR or Home and Community Care nurse in Canada or the CHW in Tanzania. Canadian participants typically meet the CHR in their office in the Band Council's health facility on reserve. In Canada, all consent forms were in English but could be translated for participants by the CHR if necessary. In Tanzania, all study information and consent forms are pretranslated into Swahili.

Attempts were made to discourage people living in the same house from enrolling in the study to reduce the potential for cross contamination between the messages. However, to respect the community leadership in both countries to make participation widely available, this could be overruled by the CHRs and CHWs if they felt it was necessary.

Generalizability

The study took place in Indigenous reserves in Canada and two rural communities in Tanzania. These communities were rural and remote, had limited access to primary care providers, and, in Tanzania, often had difficulty accessing medication for treatment continuity. In these communities, inconsistent BP measurement and follow-up, as well as poor access to antihypertensive medications, were known to contribute to poorer rates of BP control.

Statistical Analysis

All patients who receive at least one SMS message and for whom data for one or more follow-up BP reading is available will be included in the efficacy and safety analyses.

Efficacy Analyses

The primary efficacy endpoint in this study will be assessed by analysis of variance. Descriptive data will be given, with the

mean and standard deviation for continuous data and proportions for ordinal data. Preplanned exploratory subgroup analyses will include analysis by community, sex, diabetes status, phone ownership at baseline, and age. The knowledge gained from the text messages will be assessed by questionnaire at study completion, and results will be compared between the groups.

Safety Analyses

The primary study safety variable is the overall incidence of adverse events (AEs) between study entry and end. Descriptive summary statistics will be presented for the number and severity of AEs reported by each patient, overall and by individual organ system. The upper limit for the 95% one-sided CI for the incidence of the most frequent AE will be calculated.

Meta-Analysis

This study is one of the series of clinical trials being undertaken by the Global Alliance on Chronic Disease (GACD). In addition to the study-specific analyses outlined above, study data will become part of a common database for all clinical trials in the GACD hypertension series to perform meta-analyses. These analyses will be defined prospectively and are intended to identify subpopulations and other baseline characteristics of treatment patients that may influence treatment outcomes. Only denominated data will be used. Analysis and dissemination will take into account the principles of shared ownership of research findings held by university-based researchers and community partners as outlined in the research agreements.

Development of SMS Message Bank

The development of the SMS messages took place through a process of community engagement with Indigenous and Tanzanian communities who were motivated to participate in the research program. Through a series of focus groups and individual interviews with health care providers and people with hypertension, as well as with other community stakeholders, we developed culturally appropriate and acceptable SMS messages through a process that has been published [26].

Quality Control

The overall procedures for quality assurance of clinical study data follow those of Good Clinical Practice and the principles of ethical research involving the First Nations, Inuit, and Métis People of Canada as put forth in the Tri-Council Policy Statement 2 (TCPS2) [27]. A data safety monitoring board was established for this study to monitor the study annually.

Ethics Approval

Approval to conduct the study in Canadian and Tanzanian communities was granted by community leadership in each community. Furthermore, in Tanzania, approval consent and advice was also sought from the Kilimanjaro Regional Medical Officer (RMO), the Hai District Medical Officer (DMO), and the National Institute of Medical Research (NIMR), whose ethics board reviewed the protocol.

The study protocol has been approved by local ethics boards, including The Cree Board of Health and Social Services of James Bay, Ontario (July 10, 2013); the Cree Nation of Chisasibi (August 15, 2013); Manitoulin Anishnabek Research Review Committee (October 7, 2013); the National Institute for Medical Research in Dar es Salaam, Tanzania (approved on March 19, 2014); and Northwest Territories Scientific Research License number 15317 (August 8, 2013). It has also been approved by institutional ethics boards, including the University of Calgary (REB13-0573; September 23, 2013); Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board, Kingston, Ontario (DMED-1603-13 approved on June 21, 2013); Sunnybrook Research Institute Research Ethics Board, Toronto, Ontario (ID number 053-2013; May 10, 2013); and the National Institute for Medical Research Tanzania (NIMR/HQ/R.8a/Vol.IX/1698).

Privacy and Cultural Considerations

The study data are housed in a secure central server with appropriate safeguards for data security and backup and appropriate privacy provisions to avoid deidentification of personal data. The study will maintain the principles of Good Clinical Practice and the principles enunciated in the Declaration of Helsinki and the TCPS on ethical conduct for research involving humans [31,32]. This study will adhere to the principles of ownership, control, access, and possession; our group has experience of working within this important framework [33]. The partners already adhere to the principles of the Personal Information Protection and Electronic Documents Act (PIPEDA), and movement of data in this study will be compliant with this act.

Program Governance

The Dream-Global team was designed to be multidisciplinary and interprofessional, including First Nations community representatives. The research program brings together nationally recognized leaders in clinical practice guidelines' implementation and clinical trials and research in hypertension, with expertise to work collaboratively with First Nations communities. Decision makers and the multidisciplinary team members were invited to provide letters of support to clarify their roles. A steering committee was developed and tasked with ensuring that proposed intervention strategies were appropriate for the social, cultural, and economic contexts. Annual research meetings provided a forum to share plans with broader team and community members, as well as to receive feedback before implementing plans. Research reports were also developed and presented to the annual GACD research forum, which included oversight from the CIHR.

Knowledge Translation and Engagement

Annual presentations will be made to each community on the study's progress. At the end of the study, presentations are made to the community leadership, health care providers and participants, and community members through town-hall style meetings. Results will also be summarized in a poster for the communities. Annual presentations are made at the GACD study meeting, at which the other 14 study teams also present their updates.

Textbox 2. Requirements of the Dream-Global app.

- Participants must be registered securely.
- Participants' names will only show up on their community health resource's or community health worker's Dream-Global smartphone.
- Blood pressure readings on the A&D Medical monitor would transmit by Bluetooth to the smartphone.
- Blood pressure readings on the smartphone would be transmitted to the central server.
- A mean of the readings received by the central server would then be sent to the participant's own phone (different from the community health worker's smartphone).
- The central server will send the mean of the readings to the participant's health care provider by fax in the form of a letter, based on the information provided at registration (Canada only).
- The server will be programmed to assess the blood pressure reading as normal or high and, if high for the participants receiving active messages, to advise them to see their health care provider for blood pressure management. In Canada, messages will include the phone number of their health care provider; in Tanzania, messages will include the location and weekdays on which the local blood pressure assessment clinic is running.

Abstracts will be presented at local, national, and international meetings as appropriate, and there will be publications in the peer-reviewed literature documenting the study progress and results. Furthermore, semiannual presentations will be made to Health Canada, specifically for the First Nations and Inuit Health Branch that funds the Home and Community Care health delivery in most First Nations communities. Semiannual progress reports are also submitted to the National Institute for Medical Research Tanzania.

Other efforts will be made to present to policy makers and payers and to community leadership to promote sustainability and scalability at the end of the study. Interested parties will be given the chance to read (or have read to them) the information sheet and ask any questions before providing written consent. Copies of the information sheet and consent form will be given to study participants. All personally identifying information will be removed from study documents. Study participants will be identified using a unique alphanumeric number. To track participants, a list linking the name and home address of each person will be maintained in a locked filing cabinet.

Technical Aspects of mHealth Component

The app and database are hosted at a Health Insurance Portability and Accountability (HIPPA)-compliant Canadian Provincial Crown Corporation providing sufficient reliability to maintain 99.999% uptime to meet the study needs. The field interface includes automated BP measurements by CHWs trained to do BP measurements according to the guidelines. The Bluetooth-enabled automated BP device (A&D Medical, UA-767PBT-C, San Jose, California) then transmits information via Bluetooth to the Android or BlackBerry mobile device carried by the CHW. The requirements of the app are listed in Textbox 2. The tools were tested and validated in pilot focus groups in participating communities.

The messages will be sent via a central app and database server that is ISO1348 and Food and Drug Administration–certified and brokered by an International SMS Gateway to study participants. To facilitate the BP measurement and interaction between patient and provider, algorithms were developed both at the app server level (in the cloud) and on Android/Blackberry-based devices for deployment in the field.

Blood Pressure Control Study and Primary and Secondary Outcomes

For the BP control study, the primary outcome is the difference between the two groups in BP change from baseline to study end (both systolic and diastolic). One year was chosen as a target for BP monitoring to allow for sufficient measurements and to reduce the Hawthorne effect, in which improved BP control from better adherence might occur for the period after study enrolment [34]. To reduce the effect of regression to the mean, the baseline BP was defined as the mean of the BP readings (each mean of three measures) taken with the A&D UA-767PBT-C in the first 2 months after enrolling in the study. The final BP measurement is the mean of the last 2 to 3 measurement days, usually in the last 2 months, to reduce variability from a single set of readings. The secondary outcome is the proportion of participants achieving BP control during the study period.

Results

The iRREACH tool was developed and used in all study sites in both countries [24]. Text messages derived from the Hypertension Canada Clinical Practice Guidelines were developed and revised based on focus groups in both countries as has been described [26]. A process evaluation is being developed [35]. Six communities were enrolled in the study in Canada, and recruitment was completed in November 2015. The last patient completed the study in December 2016. In total, 234 participants enrolled in the program and had at least one set of transmitted BP readings.

Discussion

The purpose of this research program is to integrate technologic solutions with innovations in health service delivery to improve the treatment and control of hypertension. This requires integration of the scientific and social aspects of this study with business and governmental partners to design proper public-private partnerships that can be sustainable over time. Users and health care providers are involved in the development and refinement of this technology from its outset to ensure that it is useful for them. The data gathered will hopefully be of great interest to businesses and policy makers for developing

ongoing sustainable business models and for scaling up in more communities. It will also inform community decision makers and governmental partners so they can promote policy changes. One marker of success for this project will be obtaining funding from Health Canada to maintain the program for the communities participating in Dream-Global, as well as others who become interested in participating at study end.

In conclusion, this study is expected to provide useful insights into the acceptability and effectiveness of an innovative system of community-based screening, treatment, and follow-up for hypertension in remote Indigenous communities in Canada. If it proves successful in this environment, then it should also be beneficial in nonindigenous settings in rural and remote areas, as well as urban settings. This work will expand an already successful body of research on bringing clinical evidence into daily practice for hypertension and can serve as a model for addressing other noncommunicable diseases in settings with limited access to health care resources. Integrating innovations in technology, health service delivery, and business models is a novel potential approach to achieve sustainable control and prevention of hypertension in particular and to address the *implementation gap* in chronic diseases in general. We will demonstrate whether the simple yet practical solution of linking hypertensive individuals with their health care providers and their personal health and medical records through SMS technology on mobile phones will lead to improved BP control and, by extension, improved outcomes.

Acknowledgments

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Conflicts of Interest

NC is a consultant to Novartis Foundation (regarding hypertension control in low- to middle-income cities) and to Midmark (regarding examination table design).

Multimedia Appendix 1

CIHR peer-review report.

[PDF File (Adobe PDF File), 7KB - resprot_v6i12e244_app1.pdf]

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Abbreviations

AE: adverse events
BCW: Behavioral Change Wheel
BP: blood pressure
CBPR: community-based participatory research
CHR: community health resource
CHW: community health workers
DMO: district medical officer
DREAM3: Diabetes Risk Evaluation and Management
GACD: Global Alliance on Chronic Disease
iRREACH: Intervention and Research Readiness Engagement and Assessment of Community Health Care
LMIC: lower- and middle-income country
NIMR: National Institute of Medical Research
RCT: randomized controlled trial
RMO: regional medical officer
SMS: short message service
TCPS2: Tri-Council Policy Statement 2

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Protocol

The Effect of Group Support Psychotherapy Delivered by Trained Lay Health Workers for Depression Treatment Among People with HIV in Uganda: Protocol of a Pragmatic, Cluster Randomized Trial

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Abstract

Background: There is limited information on the effectiveness of task shifting of mental health services in populations with HIV.

Objective: This trial aims to evaluate the effectiveness of group support psychotherapy delivered by trained lay health workers to persons living with HIV (PLWH) with depression in primary care.

Methods: Thirty eligible primary care health centers across three districts were randomly allocated to have their lay health workers trained to deliver group support psychotherapy (intervention arm) or group HIV education and treatment as usual (control arm) to PLWH with depression. Treated PLWH will be evaluated at baseline, after the end of treatment, and at 6-month intervals thereafter for 2 years. Primary outcomes will be the difference in follow-up proportions of participants with Mini International Neuropsychiatric Interview criteria for major depression and difference in follow-up function scores of participants in the intervention and control arms 6 months after the end of treatment. Secondary outcomes will include measures of self-esteem, posttraumatic stress symptoms, social support, stigma, adherence to antiretroviral therapy, viral load, and number of disability days, asset possession indices, and cost-effectiveness data. Primary and secondary outcomes as well as subgroup analyses will be conducted at the individual level using multilevel random effects regression analyses adjusting for clustering in health centers.

A process evaluation using mixed methods to assess acceptability, feasibility, fidelity, causal mediating processes, and contextual influences in the trial will be conducted.

Results: The trial has been approved by the Makerere College of Health Sciences School of Health Sciences Research Ethics Committee, the AIDS Support Organization, and the Uganda National Council of Science and Technology. A data and safety monitoring board has been put in place to monitor trial progress. A total of 1140 persons living with HIV have been recruited to the trial. An analysis of baseline and 6-month data is in progress. The results of this trial will not only be presented at national and international conferences but also submitted for publication in peer-reviewed journals and as a report to the funding agencies.

Conclusions: This cluster randomized trial will provide critical evidence to support culturally sensitive group-based psychotherapy for depression treatment in sub-Saharan Africa. Process evaluation outcomes will provide contextual information that health care and public health stakeholders can use to guide implementation decisions for their particular setting.

Trial Registration: Pan African Clinical Trials Registry (PACTR): 201608001738234; http://www.pactr.org/ATMWeb/appmanager/atm/atmregistry?dar=true&tNo=PACTR201608001738234 (Archived by WebCite at http://www.webcitation.org/6vUAgAQlj)

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KEYWORDS

cluster randomized trial; group support psychotherapy; lay health workers; depression; persons living with HIV/AIDS; Uganda

Introduction

In the fight against the HIV epidemic over the past three decades, one of the major barriers to universal access to health care needed by persons living with HIV (PLWH) has been a serious shortage of health workers to deliver these interventions [1]. The shortage of well-trained health workers to address the myriad biological, social, and psychological challenges of living with HIV poses a risk for suboptimal HIV treatment outcomes, particularly in sub-Saharan African countries where the burden of HIV and acquired immune deficiency syndrome (AIDS) is greatest [2]. For example, the lack of capacity to provide mental health care such as screening for depression in HIV care programs results in undetected and untreated depression, which impairs the ability to adhere to antiretroviral (ART) medications [3,4]. Affected individuals continue to struggle with poor health, social, and economic outcomes because depression impairs their ability to function in their families, at work, and in their communities [5,6].

The World Health Organization (WHO) HIV treatment guidelines now recognize depression treatment as central to effective HIV treatment programs [7]. This, in turn, has resulted in the development and testing of a number of psychological interventions for depression that can be used in poor resource areas where the gap between the availability and need for mental health services [8-10], known as the “treatment gap,” may be as high as 90% [11]. Unfortunately, accessibility and sustainability of these interventions is impeded by the severe shortage of mental health professionals who can deliver them to affected individuals who need them [12].

Task-shifting approaches, whereby nonspecialist health workers in primary care and community settings are trained to deliver some of the mental health services that were provided solely by specialist mental health professionals, have been recommended by global mental health researchers and practitioners [13] as well as the WHO. The WHO recommends that these task-shifting approaches must use standardized and simplified interventions that can realistically be administered by less highly trained professional health care workers and nonprofessional community members [2]. However, studies describing the implementation of task-shifting approaches in delivery of psychological interventions for PLWH in sub-Saharan Africa are limited.

In a recent review of studies documenting the effectiveness of psychological interventions for PLWH in low- to middle-income countries, none of the studies that met criteria for inclusion in the review demonstrated the use of a task-shifting approach in the delivery of the intervention [14]. In a recent review of studies describing mental health training of health care workers in Africa, only three of the 37 studies reviewed described training of lay health workers (LHWs) [15]. There is a need for information on how a task-shifting approach can be used to make a psychological intervention for depression accessible and sustainable in low-resource settings.

The shifting of mental health related tasks from health professionals to LHWs has been repeatedly documented in non-HIV populations [16-19]. However, because mental health has not been integrated into HIV care in sub-Saharan Africa, little is known about the effectiveness of task shifting of mental health related services such as depression care. Also, identifying mediators and moderators of intervention response is a critical step in understanding the mediating causal factors as well as for whom and under which conditions an intervention is most beneficial [20]. This knowledge also has important implications for practice, as it can aid in tailoring and modifying interventions so as to be maximally effective for specific target populations.

To address this knowledge gap, we set out to conduct a cluster randomized trial to test the effectiveness of group support psychotherapy (GSP) delivered by trained LHWs. The recommended methodological approach to establish the efficacy of a newly developed therapy such as GSP is to first compare the therapy against a comparison group that omits the unique ingredients of the new therapy while possessing the common factors (eg, therapeutic alliance) in equal measure [21]. Thus, we compared the effects of GSP to those of group HIV education (GHE) delivered by trained LHWs on mild to moderate

depression and functioning among PLWH attending primary care health centers in northern Uganda. We hypothesized that compared with the control arm, the proportion of participants that meets the Mini International Neuropsychiatric Interview (MINI) criteria for major depression will be lower and the function scores will be higher in the intervention arm 6 months after the end of treatment.

Secondarily, we aimed to compare the effects of GSP and GHE delivered by trained LHWs to PLWH presenting with mild to moderate depression in primary care on measures of self-esteem, posttraumatic stress symptoms, social support, stigma, adherence to ART, viral load, number of disability days, asset possession, poverty indices, and cost-effectiveness measures. We hypothesized that compared with PLWH receiving GHE, those receiving GSP will achieve a greater increase in social support and positive coping skills and greater reduction in stigma; larger increases in adherence to ART and greater reduction in viral load; and greater reduction in number of disability days, greater increase in asset possession scores, and larger reductions in poverty index scores at 6, 12, 18, and 24 months after the end of treatment.

We also plan to conduct a process evaluation of trial activities informed by Linnan and Steckler's process evaluation frameworks [22] to specifically determine indicators of feasibility including *reach* (ie, the proportion of participants who received the intervention), *dose delivered and received* (ie, the amount of intervention delivered and the extent to which participants respond to it), as well as *attrition* (ie, the proportion of participants who are lost to follow-up); indicators of acceptability including satisfaction with intervention content, delivery agents and effects; *fidelity* (ie, whether the intervention is delivered as planned); and causal mediating processes and contextual influences. Given that gender has far-reaching implications for social roles, opportunities, and experience of adversities in traditional societies such as in Uganda [23], we will determine whether or not the effects of GSP are moderated by gender. Both posttraumatic stress [24] and alcohol use disorders [25] are associated with an increased risk for depression. Therefore, we will also examine whether or not the effects of GSP are moderated by psychiatric comorbidities. Extensive reviews of literature [26,27] have found that common factors such as the therapeutic relationship may account for up to nine times greater impact on patient improvement than the specific mechanisms of action found in formal treatment protocols. Therefore, we shall assess whether the strength of a therapeutic relationship will mediate the effects of GSP on depression and subsequently other study outcomes. Identifying groups of individuals for whom GSP works best will assist in the goal of developing selection criteria to guide the referral of patients for GSP.

Methods

Study Design

This is a pragmatic two-arm cluster randomized trial evaluating the effectiveness GSP delivered by trained LHWs to persons with HIV presenting with mild to moderate depression in primary care. The study involves LHWs affiliated to 30 primary care health centers (PHCs) in three districts in northern Uganda. Eligible PHCs were randomly assigned (1:1) to have their LHWs trained in the delivery of GSP (intervention) or GHE (control) to PLWH with mild to moderate depression. PLWH treated by trained LHWs will be evaluated at baseline, at the end of intervention, and at intervals of 6 months thereafter for 2 years.

A longitudinal process evaluation of the delivery of GSP by trained LHWs using mixed methods will run alongside the trial to assess acceptability, feasibility, fidelity, and how intervention recipients respond to the different intervention components. Analysis is performed according to the intention-to-treat (ITT) principle and will account for the cluster randomized design. The study protocol is registered in the Pan African Clinical Trials Registry (PACTR201608001738234), and the reporting of the trial will be in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [28] for intervention trials (see Multimedia Appendix 1) and the CONSORT statements for cluster randomized trials [29].

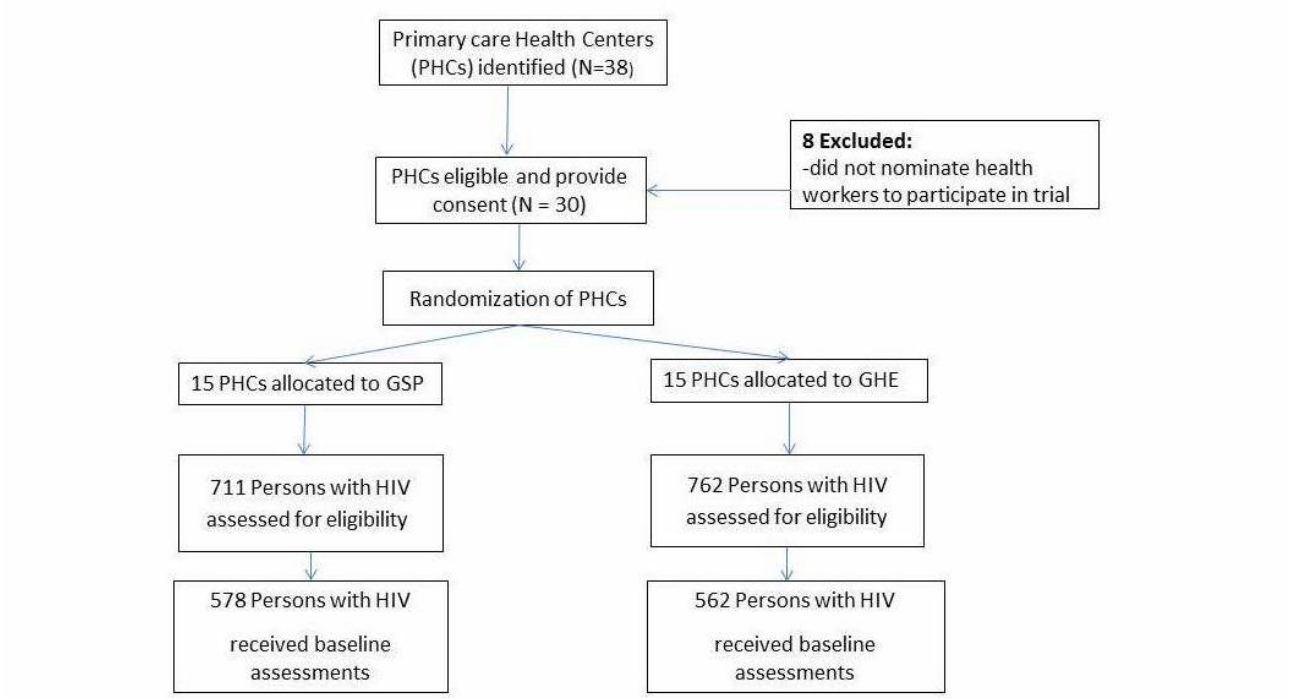
The study was submitted to and approved by both the Makerere University College of Health Sciences Research Ethics Committee and the Uganda National Council of Science and Technology. All study participants will be required to provide written informed consent. Light refreshments will be served during all group sessions in both arms, and every participant will receive a financial incentive to defray transport costs. Figure 1 summarizes the trial profile.

Study Setting

This trial has been implemented in 30 PHCs situated in three districts in northern Uganda (Gulu, Kitgum, and Pader) with a population of 450,000, 247,000, and 250,000, respectively. Over 90% of the population is engaged in small scale agriculture and animal husbandry as their major income-generating activity. The brutal civil war that the people of these districts endured for two decades (1987-2007) led to a breakdown of health care delivery systems, disorganized social and cultural life with minimal economic activity, and loss of property and infrastructure in these districts. This situation of precariousness led to high poverty rates, risky behaviors including excessive alcohol consumption, and sexual violence making the population highly vulnerable to depression and HIV/AIDS [30].

The first level of health care accessible to this study population is provided by LHWs who work in teams referred to as village health teams. The village health team is affiliated with other PHCs at the second level (Health Center II), third level (Health Center III), or fourth level (Health Center IV), which are led by professional health workers who supervise their outreach activities [31].

Figure 1. Trial flowchart: selection of clusters and participants.



Participants

Cluster Eligibility Criteria, Recruitment, and Randomization

To be eligible for the trial, the primary care health centers had to offer HIV care and treatment services, nominate at least four LHWs (2 men and 2 women) who are actively involved in HIV care, able to read and write, and reside within the villages served by the PHC. PHCs that do not offer HIV care services and those unable to nominate literate LHWs were excluded from the study.

To recruit PHCs, the project team worked with the district health officials in each of the three participating districts and identified a total of 38 PHCs that offered HIV care and treatment services. The health center managers of these centers were informed about the trial and asked to nominate health workers to participate in the trial. The first 10 PHCs in each district that expressed interest in the trial and nominated the required number of health workers were recruited to the trial. The health center managers of the 10 eligible PHCs in each district were invited to a stakeholders' meeting held at the district's local government offices with political leaders, district health officials, religious leaders, and community leaders. Study purpose and procedures were explained to facilitate district leadership understanding of the trial activities. At the end of the meeting, the eligible PHCs were randomly allocated with a 1:1 ratio to intervention and control arms. Randomization was done by urn randomization picked by each health center manager or their representative who attended the stakeholders' meeting.

Participant Eligibility Criteria, Recruitment, and Masking

To be eligible for the study, PLWH had to be 19 years and older, diagnosed with major depression assessed with the MINI depression module [32], antidepressant naïve, using ART, and residing in the villages where the trained LHWs lived. Individuals with high suicide risk [33], a severe medical disorder such as pneumonia or active tuberculosis, psychotic symptoms, and hearing or visual impairment were excluded from the study.

On a given clinic day, project research assistants worked with primary care health workers of a participating PHC in the center's HIV clinic. The primary care health worker gave a health talk on depression to clients in the waiting area. Clients who felt that they had experienced symptoms of depression described in the health talk were invited for further evaluations using the Luo version of the 20-item self-reporting questionnaire [34] and the MINI depression module. This procedure was repeated until a total of 40 PLWH diagnosed with major depression were obtained from a given PHC.

Clients diagnosed with major depression were approached by research assistants who explained study procedures, determined eligibility, and then obtained informed consent. Each client who gave informed consent received baseline assessments with a standardized questionnaire. Recruited participants from the same village were assigned to a trained LHW residing in or near their village to receive the intervention they had been trained to deliver (ie, either GSP or GHE).

By design, both experimental and control interventions were identifiable to participants but will be masked to outcome assessors, the Data and Safety Monitoring Board, and data analysts.

Interventions

The development of the GSP and GHE interventions has been described in detail in previous publications [35,36]. Multimedia Appendix 2 shows a detailed description of the content of both interventions, which has also been previously published [37].

Group Support Psychotherapy Training

Over a 4-month period (January-April 2016), Makerere University in collaboration with the Ministry of Health designed a GSP training program that consists of both formal and informal training. Between May and August 2016, the training-of-trainers model was used to deliver the training, whereby mental health specialists trained PHC health workers who in turn trained the LHWs. Formal training consisted of 8 training modules delivered in a 5-day training workshop that employed active learning techniques including role plays, brainstorming sessions, and small group discussions.

In brief, the first three modules including an overview of the training program, introduction to the GSP model, and introduction to depression and HIV/AIDS were delivered on the first day. On the second and third days, modules on basic counseling skills and effective coping strategies were delivered, respectively. On the fourth day, participants received training in basic livelihood skills (enterprise selection, basic financial skills, and resource mobilization) required to overcome poverty. The last day of training focused on self-care strategies, post-training assessments, and training workshop evaluation. Informal training consisted of conducting supervised pilot GSP sessions. Multimedia Appendix 3 summarizes the competencies targeted by the training.

Group HIV Education Training

In May 2016, Makerere University in collaboration with The AIDS Support Organization (TASO), designed a group HIV education training program that consisted of both formal and informal training. Between May and August 2016, the training-of-trainers model was used to deliver the training, whereby TASO HIV care providers trained PHC health workers who in turn trained the LHWs. Formal training consisted of five training modules delivered in a lecture format in a 2-day training workshop. In brief, on the first day, three modules including an overview of the training program, introduction to depression and HIV/AIDS, HIV progression and transmission were delivered. On the second day, modules on mother-to-child transmission and basic facts on ART were delivered. Informal training consisted of conducting supervised pilot GHE sessions.

Intervention Fidelity

Between September and December 2016, trained LHWs delivered the interventions to PLWH with mild to moderate depression recruited to participate in the trial. Strategies to ensure treatment fidelity in both treatment arms included the use of standardized intervention materials, structured health worker training, ongoing supervision, and training a larger number of LHWs than was required in order to avoid potential disruptions due to illness or job transfers. The LHWs underwent standardized training by trained primary care health workers. Each LHW delivered GSP or GHE following a manual translated into the local language. Prior to the sessions, each LHW drew up a schedule indicating which day of the week each group session would take place and handed it over to their supervisor. Of the 8 sessions to be delivered, 3-4 sessions were supervised by a trained PHC worker who assessed the LHW's basic counseling skills using a supervision checklist with items adapted from the Enhancing Assessment of Common Therapeutic Factors scale [38].

In addition, the LHWs who facilitated group sessions were required to complete a self-administered semistructured feedback questionnaire after each group session in which they described content delivered in each group session and provided feedback on facilitators and barriers faced during the group session. Their feedback was discussed with their supervisors who advised on how to address any difficult issues raised. From this feedback, supervisors were able to assess whether the intervention delivery progressed as planned or not and to intervene accordingly.

Participant Safety

During baseline assessments, participants were carefully screened and individuals for whom the interventions were deemed medically inappropriate or unsafe were excluded. Outcome assessors screened all participants for adverse events at the end of treatment and at 6 months after the end of the intervention using a standard interview and reporting form. Going forward, follow-up assessments will continue at 6-month intervals up to 2 years after the end of treatment. Any unfavorable and unintended sign or symptom associated with the participation in either intervention, regardless of whether it is considered related to the therapy is reviewed by the investigating team for seriousness, study relatedness, and expectedness. Similar information reported by participants at other times (eg, during intervention encounters) is duly noted and followed up with, as needed, to assure participant safety. Adverse events are reported according to the data and safety monitoring plan shown in Multimedia Appendix 4.

Retention

Currently, trial participants have received their 6-month outcome assessment and will be due for their 12-month outcome assessment in January-February 2018. In order to maximize adherence and retention, we formed community advisory boards to monitor community satisfaction with implementation activities and to provide feedback to investigators in real time on any conflicts or dissatisfaction arising from project implementation activities. Lay health workers who facilitated the group sessions and the primary care health workers who supervised them were provided with a financial incentive as an appreciation of their commitment to the project. For participants who missed group sessions, the LHWs made home visits to re-engage them. Given that group sessions took place in the villages, the LHWs know the homes of the participants and have been able to mobilize them to return for their follow-up assessments.

Study Measures and Data Collection Schedule

So far, assessments of study measures have been conducted at baseline, at the end of the interventions (2 months), and 6 months after the interventions. Going forward, further assessments will be conducted at 12, 18, and 24 months after the intervention. Table 1 [32,34,39-47] summarizes the study measures including the primary and secondary outcomes, process evaluation outcomes, potential effect modifiers, and mediators.

Table 1. List of study measures and data collection schedule.

Study measures	Instrument	Data collection schedule (months)					
		0	2	6	12	18	24
Primary outcomes							
Major depression	The Mini International Neuropsychiatric Interview [32]	✓		✓	✓	✓	✓
Functioning level	5-item locally developed function assessment method [39]	✓		✓	✓	✓	✓
Secondary outcomes							
Depression symptoms	Self-Reporting Questionnaire [34]	✓		✓	✓	✓	✓
Posttraumatic stress symptoms	Locally adapted Harvard Trauma Questionnaire [40]	✓		✓	✓	✓	✓
Alcohol use	10-item Alcohol Use Disorders Identification Test [44]	✓		✓	✓	✓	✓
Disability days	Single question "How many working days have you lost due to depression-related symptoms in the previous 30 days?	✓		✓	✓	✓	✓
Cost-effectiveness	Estimation of incremental costs of the GSP intervention arm as compared to the control arm	✓		✓			✓
Poverty index scores	Questions on indicators of socioeconomic status such as the building materials of the household dwelling unit, access to electricity, type of cooking fuel, source of lighting, household remoteness (distance to nearest health facility), household food security, household durable assets such as radios, televisions, and mobile phones	✓		✓			✓
Adherence to ART	One question: "During the past week, on how many days have you missed taking all your medication doses?"	✓		✓	✓	✓	✓
Viral load	Medical charts of study participants	✓		✓		✓	
Potential effect modifiers							
Sociodemographic variables	Standardized Demographic Questionnaire	✓					
Trauma events	Locally developed 16-item trauma event checklist	✓					
Potential effect mediators							
Self-esteem	Rosenberg Self-Esteem Scale [41]	✓		✓	✓	✓	✓
Social support	12-item Multi-Dimensional Perceived Social Support scale [42]	✓		✓	✓	✓	✓
HIV-related stigma	HIV-related stigma scale [43]	✓		✓	✓	✓	✓
Coping skills	COPE Inventory [45]	✓		✓	✓	✓	✓
The therapeutic relationship	The Scale to Assess the Therapeutic Relationships–Patient version [46]		✓				
Process evaluation outcomes							
Indicators of feasibility	The proportion of eligible participants who take up either intervention (Reach), the proportion who attended all 8 sessions of either intervention (dose delivered), and the proportion who are lost to follow-up (attrition) will be determined from the attendance registers		✓				
Indicators of acceptability	A 9-item questionnaire [47] will assess participant's satisfaction, the group facilitators' knowledge and attitudes, and the participant evaluation of the intervention's ability to reduce depression.			✓			
Fidelity	A semistructured self-administered questionnaire completed by group facilitators will assess whether or not the interventions were delivered as planned.		✓				
Contextual influences	A semistructured self-administered questionnaire completed by group facilitators will assess any facilitators or barriers to intervention delivery that they observed during group sessions.			✓			
Causal mechanisms	A semistructured interviewer-administered questionnaire will assess participant's knowledge, skills, or assets acquired during and after the interventions, which will give an indication as to whether or not the interventions influenced targeted risk factors for depression.			✓			

Table 2. Sample size and power calculations.

Alpha	Beta	*k*	Cluster size	Control group proportion	Intervention group proportion	Minimum clusters required	Resulting power
.01	.2	.25	32	0.25	0.15	18	0.808
.05	.2	.25	32	0.25	0.15	12	0.803
.01	.2	.25	40	0.25	0.15	16	0.818
.05	.2	.25	40	0.25	0.15	11	0.823
.01	.2	.25	32	0.3	0.15	10	0.842
.05	.2	.25	32	0.3	0.15	7	0.849
.01	.2	.25	40	0.3	0.15	9	0.851
.05	.2	.25	40	0.3	0.15	6	0.84

Sample Size and Power Calculations

Primarily, our objective is to compare the proportion of subjects with mild to moderate depression in the intervention and control arms 6 months after the end of treatment. Based on results from our pilot project, we assume that the difference in proportion of depression cases at 6 months follow-up between intervention (15%) and control arms (25%) would be 10%. Using formulae proposed by Hayes and Moulton [48], and assuming the between-cluster coefficient of variation *k* of .25, a study with 12 nonmatched pairs of clusters, and a cluster size of 32 PLWH (total expected sample size of 768 PLWH) would have 80% power of detecting a 10% reduction in major depression cases at the 5% significance level. Table 2 illustrates the sample size and power calculations for various assumptions made. The number of clusters has been increased to 15 pairs to allow for individual level analyses using multilevel random effects regression models, and the cluster size was increased to 40, accounting for a potential 20% loss to follow-up.

Data Collection and Management

Study participants in the intervention and control arms will be asked to complete an interviewer-administered face-to-face standardized questionnaire to collect data on primary and secondary outcomes at baseline (T0), after completion of their group treatments (T1), and 6, 12, 18, and 24 months after end of treatment (T2, T3, T4, and T5 respectively). All the completed survey questionnaires will be reviewed by a research team member for missing data and unusual responses. Data will be entered into an EpiData (version 3.1) database. Regular reports will be produced on (1) patient accrual and follow-up completion/retention in relation to goals and timeline, (2) the randomization process and group comparability on the balancing variables, (3) key baseline characteristics of the sample, by (blinded) group, related to the primary and secondary outcome variables and proposed effect modifiers and mediators, (4) intervention exposure and adherence, and (5) protocol violations. Any observed delays in these processes or data irregularities will be followed up and resolved in a timely manner.

The complete de-identified dataset of the trial will be publicly available when finalized. Details of the data and safety monitoring plan and the study governance structure are shown in the Multimedia Appendix 4.

Statistical Analyses

We will assess randomization across the two arms by comparing sociodemographic characteristics and other potential confounding variables using chi-square for categorical variables, and *t* tests or other equivalent nonparametric tests, as appropriate, for continuous variables. Primary outcomes will be the difference in follow-up proportions of participants who meet MINI criteria for major depression and difference in follow-up function scores of participants in the intervention and control arms 6 months after the end of treatment.

Secondary outcomes will include measures of self-esteem, posttraumatic stress symptoms, social support, stigma, alcohol use, ART adherence, viral load, number of disability days, asset possession indices, and cost-effectiveness data. Primary outcomes, secondary outcomes, and all subgroup analyses will be analyzed by ITT using a multilevel mixed model adjusting for clustering in health centers to determine effect modifiers [49]. The status of randomization (intervention/control) and baseline depression score will be included as a covariate. To account for the clustered design, we will treat clusters as a random effect. Potential confounding variables (eg, age, gender, socioeconomic status) with significant differences across intervention and control arms will be included as fixed factors. The R statistical software will be used to conduct all analyses [50]. A process evaluation using mixed methods to assess acceptability, feasibility, fidelity, causal mediating processes, and contextual influences in the trial will be conducted.

The primary analysis will follow ITT principles and use all available follow-up data, with missing data handled directly through maximum likelihood estimation in mixed modeling. We will document the extent and pattern of missing data and the reasons and will conduct sensitivity analyses of the impact of missing data on stability of the primary results. Missing values will be imputed with multiple imputations. We will verify that mixed model based results are not sensitive to violations of model assumptions with permutation tests.

Last, Cohen *d* effect sizes will be computed for the effect estimates to determine the size of the intervention effect [51].

For the qualitative data, interview transcripts will be reviewed for accuracy and then transcribed verbatim before translation into English. To control for errors in translation, two research assistants fluent in English and the local language (Luo) will

work together to translate and electronically transcribe the data [52]. QRS NVivo 10 qualitative data analysis software will be used for coding and thematic analysis [53].

The interview data will initially be coded according to a number of themes that corresponded to the focus questions. The codes will be used to construct matrix displays based on the co-occurrence of codes and the two treatment groups. The resulting matrix display will provide both the frequency of responses and the detailed content of responses, allowing us to assess how often responses varied between the two treatment groups. Intercoder reliability will be assessed.

Results

The trial has been approved by the Makerere College of Health Sciences School of Health Sciences Research Ethics Committee, TASO, and the Uganda National Council of Science and Technology. A Data and Safety Monitoring Board has been put in place to monitor trial progress. A total of 1140 persons living with HIV have been recruited to the trial. An analysis of baseline and 6-month data is in progress.

The results of this trial will not only be presented at national and international conferences but also submitted for publication in peer-reviewed journals and as a report to the funding agencies.

Discussion

Principle Findings

The GSP intervention is a complex intervention containing several interacting components, requires those delivering the intervention to acquire certain competencies and skills, and is associated with a variety of outcomes. Its development was prompted by the need to narrow the gap between the availability and need for depression treatment among HIV-positive populations in poor resource settings. The prior feasibility study [54] and pilot randomized clinical trial [36] of this intervention served to test these theories, procedures, recruitment, retention, and explore our hypothesized change processes and outcomes. The process evaluation data of this trial indicated that acquisition of knowledge and skills that enhance social connections, support, and better coping strategies with adverse situations leads to a reduction in depression symptoms. The absence of depression improves ability to work and obtain savings and other livelihood assets. The pursuit of livelihoods helps restore the dignity and independence that sustain a reduction in depression and improvement in functioning [37].

The Social, Emotional, and Economic empowerment through Knowledge of Group Support Psychotherapy (SEEK-GSP) trial will provide robust evidence for the change processes and outcomes we observed in the pilot studies. Further, the trial will demonstrate the potential for dissemination and integration into existing HIV service delivery platforms of a culturally sensitive first line treatment for mild to moderate depression. Depression poses a major burden on persons living with HIV/AIDS, particularly those in poor resource settings where poverty and mental health interact in a negative cycle [55]. Treating depression in PLWH is critical to the realization of the "90-90-90 targets" by 2020 aiming to diagnose 90% of all HIV positive people, provide ART for 90% of those diagnosed, and achieve viral suppression for 90% of those treated [56].

Prior trials of psychological therapies for depression in poor resource settings have shown that they result in significant reduction in depression symptoms and an increase in functioning levels [57,58]. However, both trials attracted mostly women. The SEEK-GSP trial specifically addresses this gap in evidence and in mental health services for a highly vulnerable HIV population in a primary care setting.

The SEEK-GSP trial targets both men and women living with HIV who have been exposed to decades of brutal civil war. Many of these individuals live in extreme poverty, with little to no education, in remote rural villages and rely on subsistence farming for survival. The vast majority have multiple experiences of war-related trauma and/or gender-based violence. This target group is a good example of what has been termed "intersecting populations"—groups that are vulnerable on multiple levels and disadvantaged across many determinants of health [59]. In this case, war survivors are made even more vulnerable by HIV/AIDS, unemployment, poverty, and food insecurity. Those living in remote villages with little access to services are even more vulnerable. This trial will demonstrate the extent to which primary care providers' influence can be leveraged to motivate affected individuals to attend group sessions, manage issues that arise during engagement, and support practice of learned skills. Such primary care based interventions also provide health care system opportunities to support culturally appropriate services that minimize unintended negative impacts and maximize positive impacts for vulnerable groups.

Limitations

Limitations of the SEEK-GSP trial relate to generalizability to other ethnic populations in Uganda. Also, the adherence measurement methods used in this study have limitations. However, to date there is no established gold standard to measure ART adherence. In the analyses of data from this trial, we shall assess the sensitivity of our adherence measure by determining whether it was able to predict viral suppression.

Despite these limitations, the trial will provide critical evidence to support culturally centered psychological therapy for depression in primary care settings. Trial outcomes will be supplemented with process evaluation outcomes that will provide contextual information that health care and public health stakeholders can use to guide implementation decisions for their particular setting [60].

Conclusions

Confirmation of our primary hypothesis and supportive secondary data can critically inform the national dissemination and implementation of GSP to treat mild to moderate depression in PLWH. Results may provide greater insight into the partnerships between LHWs and existing government health systems in low-resource settings and may lead to policy formulation regarding the integration of GSP into HIV care services on a country-wide basis.

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Authors' Contributions

EN-M, KW, JO, SM, EJM, and JBN conceptualized and designed the study protocol and EN-M sought and obtained funding. OH conducted statistical analyses. EN-M and JO managed the literature searches. EN-M, JO, EJM, and JBN wrote the study protocol. SM, RM, EJM, OH, and JBN revised the protocol critically for important intellectual content. All authors contributed to the final study protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1

SPIRIT 2013 Checklist.

[PDF File (Adobe PDF File), 173KB - resprot_v6i12e250_app1.pdf]

Multimedia Appendix 2

The content of group support psychotherapy and group HIV education group sessions.

[PDF File (Adobe PDF File), 27KB - resprot_v6i12e250_app2.pdf]

Multimedia Appendix 3

Group support psychotherapy core competencies and subcompetencies.

[PDF File (Adobe PDF File), 32KB - resprot_v6i12e250_app3.pdf]

Multimedia Appendix 4

Data safety and management plan.

[PDF File (Adobe PDF File), 66KB - resprot_v6i12e250_app4.pdf]

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Abbreviations

AIDS: acquired immune deficiency syndrome
ART: antiretroviral therapy
GHE: group HIV education
GSP: group support psychotherapy
ITT: intention-to-treat
LHW: lay health worker
MINI: Mini International Neuropsychiatric Interview
PHC: primary care health center
PLWH: person living with HIV
SEEK-GSP: Social, Emotional, and Economic empowerment through Knowledge of Group Support Psychotherapy
TASO: The AIDS Support Organization
WHO: World Health Organization

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Protocol

The Effectiveness of Exercise Therapy on Scapular Position and Motion in Individuals With Scapular Dyskinesis: Systematic Review Protocol

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Abstract

Background: Scapular dyskinesis is an alteration in normal scapular position and motion. Some researchers believe that altered kinematics of the scapula subsequent to dysfunction or weakness of scapular stabilizing muscles contributes to impingement syndrome. Scapular muscle exercises are included in the rehabilitation of patients with subacromial impingement syndrome and scapular dyskinesis because the muscular system is one of the major contributors of scapular positioning both at rest and during shoulder movement, but there is considerable uncertainty relating to the relative effectiveness of such approaches on changing scapular position and motion.

Objective: The aim of this systematic review protocol is to evaluate the effectiveness of exercise therapy on scapular position and motion in individuals with scapular dyskinesis.

Methods: A systematic review will be conducted using PubMed, Scopus, Web of Science, Elsevier, Ovid, ProQuest, Physiotherapy Evidence Database, and Cochrane Library. The reference lists of articles, other reviews, gray literature, and key journals will be searched for relevant articles. Clinical trials reporting the effect of therapeutic exercises (scapular strengthening exercise, scapular stabilization exercise, scapular muscle stretching) with the aims of changing scapular position and motion in individuals with scapular dyskinesis will be included. Two independent reviewers will select studies, extract data, and assess the quality of primary studies. Any disagreement during the selection of studies will be discussed and decided by the whole team.

Results: This systematic review began in December 2016 and is currently in progress. The findings will be synthesized to determine the effectiveness of recommended therapeutic exercise on scapular position and motion in individuals with scapular dyskinesis.

Conclusions: This is the first systematic review protocol aiming to assess the effectiveness of exercise therapy in individuals with scapular dyskinesis. The systematic review doesn't require ethics approval because all data used will be provided from published documents. The results of this study will be published in a peer-reviewed journal.

Trial Registration: PROSPERO CRD42017053923; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=53923 (Archived by WebCite at http://www.webcitation.org/6uzq32T02)

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KEYWORDS

scapula; exercise therapy; rehabilitation; systematic review; protocol

Introduction

Background

Elevation of the arm requires normal function of the rotator cuff to stabilize the humeral head in the glenoid fossa and coordinated motion of the scapula [1]. During arm elevation, the scapula upwardly rotates, posteriorly tilts, and externally rotates [2,3]. These scapular motions depend on normal function of the scapular stabilizers including trapezius, rhomboid, and serratus anterior muscles [1].

Scapular dyskinesis is an alteration in normal scapular position and motion. It is characterized by prominence of the scapular medial border and/or inferior angle relative to the thoracic cage in the static position or in dynamic motion; early scapula elevation or shrugging during arm elevation; or inadequate upward and downward rotation of the scapula during arm elevation or lowering [4,5]. Scapular dyskinesis was found to be present in 61% of overhead athletes and 33% of nonoverhead athletes [6]. It has also been revealed in 67% to 100% of athletes with shoulder injuries and also in many asymptomatic athletes [6,7]. Scapular dyskinesia or altered kinematics of the scapula (downward rotation, anterior tilt, and internal rotation) subsequent to dysfunction or weakness of scapular stabilizing muscles may contribute to impingement syndrome through decreasing the subacromial space [8-10].

Subacromial impingement syndrome and rotator cuff tendinopathy account for 44% to 65% of all complaints of musculoskeletal shoulder pain, and they have been linked to scapular dyskinesis [11,12]. The researchers have suggested that scapular position and movements are altered in patients with subacromial impingement syndrome [8-10], rotator cuff tendinopathy [13], shoulder instability [14,15], and even neck pain [16]. It is not clear that the association between scapular dyskinesis and shoulder pathology represents a cause or effect of the pathology [6,17,18].

The clinical evaluation of scapular motion is challenging because of the 3-dimensional scapular motion. Previous studies have described different methods of identifying scapular dyskinesis including an electromagnetic kinematic motion analysis system, 3-dimensional digitizer, visual observation, linear measurement, and manual correction maneuvers [19-22].

Exercise is a key component of shoulder rehabilitation. A systematic review by Hanratty et al [23] showed that physiotherapy exercises are effective in decreasing pain and improving function in patients with subacromial impingement syndrome at short-term follow-up. Scapular muscle exercises are included in the rehabilitation of patients with subacromial impingement syndrome and scapular dyskinesis because the muscular system is one of the major contributors of scapular positioning both at rest and during shoulder movements [24], but there is considerable uncertainty relating to the relative effectiveness of such approaches on changing scapular position and motion.

A recent systematic review and meta-analysis of 4 randomized clinical trials (RCTs) in patients with rotator cuff disorders concluded that a scapula-focused approach is more effective than generalized approaches in reducing shoulder pain up to 6 weeks, but this benefit is not apparent by 3 months. This systematic review also showed a conflicting result regarding the effect of a scapula-focused approach in comparison to generalized approaches on scapula position and movement [25]. In the aforementioned systematic review, the primary objective was to synthesize the impact of scapular intervention on rotator cuff–related shoulder pain, with the secondary objective being evaluating the effect of scapular exercises on scapula position and movement; however, it did not include gray literature, probably missing some related studies. There are some studies in which changing scapula kinematics in asymptomatic individuals has been studied.

Previous studies have shown scapular dyskinesis to be detrimental to shoulder function, and they recommend improvement or correction of abnormal scapular mechanics [6,22,26]. The correction of scapular dyskinesis has been recommended for decreasing the symptoms associated with shoulder pathology [6,22,26], but the effects of scapular dyskinesis interventions on correcting scapular position and motion is not clear yet. Therefore, the main aim of this systematic review will be the evaluation of the effectiveness of exercise therapy on scapular position and motion in individuals with scapular dyskinesis.

Objectives

Primary Objective

- Identify the effectiveness of exercise therapy (scapular strengthening exercise, scapular stabilization exercise, scapular muscle stretching) on scapular position and motion of individuals with scapular dyskinesis

Secondary Objectives

- Identify the effectiveness of scapular exercise on shoulder pain in rotator cuff disorder patients with scapular dyskinesis
- Identify the effectiveness of scapular exercise on changing scapular kinematics in asymptomatic individuals with scapular dyskinesis
- Identify the effectiveness of scapular exercise on scapular position and motion of individuals with different types of scapular dyskinesis
- Find potential sources of heterogeneity in primary studies

Methods

Study Characteristics

This systematic review will include any types of clinical trials (RCTs with or without concurrent control; double blind, single blind, and open-label RCTs; and before-after clinical trials) in which scapular position or motion is considered one of the main independent variables. Case studies and simulation studies will not be included.

Types of Participants

This systematic review will include studies with adult participants (aged 16 years and older, athletes and nonathletes) in which a clear diagnosis of scapular dyskinesis is defined according to any of following criteria:

Abnormalities in Scapular Rest Position

- Scapular winging: prominence of scapular medial border and/or inferior angle relative to the thoracic cage
- Scapular tilt or protraction
- SICK scapula syndrome: scapular malposition, inferior medial border prominence, coracoid pain, malposition and dyskinesis of scapular movement

Abnormalities in Scapular Motion

- Scapular dysrhythmia: early scapula elevation or shrugging during arm elevation and inadequate upward and downward rotation of the scapula during arm elevation and lowering (scapular downward rotation syndrome) [22]

The studies that focused on the effects of changing scapular kinematics in asymptomatic individuals or individuals with rotator cuff tendinopathy and subacromial impingement syndrome will be included. The studies without a clear diagnostic criterion and clinical measures for scapular dyskinesis will be excluded.

Types of Intervention

The intervention in the treatment group should be scapular focused exercises with or without general shoulder exercise. The control group will include other forms of interventions, such as manual therapy and taping, or no treatment.

Studies reporting any type of therapeutic intervention (scapular strengthening exercise, scapular stabilization exercise, scapular muscle stretching) with the aims of changing scapular biomechanics, including position and movement, and addressing the pain and disability found with scapular dyskinesis will be included. Also, scapular exercise combined with patient education and instruction on exercises will be included. Clinical trials that compare scapular kinematics after using other techniques such as manual therapy and taping and studies in which exercise has been a minor component of a multimodal approach will be excluded.

Outcome Assessment

The primary outcome will be measurements reported on scapular kinematics outcomes such as scapular rest position, static scapular positioning, scapulohumeral rhythm, and scapular dynamic control (eg, lateral scapular slide test, measurement of scapular upward and downward rotation, measurement of scapular anterior and posterior tilt, and measurement of scapular medial and lateral tilt). Our secondary outcome will include shoulder pain intensity.

Information Sources

Our electronic search database includes PubMed, Scopus, Web of Science, Elsevier, Ovid, ProQuest, Physiotherapy Evidence Database, and the Cochrane Library. The reference lists of articles, other reviews, gray literature, and key journals will be also searched for relevant articles. All studies will enter the initial screening stage without any time limit or restrictions of language and publication type.

Search Strategy

The strategy for searching will be developed and completed in the PubMed database, and then the same strategy will be applied to the other electronic databases. Textbox 1 shows the suggested PubMed search strategy.

Study Records

Two authors will search information sources independently and perform the primary article screening. At first, they will screen the titles and abstracts of all the articles independently, and then their selected articles will be categorized as eligible, not eligible, or may be eligible. When a study cannot be clearly excluded according to its title and abstract alone, its full text will be reviewed before the final decision. Articles categorized as not eligible by both reviewers will be eliminated. Each reviewer will then review the full text of the remaining articles, and a study will be included when both reviewers independently assess it as satisfying the eligibility criteria. Any disagreement during the selection of studies will be discussed and decided by the whole team.

Data Extraction and Management

Data will be extracted from papers by 2 reviewers and entered into a data extraction form. Any disagreement will be discussed and decided on by the whole team. If there are incomplete or unclear data in articles, inquiries will be sent to the authors. All searched studies will be managed through EndNote (Clarivate Analytics) software.

Data Items

From each article, the following information will be extracted: general information (author name, year of publication, journal title, date of extraction), study characteristics (title of study, study design, study setting, sample size), participant characteristics (demographics data, main inclusion criteria, sports history, healthy condition, and type of scapular dyskinesis), methods and tools of scapular dyskinesis diagnosis (observational, 2- and 3-dimensional assessment methods), intervention characteristics (exercise type, frequency, and duration), scapular outcome measurements and results (eg, lateral scapular slide test, measurement of scapular upward and downward rotation, measurement of scapular anterior and posterior tilt, and measurement of scapular medial and lateral tilt), and pain outcome measure.

Textbox 1. Suggested PubMed search strategy.

1. Scapular dyskinesis
2. Scapular orientation
3. Scapular position
4. Scapular winging
5. Scapular protraction
6. Scapular malposition
7. SICK scapula (SICK: scapular malposition, inferior medial border prominence, coracoid pain, and abnormal movement of the scapula)
8. SICK scapular syndrome
9. Scapula* dyskines*
10. Scapular posterior tilt
11. Scapular posterior tipping
12. Scapular anterior tilt
13. Scapular anterior tipping
14. Scapular upward rotation
15. Scapular downward rotation syndrome
16. Scapulothoracic*
17. Scapulohumeral rhythm
18. Scapular kinematics
19. Scapular dysrhythmia
20. Rotator cuff tendinopathy
21. Shoulder impingement syndrome
22. Subacromial impingement syndrome
23. Scapula* exercise*
24. Scapular stabilization exercises
25. Scapula* stabili*
26. Shoulder rehab*
27. Shoulder stretch*
28. Shoulders strengthen*
29. Shoulder exercise*
30. Scapular approaches
31. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
32. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
33. 31 and 32

Assessment of Risk of Bias in Included Studies

The risk of bias assessment will be based on the Cochrane Collaboration Risk of Bias [27]. Risk of bias in each study will be independently assessed by 2 reviewers. Each reviewer will evaluate methodological quality using the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. After critical appraisal of studies, each trial will be categorized into low risk, high risk, and unclear risk. In case of disagreement, discussion will take place to achieve consensus.

Data Synthesis

If enough studies are included, a meta-analysis will be conducted using the scapula and pain outcome data. For scapular outcome data, mean differences and standardized mean differences will be used for meta-analysis. In cases where data are missing, they (eg, standard deviation) will be calculated from available data (eg, standard error will be calculated from *P* values or 95% confidence intervals) [28] or we will contact the authors.

If sufficient comparable studies are included, a subgroup analysis will be carrying out. The subgroups will be formed by quality of primary studies, type of study participants (athlete

and nonathlete studies and asymptomatic individuals or individuals with rotator cuff–related shoulder pain), and types of scapular dyskinesis (scapular outcomes measurements and results).

Results

This systematic review began in December 2016 and is currently in progress. This is the first systematic review protocol aiming to assess the effectiveness of exercise therapy in individuals with scapular dyskinesis. The findings of this systematic review will be synthesized to determine the effectiveness of recommended therapeutic exercise on scapular position and motion in individuals with scapular dyskinesis. On completion of this project, the results of this study will be published in a peer-reviewed journal.

Discussion

Scapular dyskinesis is a condition that is commonly associated with shoulder pathology but is also present in asymptomatic individuals, and it is believed to be a risk factor for further injury [6]. Evidence suggests that patients with rotator cuff–related shoulder pain present scapular kinematic abnormalities such as decreased scapular upward rotation, decreased scapular posterior tipping, and external rotation [8,29,30]. It has been proposed that abnormal scapular kinematics may be linked to weakness of scapular muscles [31-33]. Specifically, increased activation of the upper trapezius with decreased activation of the lower trapezius and serratus anterior has been proposed to be related to altered scapular position and motion [34]. However, it is not clear if these differences are compensatory strategies or causative factors [6,17,18].

Conservative treatment, including exercise therapy, is thought to influence various shoulder conditions and outcomes such as pain, restricted range of motion, and functional disability [23,24], but there is considerable uncertainty relating to the relative effectiveness of such approaches on changing scapular position and motion. The results of this systematic review can help clinicians relating to effectiveness of therapeutic exercise on scapular dyskinesis and associated shoulder pain.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report.

[PDF File (Adobe PDF File), 29KB - resprot_v6i12e240_app1.pdf]

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Abbreviations

RCT: randomized clinical trial
SICK: scapular malposition, inferior medial border prominence, coracoid pain, and abnormal movement of the scapula

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Protocol

The Impact of mHealth Interventions on Breast Cancer Awareness and Screening: Systematic Review Protocol

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Abstract

Background: Mobile health (mHealth) is the use of mobile communication technologies to promote health by supporting health care practices (eg, health data collection, delivery of health care information). mHealth technologies (such as mobile phones) can be used effectively by health care practitioners in the distribution of health information and have the potential to improve access to and quality of health care, as well as reduce the cost of health services. Current literature shows limited scientific evidence related to the benefits of mHealth interventions for breast cancer, which is the leading cause of cancer deaths in women worldwide and contributes a large proportion of all cancer deaths, especially in developing countries. Women, especially in low- and middle-income countries (LMICs), are faced with low odds of surviving breast cancer. This finding is likely due to multiple factors related to health systems: low priority of women's health and cancer on national health agendas; lack of awareness that breast cancer can be effectively treated if detected early; and societal, cultural, and religious factors that are prevalent in LMICs. The proposed systematic review will examine the impact of mHealth interventions on breast cancer awareness and screening among women aged 18 years and older.

Objective: The objectives of this study are to identify and describe the various mHealth intervention strategies that are used for breast cancer, and assess the impact of mHealth strategies on breast cancer awareness and screening.

Methods: Literature from various databases such as MEDLINE, EMBASE, PsycINFO, CINAHL, and Cochrane Central Register of Controlled Trials will be examined. Trial registers, reports, and unpublished theses will also be included. All mobile technologies such as cell phones, personal digital assistants, and tablets that have short message service, multimedia message service, video, and audio capabilities will be included. mHealth is the primary intervention. The search strategy will include keywords such as "mHealth," "breast cancer," "awareness," and "screening," among other medical subject heading terms. Articles published from January 1, 1964 to December 31, 2016 will be eligible for inclusion. Two authors will independently screen and select studies, extract data, and assess the risk of bias, with discrepancies resolved by dialogue involving a third author. We will assess statistical heterogeneity by examining the types of participants, interventions, study designs, and outcomes in each study, and pool studies judged to be statistically homogeneous. In the assessment of heterogeneity, a sensitivity analysis will be considered to explore statistical heterogeneity. Statistical heterogeneity will be investigated using the Chi-square test of homogeneity on Cochrane's Q statistic and quantified using the I-squared statistic.

Results: The search strategy will be refined with the assistance of an information specialist from November 1, 2017 to January 31, 2018. Literature searches will take place from February 2018 to April 2018. Data extraction and capturing in Review Manager (RevMan, Version 5.3) will take place from May 1, 2018 to July 31, 2018. The final stages will include analyses and writing, which is anticipated occur between August 2018 and October 2018.

Conclusions: The knowledge derived from this study will inform health care stakeholders, including researchers, policy makers, investors, health professionals, technologists, and engineers, on the impact of mHealth interventions on breast cancer screening and awareness.

Trial Registration: Prospero registration number CRD42016050202

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KEYWORDS

mHealth; breast cancer; women; awareness; screening

Introduction

Mobile health (mHealth) is a component of electronic health (eHealth) and involves the use of mobile communication technologies to promote health by supporting health care practices (eg, health data collection, delivery of health care information, or patient observation and provision of care) [1]. mHealth is considered to have a positive impact on health systems through improved access to and quality of health care, as well as reduction in the cost of health services [2]. In addition, mHealth can facilitate continuous health monitoring individually and at the population level. mHealth has the potential to support chronic disease self-management, reduce the number of patient visits to health care facilities, and provide personalized, localized, and on-demand interventions [3,4].

The mobile devices or technologies applied to health include mobile phones as well as smartphones, tablets, portable media players, and their mHealth apps [5]. The growing enthusiasm for mHealth is driven not only by its demonstrated benefits, but also by the widespread availability of mobile phones, and the relatively low levels of literacy required to use them [1]. mHealth technologies enable timely collection, transmission, storage, and transformation of data, as well as data analyses and automated reporting [1]. The modes of communication of these technologies take the form of short message service (SMS), instant messaging, voice calls, social media, the Internet, and email [1,6].

mHealth applications also contribute to improvements in health care through diagnoses, monitoring, and/or treatment. One application developed for use in treatment is *WE-CARE*, which is an intelligent telecardiology system using mobile 7-lead electrocardiogram devices [7,8]. Another mHealth application example known as *PIERS on the Move* is a low-cost, easy-to-use application for accurately predicting the risk of adverse outcomes associated with preeclampsia in pregnant women [9]. *MEDITECH* allows access to clinical data including lab results, vital signs, intake and output, allergies, active medications, and documents (reports and notes) on a smartphone [9]. *Wireless System for Emergency Responders* is an application for emergency medical service specialists that identifies chemical and biological hazards on the basis of symptoms and signs by providing access to the National Library of Medicine (NLM) Hazardous Substances Data Bank radiological and biological substance report [10].

Breast cancer is the most common cancer in women worldwide, with an estimated 1.67 million new cases diagnosed in 2012 [11]. Most women diagnosed in high-income counties are likely to survive this disease, whereas those in low- and middle-income countries (LMICs) are faced with odds of survival as low as 10-25% [11]. This result is likely due to multiple factors related to health systems: low priority of women's health and cancer on national health agendas; lack of awareness that breast cancer can be effectively treated if detected early; and societal, cultural, and religious factors that are prevalent in LMICs [11]. Breast cancer mortality can be dramatically reduced via screening and early detection, especially in LMICs that have high mortality rates [11]. Male breast cancer is rare but exists, with approximately 2000 men diagnosed with breast cancer per year in the United States [12]. Male patients are slightly older at presentation but their cancers show similarities to female breast cancer [12].

Evidence has shown that intervention by health care practitioners can be effective in improving awareness, knowledge, attitudes, and screening practices for early detection of breast cancer among women [13]. Current literature shows insufficient scientific evidence related to the benefits of mHealth interventions for breast cancer [5,14-16]. Available studies involving mHealth strategies for breast cancer-related interventions have addressed breast health promotion, clinical breast examination, patient navigation, and breast cancer education [11,14]. A systematic analysis of breast cancer-related apps has found that their most common purposes are education, behavior change, fundraising, and advocacy [17].

Several mHealth intervention strategies have been implemented to address breast cancer. One example is an investigation of the effect of mHealth with pedometer use on function and quality of life (QOL) among breast cancer patients [18]. The results reported in this study showed improvements in these parameters [18]. QOL in breast cancer survivors was also shown to be improved by an imagery-based group behavioral intervention for breast cancer survivors using telemedicine [19]. Quintiliani et al demonstrated the feasibility of an mHealth-supported behavioral counselling intervention among breast cancer survivors and found some positive physiological and behavioral changes [20]. A patient-centered, Web- and mobile-based educational and behavioral mHealth intervention strategy has been shown to assess patients' lymphedema symptoms with high reliability and validity, and was able to enhance self-care strategies for lymphedema symptom management [21]. mHealth has also been used for general cancer applications. An example is the study by Banas et al who developed a peer-to-peer mHealth tool, which is culturally tailored to Spanish speakers (available in Spanish), and connects cancer patients with survivors [22]. In Nigeria, mobile phones were used as tools for improving cancer care by developing helplines for cancer

information related to prevention, treatment, and palliative care [23].

Current evidence supports the use of mHealth for addressing cancer broadly. Our intention is to systematically review the literature to aid us in assessing the impact of mHealth on breast cancer screening and awareness. The study examines the impact of mHealth technology as an intervention on breast cancer awareness and screening attendance of women, compared to conventional interventions that promote awareness and screening.

Methods

This manuscript adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocols (PRISMA-P) 2015 checklist as a condition of submission for systematic review protocols [24]. This protocol has been registered with PROSPERO, the International Database of Prospective Register of Systematic Reviews, with registration number CRD42016050202 [25].

Study Design

The study design for this review will include randomized and nonrandomized studies. Nonrandomized studies will include case-control, cohort, and cross-sectional studies in which mHealth was the primary intervention used for breast cancer awareness and screening.

Study Participants

Study participants will be women aged 18 years and older. All races, ethnicities, employment statuses, occupations, and roles of women in the reviewed studies will be eligible for inclusion.

Types of Interventions

The relevant mHealth interventions to be included in the study should focus primarily on positively impacting breast cancer awareness and screening. mHealth interventions for health care consumers (women >18 years of age) have been designed to increase healthy behaviors (eg, to increase breast cancer awareness) or increase hospital attendance (eg, increasing the participation of hospital workshops by women to improve their understanding of early breast cancer detection, management, and treatment thereof) [3]. The interventions will be described using the Free et al strategy that categorizes by device (mobile phone, personal digital assistant [PDA]) and modality (eg, SMS, text messaging, multimedia message service [MMS], video) [26].

Types of Technology

The technology used for mHealth includes mobile devices that have cellular communication capabilities that allow for wireless and/or 3G/4G capabilities. These devices include: mobile phones (including Android, smart, and feature phones), PDAs and PDA phones, tablets, mobile/smart phone apps, ultra-portable computers, and smart books [3,5,26].

The mHealth functions that will be considered comprise voice over Internet protocol (VOIP), SMS, text messaging, MMS, email, social media, and Internet [27]. Some mHealth projects have used single or multiple applications employing one or more mobile phone functions–such as voice, SMS, MMS, and interactive voice response (IVR)–to accomplish mHealth-related tasks [1]. Common applications using various mHealth modalities include: client education and behavior change communication (SMS, MMS, IVR, audio, video, images); sensors and point of care devices (mobile phone camera); registries and vital event tracking (SMS, voice communication); data collection and reporting (voice communication, SMS); electronic health records (mobile Web); electronic decision support (mobile web, IVR); provider communication (SMS, MMS, mobile phone camera); provider work planning and scheduling (SMS, mobile phone calendar); provider training and education (SMS, MMS, IVR, audio, video); human resource management (voice communication, SMS); supply chain management (global positioning system, SMS); and financial transactions and incentives (mobile banking service, airtime transfers) [5,28,29].

Outcomes

The impact of mHealth interventions on breast cancer awareness and screening will be assessed by reviewing: (1) increased attendance at breast cancer clinics; (2) the stage of breast cancer when diagnosed, as this would assist in determining whether mHealth has promoted early detection and screening; and (3) increased breast cancer enquiries via call centers, online forums, and social media.

User acceptability will not be assessed as an outcome. Breast cancer awareness in this study is described as the ability to be fully informed and knowledgeable of the breast cancer disease [30]. In addition, screening is a system of checking for the presence or absence of a disease (in this study, breast cancer). In situations where actual numbers of women cannot be determined, the baseline for assessment will be determined by the keywords “increase” or “improvement” used in the study. The same criteria will apply to women visiting hospitals for breast cancer screening.

Study Setting

The setting of the study will not be limited by geographic location. All continents, countries, and health facilities where mHealth research on breast cancer was conducted will be included. This approach allows for all relevant information sources to be captured.

Exclusion Criteria

The following study types will be excluded from the review: (1) all studies on male breast cancer, due to the rarity of this disease in men; (2) breast cancer detection and treatment studies; (3) studies not performed on human subjects; (4) studies reported before January 1, 1964 and after December 31, 2016; (5) letters, reviews, commentaries, and editorials; (6) studies lacking primary data and/or explicit method description; (7) non-English studies and publications; and (8) duplicate studies that are published in more than one report (the most comprehensive and up-to-date version will be used).

Search Strategy

While the earliest keyword “mobile health” was identified in the literature in 1991 by Casson and Leder [31], relevant

literature will be identified from 1964. This start date corresponds to the earliest identifiable mention of the keyword "telemedicine" in a preliminary search of all the major databases such as Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (EMBASE), Psychological Information Database (PsycINFO), Cumulative Index to Nursing and Allied Health Literature (CINAHL), The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register), National Health Services Health Technology Assessment Database, Web of Science, and Google scholar. The language of publication will be limited to English for reasonable analysis purposes.

Other databases to be considered within the study scope and objectives will include trial registers, SpringerLink, Wiley InterScience, Institute of Electrical and Electronics Engineers, Association for Computing Machinery Digital Library; and CiteSeer [29]. For trial registers, the authors will identify ongoing studies and recently completed trials. The studies to be included will be selected using predefined search terms adapted for the databases to be used. The authors will adapt the experimental findings proposed by Fortuin et al [5] in identifying accurate search terms in the development of an optimum search strategy.

The search strategy will include key terms, as detailed in Table 1 (MEDLINE format). This format was developed with the assistance of a library sciences specialist and will be adapted to all other databases to be searched. A preliminary search was conducted and the number of identified references is reported in Table 1.

Manual searches of reference lists of primary studies included in the review, and the reference lists of relevant and previously published reviews, will be undertaken. Full text articles of the studies extracted from the reference lists will be reviewed. Unpublished studies will be identified from universities and other databases, and the same eligibility criteria will be applied.

Study Selection

The first author will retrieve all the relevant articles from the various databases, based on the finalized search strategy. All of the literature obtained will be saved using reference management software. Two contributing authors will independently screen the titles and abstracts of retrieved studies for eligibility. These authors will make a final assessment for inclusion using the full text article, and discrepancies and disagreements will be resolved by the third author.

Data Extraction

A data extraction form will be used for the extraction of key information, including: (1) country of study setting; (2) type of participant/study population/demographic characteristics (eg, women aged 18 years and older); (3) type of mHealth device used (eg, mobile phones, PDAs, smartphones, tablets); (4) method of communication (eg, voice call, SMS, MMS, Unstructured Supplementary Service Data and Web); (5) nature of the mHealth intervention; (6) type of study (ie, study design); (7) type of outcomes measured; and (8) findings/results.

If discrepancies are identified when extracting data, these will be discussed by the first two authors. If no consensus is reached, the third author will mediate. Missing data will be requested from study authors via email [3]. If we receive no response from study authors, an attempt will be made to impute missing standard deviations or standard errors using data from other similar studies in the review, utilizing similar methods and sample sizes, as recommended by Wiebe et al [32].

Table 1. A preliminary search query classification.

Number	Query	Items
#1	Search ((((((((((mHealth) OR telemedicine) OR wireless technology) OR mobile phone) OR smartphone) OR cell phone) OR mobile technology) OR mobile device) OR mobile-based phone) OR tablet computer) OR IPAD) OR pda) OR mHealth application Filters: Publication date from 1964/01/01 to 2016/12/31	65,265
#2	Search ((((((((((((((mHealth) OR telemedicine) OR wireless technology) OR mobile phone) OR smartphone) OR cell phone) OR mobile technology) OR mobile device) OR mobile-based phone) OR tablet computer) OR IPAD) OR pda) OR mHealth application)) AND ((voice calling) OR VOIP) OR sms) OR mms) OR texting) OR social media) OR Internet) OR IVR) OR video) OR images)) AND (((voice calling) OR VOIP) OR sms) OR mms) OR texting) OR social media) OR Internet) OR IVR) OR video) OR images Filters: Publication date from 1964/01/01 to 2016/12/31))	211,700
#3	Search ((((((((((((mHealth) OR telemedicine) OR wireless technology) OR mobile phone) OR smartphone) OR cell phone) OR mobile technology) OR mobile device) OR mobile-based phone) OR tablet computer) OR IPAD) OR pda) OR mHealth application)) AND (breast cancer) OR neoplasm Filters: Publication date from 1964/01/01 to 2016/12/31)	421
#4	Search ((((((((((((((mHealth) OR telemedicine) OR wireless technology) OR mobile phone) OR smartphone) OR cell phone) OR mobile technology) OR mobile device) OR mobile-based phone) OR tablet computer) OR IPAD) OR pda) OR mHealth application)) AND (breast cancer) OR neoplasm Filters: Publication date from 1964/01/01 to 2016/12/31))) AND (((((awareness) OR education) OR promotion)) Filters: Publication date from 1964/01/01 to 2016/12/31	88
#5	Search ((((((((((((((((mHealth) OR telemedicine) OR wireless technology) OR mobile phone) OR smartphone) OR cell phone) OR mobile technology) OR mobile device) OR mobile-based phone) OR tablet computer) OR IPAD) OR pda) OR mHealth application)) AND (breast cancer) OR neoplasm Filters: Publication date from 1964/01/01 to 2016/12/31))) AND (((awareness) OR education) OR promotion)) AND ((screening) OR diagnosis) Filters: Publication date from 1964/01/01 to 2016/12/31	52

Assessing Risk of Bias

Two authors will use the recommendations by the International Cochrane Collaboration [8] to independently assess the risk of bias. These criteria include randomization sequence generation, treatment allocation concealment, blinding of participants, incomplete outcome data, selective outcome reporting, and other sources of bias. All included studies will be scored for bias using these criteria. A descriptive summary for each scoring will be recorded. Discrepancies between the review authors regarding the risk of bias in particular studies will be resolved by dialogue, with involvement of a third author if necessary [3].

Data Analyses

A descriptive synthesis will be undertaken in accordance with the Centre for Reviews and Dissemination [33]. The characteristics of included studies will be summarized using text and tables, which will include the key data extraction elements (eg, study setting, authors, journal, and study type).

Mean differences and standard deviations will be calculated for continuous outcomes. Ratios and their corresponding 95% confidence intervals will be determined for dichotomous outcomes. Participants, interventions, and outcomes of each study will be examined to ascertain heterogeneity. Data will be pooled; if the collected data is sufficiently similar, a meta-analysis will be conducted. However, if the variability between studies is high the results will not be pooled and a narrative synthesis will take place.

The statistical software Review Manager (RevMan, Version 5.3) will be utilized to capture the data and perform the meta-analysis. The statistical test for heterogeneity includes the I-squared (I^2) test which quantifies heterogeneity; this test will allow for the quality of the evidence to be validated [8]. When appropriate, a subgroup analysis will be used to determine if varying mHealth applications have an impact on breast cancer awareness and screening among women, and in what context this occurs. Subgroups to be considered for this analysis will include age grouping and geographical region.

Various sensitivity analyses will be undertaken. The first sensitivity analysis will be conducted based on the study quality (risk of bias and level of participant dropout) to investigate possible sources of heterogeneity. The second analysis will determine how excluded studies could have influenced the overall result. The third analysis will be to determine how the result would differ should only high-quality studies be included [8].

Results

The sourcing of literature in accordance with the inclusion and exclusion criteria of the study is underway. All data extracted are grouped under the various headings as specified in the data extraction form (eg, country of study setting, study population, mHealth device used, communication method, nature of mHealth intervention, type of study, outcomes and findings). It is anticipated that the review will be completed in mid-2018.

Discussion

This review will identify and describe the impact of mHealth interventions for breast cancer awareness and screening on women of aged 18 years and older. The findings of the systematic review will inform the design of mHealth interventions for breast cancer. Furthermore, the study will highlight which mHealth technology modalities (eg, SMS) are appropriate for the target audience when creating awareness of breast cancer.

Availability of Data and Material

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

Acknowledgments

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Authors' Contributions

TT and JF conceptualized and coordinated the study, and drafted the manuscript. TD reviewed the content of the protocol and edited the manuscript. All authors read and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

eHealth: electronic health
IVR: interactive voice response
LMIC: low- and middle-income country
mHealth: mobile health
MMS: multimedia message service
NRF: National Research Foundation
NLM: National Library of Medicine
PDA: personal digital assistant
QOL: quality of life
SMS: short message service
VOIP: voice over Internet protocol

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Protocol

A Peer-Led Electronic Mental Health Recovery App in an Adult Mental Health Service: Study Protocol for a Pilot Trial

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Abstract

Background: There is growing demand for peer workers (people who use their own lived experience to support others in their recovery) to work alongside consumers to improve outcomes and recovery. Augmenting the workforce with peer workers has strong capacity to enhance mental health and recovery outcomes and make a positive contribution to the workforce within mental health systems and to the peer workers themselves. Technology-based applications are highly engaging and desirable methods of service delivery.

Objective: This project is an exploratory proof-of-concept study, which aims to determine if a peer worker-led electronic mental (e-mental) health recovery program is a feasible, acceptable, and effective adjunct to usual treatment for people with moderate to severe mental illness.

Methods: The study design comprises a recovery app intervention delivered by a peer worker to individual consumers at an adult mental health service. Evaluation measures will be conducted at post-intervention. To further inform the acceptability and feasibility of the model, consumers will be invited to participate in a focus group to discuss the program. The peer worker, peer supervisor, and key staff at the mental health service will also be individually interviewed to further evaluate the feasibility of the program within the health service and further inform its future development.

Results: The program will be delivered over a period of approximately 4 months, commencing June 2017.

Conclusions: If the peer worker-led recovery app is found to be feasible, acceptable, and effective, it could be used to improve recovery in mental health service consumers.

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KEYWORDS

peer work; tablet app; study protocol; pilot trial; recovery; mental illness

Introduction

Peer work is a rapidly growing industry in Australia and internationally [1-4]. Current evidence suggests that peer work can make a positive difference in mental health services [1,5]; however, the role and definition of peer work is flexible and the practice is implemented in a variety of ways and settings [2]. Questions still remain as to how positive outcomes are best achieved and under what circumstances [5]. It is important to evaluate the feasibility of new peer work programs and to assess the acceptability of these programs for consumers, peer workers, and other staff.

Technology-based electronic mental (e-mental) health is a rapidly growing industry. These mental health interventions can be cost-effective to implement and there is growing evidence to support their effectiveness [6]. However, much more research is needed to understand how best to implement these tools in routine care [7]. Implementation challenges include low uptake and completion rates [8]. It has been proposed that peer support interventions may be able to increase the uptake and completion of e-mental health interventions [8]. The proposed project will assess the acceptability of presenting an e-mental health app led by a peer worker.

Peer support can be defined as "...a system of giving and receiving help founded on key principles of respect, shared responsibility, and mutual agreement of what is helpful" (page 1) [9]. Peer work can be paid or volunteer and workers use their lived experience of mental illness to inform their practice in providing emotional and social and instrumental support to other consumers [5,10]. Peer work is distinguished from other support work by several key factors, including (1) peer workers can instill hope through positive self-disclosure; (2) they can role-model skills for self-care and coping; and (3) they are able to develop a peer-to-peer relationship that is qualitatively different to a clinician-to-patient relationship [1]. The peer-to-peer relationship is characterized by trust, understanding, acceptance, and authentic empathy facilitated by shared or similar lived experiences [1,4,5].

Peers are found to be as effective or slightly more effective at producing desired outcomes, compared to usual staff, when employed in conventional roles in mental health services [1,11]. In these positions, peer workers have been found to increase the engagement of difficult to reach consumers, reduce rates of hospitalization and hospital stay duration, and decrease consumer substance use [1,5,12]. Peers can also be employed in diverse and flexibly defined peer specific roles [4]. There is evidence to suggest that in these circumstances peer workers can produce a range of benefits for consumers, particularly in regard to facilitating recovery. These benefits include an increased sense of independence and empowerment, improved self-esteem and confidence, improved social support and community integration, breaking down perceived stigma, and fostering a sense of hope through positive role modeling [1,5]. The current research protocol focuses on paid peer workers delivering a novel, technology-based recovery intervention in a public mental health care setting.

Peer work is not without challenges. The nature of peer support, particularly the requirement for self-disclosure, can make it difficult for peer workers to balance personal and professional boundaries in a workplace context [3-5,13]. In addition, the diverse and flexible definitions of peer work can lead to a lack of role clarity [13]. This can result in a range of workplace issues, including a lack of understanding and recognition of the value of peer work [3,4,13]. Effective training, appropriate management, professional supervision, and defined roles have been identified as key strategies for overcoming these challenges [3,13]. It is important to evaluate new peer work positions and programs to ensure the professional environment facilitates effective peer work and to identify areas that require improvement. In addition, reciprocity is a key element of peer support and peer workers have reported experiencing personal benefits from their occupation, including improved self-esteem and a sense of empowerment [4,5]. Through peer support training, voluntary work, and paid work, peers also have the opportunity to develop job skills and confidence [5,14,15]. Thus, peer work can provide people with a pathway to re-enter the workforce and facilitate a person's continuing recovery. Due to the reciprocal nature of peer support, it is also important to determine whether peer-delivered services are acceptable for both consumers and peer workers.

Aims

The aim of this project are to determine if a peer worker-led e-mental health recovery intervention is a feasible, acceptable, and effective adjunct to usual treatment for people with moderate to severe mental illness, as determined by the type of diagnosis, duration and/or intensity of symptoms and degree of functional impairment [16]. As an exploratory proof-of-concept study, the primary focus will be on elements of the program that consumers find useful or not useful, barriers and facilitators to implementation from the peer worker and service perspective, and primarily qualitative investigations of effectiveness for recovery outcomes. The findings of the research will help inform a larger investigation of the role of peer workers and e-mental health, which can guide the future implementation of these initiatives within existing mental health services.

Objectives

The primary objectives of the study are (1) to investigate the feasibility and acceptability of embedding a peer worker in a public mental health service, from both the consumer and service perspectives; and (2) to assess the acceptability and effectiveness of a recovery-focused e-mental health program as an adjunct to treatment as usual for people with moderate to severe mental illness.

Project Design

The exploratory project design involves the post-intervention evaluation of a single cohort of participants using the recovery-focused e-mental health program. To inform this proof-of-concept study, we will also conduct interviews with the peer worker and mental health service staff and a focus group to collect qualitative perspectives with participants. The study protocol, in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [17], is shown in Multimedia Appendix 1.

Ethics Approval

The ethical aspects of this research were approved by the Australian Capital Territory (ACT) Health Human Research Ethics Committee (ETH.2.17.028) and The Australian National University Human Research Ethics Committee (ANU HREC 2017/338).

Methods

Researchers

Three of the researchers involved in the development and conduct of the study (AG, MB, ARM) have lived experiences

of mental health problems and are currently working as consumer researchers. These experiences, together with a consumer and carer advisory group, offer unique insight into the development of the questionnaires and the evaluation of the study.

Intervention

Peer Worker

A part-time (7 hours per week) peer worker with lived experience was recruited by ACT Health for the trial of a peer worker-led e-mental health program within its mental health service. The peer worker was required to have a qualification equivalent to a Certificate IV in Mental Health Peer Work, which is a professional course to develop specialist skills for working with clients facing mental health challenges [18]. The peer worker was required to (1) have direct personal lived experience of using mental health services; (2) have had a positive experience of recovery; and (3) have the ability and willingness to disclose personal experience of recovery in order to influence others positively. Their general duties were varied and included delivering programs, providing emotional support, developing trusting and professional relationships, and assisting other staff with the creation and review of recovery plans. The peer worker role statement is presented in Multimedia Appendix 2. The peer worker will be trained on the use and support of the Stay Strong app and will receive professional supervision and support for implementing the program by an experienced peer supervisor. However, they will not have experienced the recovery app as a client.

Stay Strong E-Mental Health App

The Stay Strong Care plan was developed and evaluated by Professor Tricia Nagel and developed into a mobile electronic app for iPads and other tablets in collaboration with Queensland University of Technology [19,20]. The app is a structured mental health and substance misuse intervention available through iTunes or Google Play. It is designed to be used as a collaborative tool between workers and service users and assists workers to guide service users through a structured, evidence-based mental health and substance use intervention.

Mental health workers may take on a range of roles when delivering e-mental health interventions, depending on the nature of the intervention and existing mental health skills of the worker [7]. Previous research with the Stay Strong app found that it may be most suitable for workers who are able to take on a coaching or therapist role [21]. In the current study, the peer worker will act in a coaching role and assist the person to complete the app and apply its concepts to their personal situation. We expect that the unique nature of the peer worker relationship, including the ability to provide hope for the future through role modeling, shared experience, and the capacity for assisting the person to disclose difficult personal issues [22] will facilitate and maximize the engagement of participants with the app content. Feedback from the peer worker will help inform the development of future protocols for the use of the app in mental health services.

Although the app was initially designed for use with Aboriginal and Torres Strait Islander service users and has some culturally-specific imagery and content [19], it has been approved by the authors for use in non-Aboriginal and Torres Strait Islander populations. It comprises a simple, highly visual design that does not rely on literacy and concentration levels. The Stay Strong tablet (iPad) app focuses on the consumer's strengths and worries and helps them to set goals for change [23]. Consumers are first asked to identify the people in their life that help keep them strong, their relationships, and the role they play in the person's life. They are then asked to identify their strengths in 4 areas of their life and this is represented visually as leaves on a tree. The more strengths they identify, the stronger and healthier the leaves become. Consumers also identify things in their life that take away their strength in the same 4 areas. The more worries that are input, the more the leaves on the tree wilt and turn yellow. This creates an interactive and visual representation of the parts in their life where they are strong and parts where they are not as strong. The app is designed for use by workers who have some training in mental health [19] but are not health professionals; its content focuses on goal setting and understanding strengths and vulnerabilities in relation to recovery.

Eligibility Criteria

The mental health consumers who will be invited to participate are all existing consumers of an ACT Health community-based mental health service in Canberra, Australia. All consumers who have given informed consent will be eligible to participate in the study. Intended staff participants are the peer worker conducting the e-mental health program, the peer supervisor, and other staff of the mental health service.

Recruitment

The e-mental health program will be delivered in 4 sessions to attendees at drop-in clinics during their usual appointments at the mental health service. It is anticipated that the program will be delivered over a period of approximately 4 months, commencing June 2017.

Recruitment into the e-mental health program will be conducted by staff at the mental health service. Attendees at drop-in clinics will be offered the opportunity to take part in a peer worker-led recovery program during their appointments at the clinic. This is partly to assess the utility of the app during a time in which the consumers must be present at the clinic to receive medication. The program will consist of completing the Stay Strong recovery app on iPads with the support of the peer worker over approximately 4 sessions. We initially conceptualized the peer worker to lead a group session for the app; however, group delivery is not feasible in the drop-in clinic setting, where consumers arrive and depart at varying times.

Research Study

Evaluation Survey

After completion of the e-mental health recovery program, the consumer researchers will invite those who took part to participate in the evaluation survey. Participation will involve completion of a short questionnaire about experiences with the peer worker and the e-mental health program. We will also offer consumers the opportunity to take part in a focus group

discussion to evaluate the program in more depth with researchers and each other. Participation in the recovery program and in the research for consumers will be handled separately—consumers will be offered the opportunity to take part in the program by the peer worker as part of their usual contact with the mental health service. The researchers will recruit consumers for the evaluation and it will be made clear to consumers that participation in the evaluation is completely voluntary and independent of their participation in the recovery program or the services they receive at the mental health service. Potential participants will also be informed that staff will not see their individual answers to minimize the chance of social desirability responses. The recruitment target for the research is 30 consumers across 3 clinics. Staff of the mental health service predicted this is a feasible target based on current attendance at the service.

Focus Groups

We will recruit up to 10 consumers who complete the questionnaire to participate in the focus group discussion(s). The focus group(s) will be described during the administration of the questionnaire. We will collect details for consumers who are interested in participating in the focus group and will follow-up with these consumers to schedule the focus group(s).

Staff Interviews

In addition to the consumers of the mental health service, staff involved in the trial of the peer worker-led e-mental health program will also be invited to participate in an interview. The peer worker will be interviewed about their experience of the delivery of the app. Supervisory and management staff at the service will not be involved in the delivery of the app, but will be asked to participate in one-on-one interviews to discuss their observations of the feasibility of embedding a peer worker and e-mental health program within the service from an operational point of view.

The evaluation materials for the survey, focus groups, and interview are presented in Multimedia Appendix 3.

Outcomes

Consumer Questionnaire

We will measure the participants' perception of their own recovery using the Self-Identified Stages of Recovery (SISR) measure [24]. The SISR is a single-item scale describing stages of recovery and the participants' perception of the stage of recovery with which they currently identify. Participants are asked to indicate which of 5 statements most closely describes how they have been feeling over the past month, with higher ratings indicating more positive perceptions of recovery. Examples of statements are:

> *I don't think people can recover from mental illness. I feel that my life is out of my control, and there is nothing I can do to help myself.* [Question 1]
>
> *I feel I am in control of my health and my life now. I am doing very well and the future looks bright* [Question 5]

The single-item of the SISR has been argued to measure a unique aspect of recovery not assessed by continuous measures [25]. In addition, the single-item SISR has demonstrated reliability and concurrent validity [26] as well as convergent validity for the staged model of recovery [25].

Seven questions designed by consumer researchers will subsequently ask participants to rate their experience with the peer worker and the program on a 4-point scale from "Not at all" to "Yes definitely." The questions were designed to explore the acceptability of a peer worker and an e-mental health program as a part of the service, as well as investigate recovery and self-efficacy. There is an open-ended section for any further remarks. The questionnaire will be conducted at the conclusion of the final session of the program delivery, within the usual time that consumers are attending the clinic for treatment.

Focus Group

The focus group will follow a semi-structured protocol, investigating experiences with the Stay Strong program and its delivery. This will provide consumers with an opportunity to discuss and reflect on their experiences with the peer worker and the program in more detail than the rating scales allow. It will also enable identification of aspects of the program that consumers like and dislike to inform possible future delivery. The focus group method was selected to facilitate richer information where participants can share and build on each other's ideas. However, we will consider an interview method if we cannot secure sufficient participants for a focus group. The focus group will also be scheduled during usual clinic hours in a meeting room at a mental health service clinic.

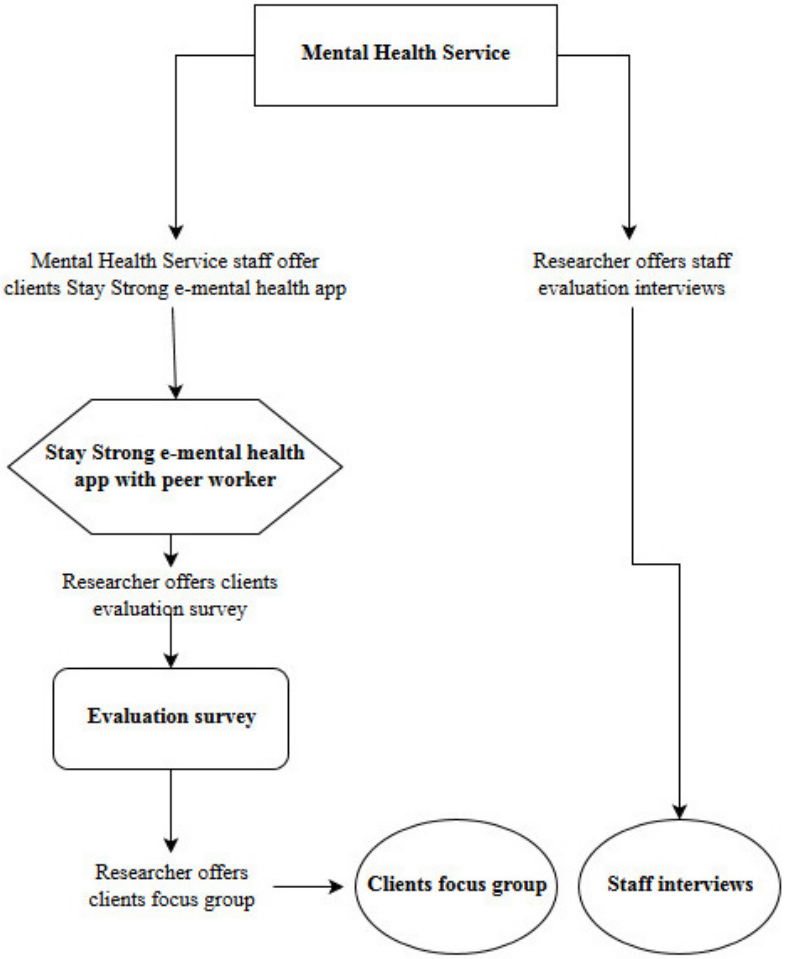
The focus group will be facilitated by one researcher with a second researcher as note taker/assistant. The group will be audio-recorded and participants will be advised in the information sheet and accompanying explanation that this is necessary to avoid missing anything and they should decline to participate if not comfortable with recording. They will also be advised that if they choose to withdraw during the focus group—it will not be possible to delete their contributions to that point.

Staff Interviews

Interviews will also follow a semi-structured protocol. The peer worker and other staff associated with the implementation of the program (eg, peer supervisor, health service coordinator) will be asked to discuss the benefits and challenges of the program, their experiences with both the peer worker model and the e-mental health program, and issues that may need to be considered for future delivery. Interviews with staff will be scheduled at a time and location convenient for the staff member. Interview participants will be asked if they consent to recording; if they refuse, the researcher will rely on written notes (Figure 1).

Questionnaires with consumers will be conducted across a period of approximately 4 months. The focus group and staff interviews will be conducted at the conclusion of the program. Data analysis and write-up is planned for completion by December 2017.

Figure 1. Recruitment flowchart.



Data Collection

All data collection will be conducted by members of the research team who will discuss protocols prior to commencing data collection to ensure consistency. Each participant will only be required to take part in the research on one occasion, with the exception of consumers who also choose to take part in the focus group. Due to the small sample and study location, no demographic data will be collected to minimize the chance of identifying individuals. All participants in the qualitative data collection will be advised that while every effort will be made to remove identifying information, they may still be identifiable from their comments.

Data Management

All data will be stored securely in locked offices at The Australian National University (ANU). Consent forms and written questionnaires will be kept separately in locked filing cabinets. Digital data, including audio recordings, transcripts, and analysis files will be kept on password-protected computers at the ANU, accessible only to the research team. Identifying information will be removed from interview and focus group data during transcription and this will be reviewed by a member of the research team. Interview participants will have the opportunity to review their transcripts for accuracy and to identify any comments they do not wish to have included in publications. Data will be stored for a period of 5 years from last publication, after which it will be deleted and paper records destroyed.

Analysis Strategy

Quantitative analyses of questionnaire responses will comprise descriptive statistics and will be conducted in SPSS (IBM) by 1 member of the research team. These will include mean SISR scores and mean ratings on each of the experience questions. Qualitative analyses of the focus group and interview transcripts will be managed using NVivo qualitative analysis software (QSR International). A framework analysis approach [15], incorporating both inductive and deductive coding, will be used to identify the key issues raised by consumers and staff. Initial coding will be conducted by 1 member of the research team and the coding frame discussed with the rest of the research team before coding is finalized.

Risks and Benefits

The primary risk to consumers is that working through a recovery-oriented mental health program and answering questions related to recovery may raise uncomfortable memories or feelings, and may exacerbate mental health problems. However, the presence of a peer worker to support people as they work on the program, together with the specific purpose and format of the Stay Strong program are designed to minimize

these risks. The study is being conducted as an adjunct to treatment as usual for this group, ensuring ongoing monitoring by mental health professionals.

It is expected that the people with mental health problems who participate in the study will increase their understanding of the psychosocial factors that influence their mental health, may develop skills in self-advocacy and self-support, and will develop a better understanding of the tools and skills they have to help them manage their well-being. They may also experience a sense of shared experiences and belonging with the peer worker and feel empowered by the opportunity to contribute to evaluating services.

The staff involved in the research will experience a different, non-clinical way of providing services to their consumers that may inform their own recovery-oriented practice. The standardized use of peer workers and e-mental health recovery interventions has the potential to improve both the availability of services (increased workforce) and to enhance self-help and maintenance of well-being in clinical care. This proof-of-concept study will provide preliminary data on the feasibility and acceptability of this approach.

Quality Assurance and Monitoring

The design and progress of the study will be discussed with the Consumer and Carer Advisory Group for ACACIA: The ACT Consumer and Carer Mental Health Research Unit. This group comprises representatives from the ACT Mental Health Consumer Network, Carers ACT, ACT Health and independent consumers and carers from the community. The role of the advisory group is to provide feedback and assistance on ACACIA research projects, such as suggesting improvements to design and materials and assisting with recruitment.

Regular email and face-to-face meetings between the research team and the ACT Health team managing the program will also occur to monitor the progress of the program and the implications for the research study.

Ethical Issues

The mental health consumers who will be invited to participate are all existing consumers of the mental health service and the intended staff participants are all employees of ACT Health. To minimize the risks presented by these existing relationships, recruitment of consumers into the e-mental health program will be undertaken by staff of ACT Health, whereas recruitment of consumers into the evaluation will be undertaken by a member of the research team employed by The Australian National University (ie, not an ACT Health employee and not a person involved in treatment). The information sheet details the principles of voluntary consent and participation, including that there will be no adverse consequences of choosing not to participate. The researcher present during the questionnaires, focus group(s), and interviews will verbally confirm understanding of the voluntary nature of participation before collecting written consent to proceed. Consumers can take part in the peer worker-led program and not be required to take part in its evaluation. In addition, the principles of voluntary participation for staff will also be discussed with the potential staff participants to ensure staff and their managers understand their rights to refuse to participate or withdraw without consequence.

Informed Consent

All participants will be provided with a participant information sheet when invited to take part in the study. The key aspects of the study and ethical considerations will also be described verbally and participants will have the opportunity to discuss the study with researchers before agreeing to participate. In particular, the researchers will ensure that both consumers and staff understand that they are not obliged to participate in the research, regardless of their participation in the program and there are no consequences for refusing to take part. All participants will complete a written consent form (Multimedia Appendix 4). Consumers who choose to participate in the focus group in addition to the questionnaire will receive an additional information sheet explaining the issues particular to a group discussion and will sign a separate consent form.

Results

Dissemination

Results will be published in a report to ACT Health. A plain language summary will be provided to participants, to the consumer and carer organizations involved with ACACIA, and in ACACIA's newsletter. A peer-reviewed publication will also be prepared and opportunities for conference presentations explored. Preparation of publications will be led by the principal investigator; authorship will be determined by contributions of each researcher to the entire process of conducting the project in accordance with publication guidelines. ACT Health partners will be offered the opportunity to contribute to the peer-reviewed publication and conference presentations. To minimize perceptions of conflict of interest, the research team will manage the research report and summaries for participants and the community.

Funding and Declaration of Interests

Funding for the iPads to conduct the program and funding to employ the peer workers was provided by the Canberra Hospital Foundation and ACT Health, respectively. This funding applied to the e-mental health program delivery only.

The research study is being conducted using in-kind resources at the Centre for Mental Health Research. This includes funding provided by ACT Health for ACACIA: The ACT Consumer and Carer Mental Health Research Unit. The funding support for ACACIA is managed by a separate area from the one involved in program delivery and the research will be conducted independently of program implementation.

Discussion

Principal Findings

The current protocol describes an exploratory proof-of-concept study with results focused primarily on the feasibility of implementing the e-mental health program into service delivery models. We will also provide a post-intervention evaluation of the effectiveness of the program on recovery outcomes and the

usefulness of the program from the consumers' perspective. The study design is appropriate for the evaluation of an intervention and its feasibility in a real-world setting, using multiple perspectives and data collection methods. In addition, key strengths of the study include the consumer input into the evaluation design and the consideration of staff, peer worker, and consumer viewpoints in evaluating the intervention.

Limitations

The study design does not allow clear separation of the concept of the peer worker and the app itself. However, participants will be explicitly asked to rate the aspects of the program separately to attempt to evaluate core aspects individually. Moreover, due to budget constraints, the study is utilizing a single peer worker, meaning that it will be difficult to differentiate opinions about the specific peer worker from the concept of a "peer worker". We will attempt to ascertain this from the flexible questions in the participant focus group discussions and interviews with staff. In addition, we have acknowledged that there are challenges associated with peer work [3,13]; however, the purpose of this pilot study was not to overcome them per se. We have attempted to address these issues by providing specific training for the peer worker on the delivery of the app, evaluating the management and supervision of the peer worker (as indicated in the interview questions in Multimedia Appendix 3), and clearly defining the peer worker's role in assisting the participants through the app.

Conclusion

The findings from this study will have important implications for informing large-scale investigations into the role of peer workers using e-mental health, which can enable the development of guidelines to inform the future implementation of the provision of e-mental health using peer workers in mental health services.

Acknowledgments

MB and AG wrote the draft manuscript and ARM wrote the draft introduction. All authors approved of the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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

[PDF File (Adobe PDF File), 129KB - resprot_v6i12e248_app1.pdf]

Multimedia Appendix 2

Peer worker role statement.

[PDF File (Adobe PDF File), 203KB - resprot_v6i12e248_app2.pdf]

Multimedia Appendix 3

Evaluation materials.

[PDF File (Adobe PDF File), 380KB - resprot_v6i12e248_app3.pdf]

Multimedia Appendix 4

Model consent form for consumers.

[PDF File (Adobe PDF File), 140KB - resprot_v6i12e248_app4.pdf]

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Abbreviations

ACACIA: The ACT Consumer and Carer Mental Health Research Unit
ACT: Australian Capital Territory
ANU: The Australian National University
e-mental: electronic mental

SISR: Self-Identified Stages of Recovery

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Protocol

MyVoice National Text Message Survey of Youth Aged 14 to 24 Years: Study Protocol

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Abstract

Background: There has been little progress in adolescent health outcomes in recent decades. Researchers and youth-serving organizations struggle to accurately elicit youth voice and translate youth perspectives into health care policy.

Objective: Our aim is to describe the protocol of the MyVoice Project, a longitudinal mixed methods study designed to engage youth, particularly those not typically included in research. Text messaging surveys are collected, analyzed, and disseminated in real time to leverage youth perspectives to impact policy.

Methods: Youth aged 14 to 24 years are recruited to receive weekly text message surveys on a variety of policy and health topics. The research team, including academic researchers, methodologists, and youth, develop questions through an iterative writing and piloting process. Question topics are elicited from community organizations, researchers, and policy makers to inform salient policies. A youth-centered interactive platform has been developed that automatically sends confidential weekly surveys and incentives to participants. Parental consent is not required because the survey is of minimal risk to participants. Recruitment occurs online (eg, Facebook, Instagram, university health research website) and in person at community events. Weekly surveys collect both quantitative and qualitative data. Quantitative data are analyzed using descriptive statistics. Qualitative data are quickly analyzed using natural language processing and traditional qualitative methods. Mixed methods integration and analysis supports a more in-depth understanding of the research questions.

Results: We are currently recruiting and enrolling participants through in-person and online strategies. Question development, weekly data collection, data analysis, and dissemination are in progress.

Conclusions: MyVoice quickly ascertains the thoughts and opinions of youth in real time using a widespread, readily available technology—text messaging. Results are disseminated to researchers, policy makers, and youth-serving organizations through a variety of methods. Policy makers and organizations also share their priority areas with the research team to develop additional question sets to inform important policy decisions. Youth-serving organizations can use results to make decisions to promote youth well-being.

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KEYWORDS

adolescents; text messaging; longitudinal study; mixed methods; health policy

Introduction

Youth are central to every major health problem today [1]. Addressing the health and well-being of youth can influence their attitudes, beliefs, and behaviors that ultimately impact health outcomes throughout their life span [2-8]. For example, behaviors that influence chronic disease such as diet and exercise are developed and reinforced during youth [9-11]. Further, symptoms of mental illness often manifest before age 25 [12,13], and sexual health issues are also prominent during adolescence. Despite the need to influence and improve youth health and behavior, there has been little progress in adolescent health outcomes in recent decades [1,14]. Initiatives to address poor health outcomes have largely been unsuccessful [15-18], likely because they are not informed by the adolescent perspective [1]. Instead, program and policy recommendations rely heavily on the perspectives of adults because youth often exert little autonomy in society and in health care settings [19-21].

Previous efforts to gather the perspectives of youth to investigate adolescent health have employed more traditional quantitative and qualitative data collection methods. For example, studies that have employed quantitative strategies, such as surveys, are challenged by a long turnaround time for collection, analysis, and dissemination [8,22,23]. In other studies, researchers have used qualitative focus groups and individual interviews to understand the contextual experiences of youth, or the how and why particular health problems and phenomena persist. However, sample sizes in qualitative studies are relatively small and therefore hard to scale or make inferences about the broader population that can inform policy [24,25]. Finally, many of these approaches rely on samples from secondary school, university, clinic, or community settings that underrepresent low-income, minority, and out-of-school individuals [3,4]. This suggests that adolescent health research has largely ignored the perspective of diverse groups of youth, limiting a full understanding of the issues facing adolescents and perpetuating health disparities [26,27]. In sum, the quality of data collected about this age group is lacking and translation into clinical practice or policy recommendations may be misguided. Research is needed that engages youth—particularly high-risk youth left out of traditional research—to understand their perspectives on health policies and practices that impact their lives to ultimately improve the health and well-being of youth.

One promising method for engaging youth in research is through text messaging. Studies that employ text messaging support the use of this novel strategy for data collection, concluding that the method is effective, easy to implement, and preferable among low-income communities [28,29]. This method seamlessly integrates into the day-to-day lives of youth, not adding the unnecessary burden of travel or time. In addition, text messaging has also been shown to result in more candid responses than voice interviews, even to sensitive questions [30]. As a result, text messaging offers an innovative, youth-friendly way to significantly increase access to and participation of low-income, high-risk, and otherwise excluded populations.

The use of text messaging can also address the problems with more traditional approaches (eg, interviews, surveys, school-based samples) to adolescent research described previously [28,31,32]. Text messaging is used by nearly all adolescents in the United States (97%) and is their preferred mode of communication due to its convenience and efficiency [33,34]. In contrast to quantitative survey methods, which have a long turnaround time and therefore can fail to influence critical or urgent policy decisions, text messaging has the potential to be used for real-time feedback on current health issues [35]. Unlike qualitative approaches such as interviews and focus groups, data collection via text messaging allows for rapid data collection and analysis for a large population-based sample allowing researchers to make generalizations that can inform policy and practice. Finally, rather than relying on school, clinical, or nonrepresentative community samples, text messaging is convenient and accessible to the vast majority of youth.

The MyVoice study was designed in response to calls for "strategic science," defined as research that addresses gaps in knowledge important to policy decisions. Strategic science is research derived from the reciprocal flow of information between researchers and policy makers, and communicated not only in scholarly publications but also in forms relevant to policymakers [36].

MyVoice collects real-time data from youth via text messaging. The purpose of MyVoice is to harness youth perspectives to connect youth attitudes, beliefs, and behaviors to researchers and policymakers who can bridge the divide between youth and youth-centered policies. The aim of this paper is to describe the research protocol used to engage youth in an ongoing longitudinal research study to investigate youth perspectives on health and well-being. In addition, plans for dissemination of findings to inform policies that impact youth are described.

Methods

Overview

MyVoice uses a longitudinal mixed methods research design [37] to gain insight into youth perspectives on health, health care policy, and related issues important to the well-being of adolescents and young adults (see Figure 1). We seek to gain insight into matters that impact young people by gathering the voices of those directly affected by programs and policies—youth themselves. Each week, we will ask youth to respond to quantitative and qualitative survey questions via text message. The results will be quickly analyzed in real time and disseminated to youth, community members, academic researchers, and policymakers. In this way, the perspectives of youth can be central to the decisions made by community organizations, program directors, researchers, and lawmakers.

Figure 1. MyVoice research study design.

We assembled an interdisciplinary team of clinicians, academic investigators, methodologists, policymakers, and youth to bring together clinical, topical, methodological, and lived experiences relevant to youth health. The research team includes high school and college students to ensure that youth perspectives are incorporated into the full research process [38,39]. Youth research team members take on leadership roles, participate in decision-making processes, lead and support manuscript writing, generate research questions, support data collection and analysis, and create dissemination strategies. This study has been approved by the University of Michigan Institutional Review Board (HUM00119982).

Project Development and Timeline

The MyVoice study has been iteratively developed through a yearlong pilot study from June 2016 to June 2017. The first phase of pilot testing was used to understand how to recruit and maintain a racially and economically diverse sample, and how to maximize the user experience for participants. The first phase was tested with 114 individuals and revealed key insights that were applied to improve the project. For example, we collected quantitative and qualitative evaluation data about recruitment and consenting procedures, participant preferences for style and content of questions, and technical glitches encountered while participating in the pilot phase. Although the full findings of the pilot evaluation are beyond the scope of this protocol, results were used to make the following changes to the study design: (1) focusing questions on political topics and current events, (2) waiving parental consent for participants younger than age 18 years, (3) addressing technical issues with the text messaging platform, and (4) using targeted advertisement to meet sampling quotas for demographics.

The next phase aims to enroll a national population-based sample of approximately 1000 participants. To date, MyVoice has enrolled approximately 800 participants and is nearing quota goals for all demographics.

Recruitment

Youth are recruited in person, at community and youth-centered events, and online via Facebook and Instagram advertisements. Recruiting on Facebook and Instagram is an effective way to reach populations not traditionally reached through research because Facebook is used by 71% of adolescents and more likely to be used by teens that are from disadvantaged households [40]. Facebook and Instagram allows for targeted recruitment of specific populations, including low-income, minority youth, and youth not in high school or college. Eligibility criteria include age 14 to 24 years, ability to read and communicate in written English, and use of a phone with text messaging capabilities. Phones with text message capabilities from any operating system and carrier are able to participate. If eligible, consent is obtained from participants and parental consent is not required. Participants are only asked to report their nickname and their cell phone number, which is used only to send weekly surveys but are removed from the dataset before analysis to ensure confidentiality. At the time of enrollment,

participants are sent a link to an online demographic survey (see Table 1). Demographic survey items include validated measures for gender, race, zip code, highest level of education, highest level of parent/guardian education, and an age-appropriate measure of socioeconomic status. Participants receive weekly surveys until they actively unenroll or when they reach age 25 years.

Sampling

Quota sampling is used to achieve a population-based sample of youth participants. Recruited samples are matched with demographic characteristics of a national sample of youth aged 14 to 24 years. Facebook advertisements are created to target specific demographic characteristics, including age, gender, race/ethnicity, education, family income, and region of the country using weighted samples from the most recent American Community Survey. Creating a national sample of youth requires regular monitoring of participant demographics and tailoring online advertisements to meet predetermined quotas. Specifically, the study team is (1) opening recruitment on Facebook and Instagram and conducting weekly checks of participant demographics currently enrolled; (2) adjusting Facebook and Instagram recruitment advertisements to meet benchmarks, such as pausing advertisements targeting groups that have met the benchmark while increasing advertisements targeting populations that have not met the benchmark; and (3) continuing recruitment until all benchmarks are met and the sample is adequately powered for quantitative calculations.

Incentives

Modest incentives are provided for participation throughout the study. Participants receive a one-time US $5 incentive for completing the online demographic survey on the study website following enrollment in the study. For the weekly surveys, participants receive US $1 for each completed survey. Every 12 weeks, participants also receive a US $3 bonus if all 12 weekly surveys are completed (total incentive of US $15 every 12 weeks for completed surveys). MyVoice also offers occasional "bonus" questions to elicit perspectives on time-sensitive policy issues. Participants receive an additional US $1 for completion of each bonus survey.

Longitudinal Engagement

Based on our iterative pilot phases, we developed three primary strategies beyond the incentives described previously to promote participation and reduce attrition. First, the study design focuses on the perspectives of youth and asks youth to share their experiences. Second, with a goal to better understand and improve the health of youth, we actively generate weekly question sets that address topics that have real-world implications. Third, we regularly disseminate results to the youth participants, through infographics, summaries of findings, or select quotations (see Dissemination for more detail).

Question Development

Generating

In weekly MyVoice research team meetings, upcoming topics are identified and discussed. A research question is identified to structure each week's question set. Each week of questions focuses on one topic or issue identified by the MyVoice team, external youth-serving organizations, researchers, or policy makers. Topics are selected that align with upcoming policy priorities or timely policy concerns specific to the health of youth. In pilot testing, topics that have been fielded included stress, weight, nutrition, substance use, health insurance, relationships, and sexual health education.

Writing

Weekly text message surveys consist of three to five questions. Although topics and question structure varied, we include closed- and open-ended questions that assess the knowledge, attitudes, and beliefs of study participants. During team meetings, we revise questions to maximize comprehension, appropriateness for youth, and adherence to the research question. The team also discusses how to structure the questions to optimize the use of the text messaging platform.

Piloting

Once written and edited by the research team, weekly surveys are sent to a pilot team of youth, community members, survey experts, methodologists, and topical experts. Participants in the pilot-testing sample provide feedback regarding topics, sentence structure, phrasing, and word choice. The research team makes modifications to weekly surveys in response to pilot feedback before data collection.

Data Collection

Tutorial

After participants provide consent/assent via the study website, they receive a text message tutorial that briefly describes the study process (see Figure 2). Participants are reminded that their participation is voluntary, responses are confidential, and any question can be skipped. In addition, the MyVoice tutorial provides a telephone number where study staff can be reached.

Weekly Survey

Questions are created in 12-week blocks. Textizen is the Web-based platform used to deliver surveys via text message. One-week delays are placed between each weekly question set. Weekly surveys are sent out to participants via Textizen on a consistent day and time.

Question Rating

Each week's questions are rated by respondents on a scale of 1 to 5 "stars." Ratings for questions are used to inform future surveys.

Data Analysis

All responses are downloaded as a comma-separated values file. Data analysis depends on the nature of the questions from each weekly survey. Closed-ended and categorical (quantitative) responses are cleaned for case mismatch, spelling variants, and typographic errors to prepare for analysis using descriptive statistics.

Table 1. MyVoice demographic survey completed on enrollment.

Question	Response options
What is your date of birth? Please enter it in the following format: mm/dd/yyyy.	Open-ended
What is your cell phone number? Please enter in the following format: 1 555 555 5555	Open-ended
What is your gender?	Male; female; transgender (FTM); transgender (MTF); nonbinary; other (please specify)
What is your race? Check all that apply.	American Indian or Alaska Native; Asian; black or African American; Native Hawaiian or other Pacific Islander; white or Caucasian; other (please describe)
Are you Hispanic or Latino?	Yes; no
What zip code do you live in?	Open-ended
What is the highest level of education you have achieved?	Eighth grade or less; some high school; high school graduate; some vocational/technical training; completed vocational/technical training; some college; completed an associate's degree; completed a bachelor's degree; some graduate school; completed a master's degree; some graduate training beyond a master's degree; completed a doctoral degree
What is the highest level of education any parent/guardian has achieved?	Eighth grade or less; some high school; high school graduate; some vocational/technical training; completed vocational/technical training; some college; completed an associate's degree; completed a bachelor's degree; some graduate school; completed a master's degree; some graduate training beyond a master's degree; completed a doctoral degree
Who do you live with most of the time?	My parent(s)/guardian(s); my aunt/uncle; my kids; in a dorm; in apartment or house with other people, not family; in a fraternity/sorority; I live alone; other; my spouse, partner, or significant other
How many people are in your immediate family? (Include you, any parents/guardians, siblings, step-siblings, etc)	1-3; 4-6; 7-10; ≥10
What is your parent(s)/guardians' current marital status?	Married; together but not married; separated; divorced; widowed; unsure
How did you hear about MyVoice?	From a family member; from a friend; Facebook; Instagram; other
Socioeconomic status measure for respondents under age 18 (version received determined by participant's date of birth)	
Thinking about the house you live in at the moment, do your parents own it or rent it? (If they have a mortgage, tick "they own it")	They own it; they rent it; I don't know
Do you have a car or van at home?	Yes, one car or van; yes, more than one car or van; no, we don't own a car or van
Which of the following Internet technology devices do you have at home?	Desktop computer; laptop computer; iPad or other tablet; other (please specify)
When you were in middle/high school, did you receive free or reduced price school lunch?	Yes; no
Socioeconomic status measure for respondents age 18 and older (version received determined by participant's date of birth)	
What is your annual household income? (Just an estimate of the total amount of everyone in your household)	Open-ended

Figure 2. Screenshot of tutorial sent to new participants.

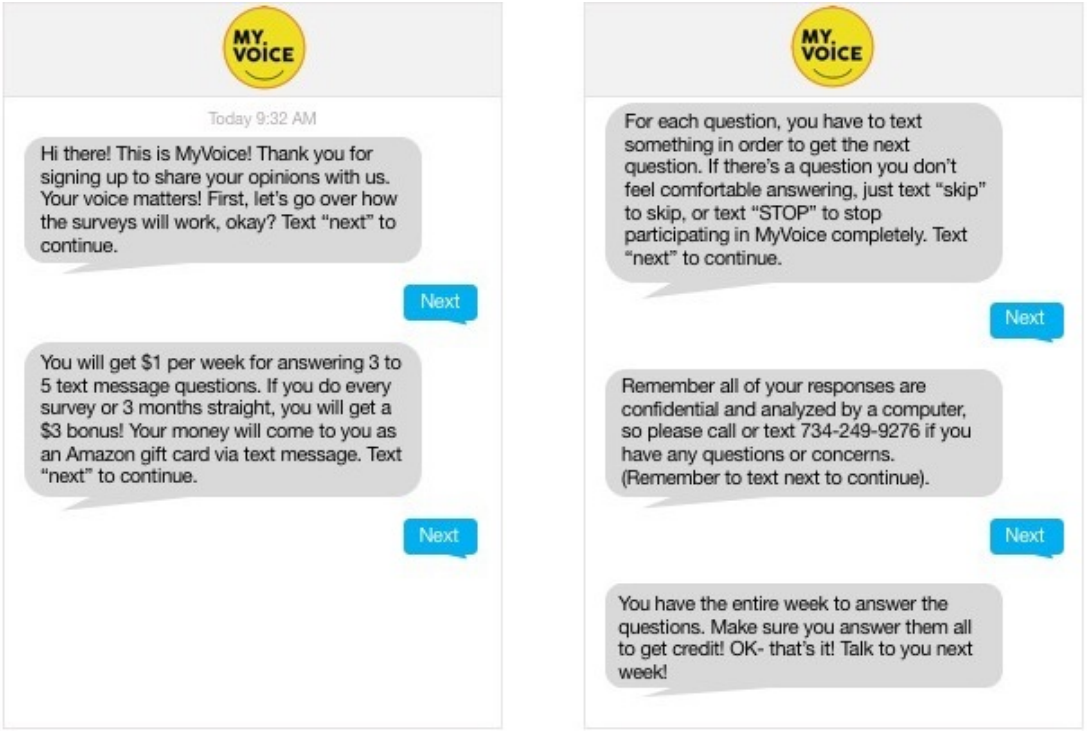
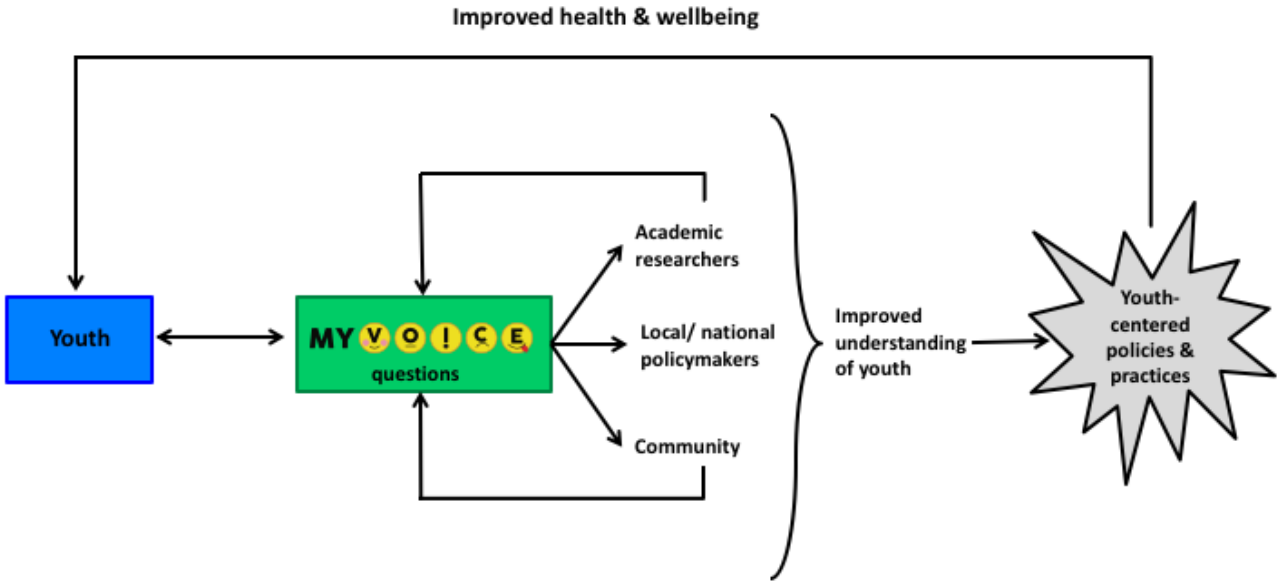


Figure 3. MyVoice dissemination model.



For open-ended (qualitative) responses, natural language processing (NLP) techniques are applied to cluster responses. Using NLP, responses are parsed and synonymous words are first grouped into word clusters. These word clusters are further grouped using word similarity measures resulting in semantic word clusters. Our initial analysis of these semantic word clusters shows sufficient agreement with traditional qualitative methods based on manual review and coding responses. Effectiveness of this approach will be reported in a future paper.

Results may be stratified by demographic characteristics to better understand differences and meet the needs of specific stakeholder organizations. For example, responses to surveys may be stratified by age to distinguish between younger (age 14-18 years) and older (age 19-24 years) respondents.

Dissemination

Results will be disseminated to multiple audiences, including academics, policymakers, and youth (see Figure 3). Dissemination products include media/online graphics or GIFs, presentations to community groups, one-page reports, policy briefs, academic presentations, and academic manuscripts. These products are determined by the audience and specific study and content area being disseminated. For example, a lawmaker interested in findings related to beliefs about sexually transmitted diseases may request a one-page infographic to be

distributed during community town halls to influence local policy, whereas a study on eating behavior may be reported in a peer-reviewed manuscript.

For youth, findings are shared via text message as #WeHearU messages (see Figures 4 and 5). Following data analysis, #WeHearU infographics or narratives are created to build engagement, encourage participation, and share the depth and breadth of responses. We also demonstrate the commitment of the MyVoice team to translate the words of youth into messages for lawmakers and youth-serving organizations by creating and distributing postcards featuring summaries of results or quotes from study participants (see Figure 5).

Figure 4. Example of #WeHearU sent to participants.

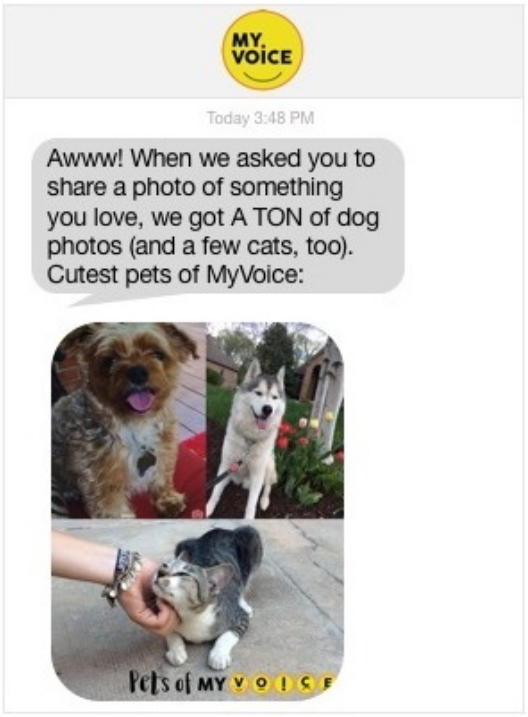
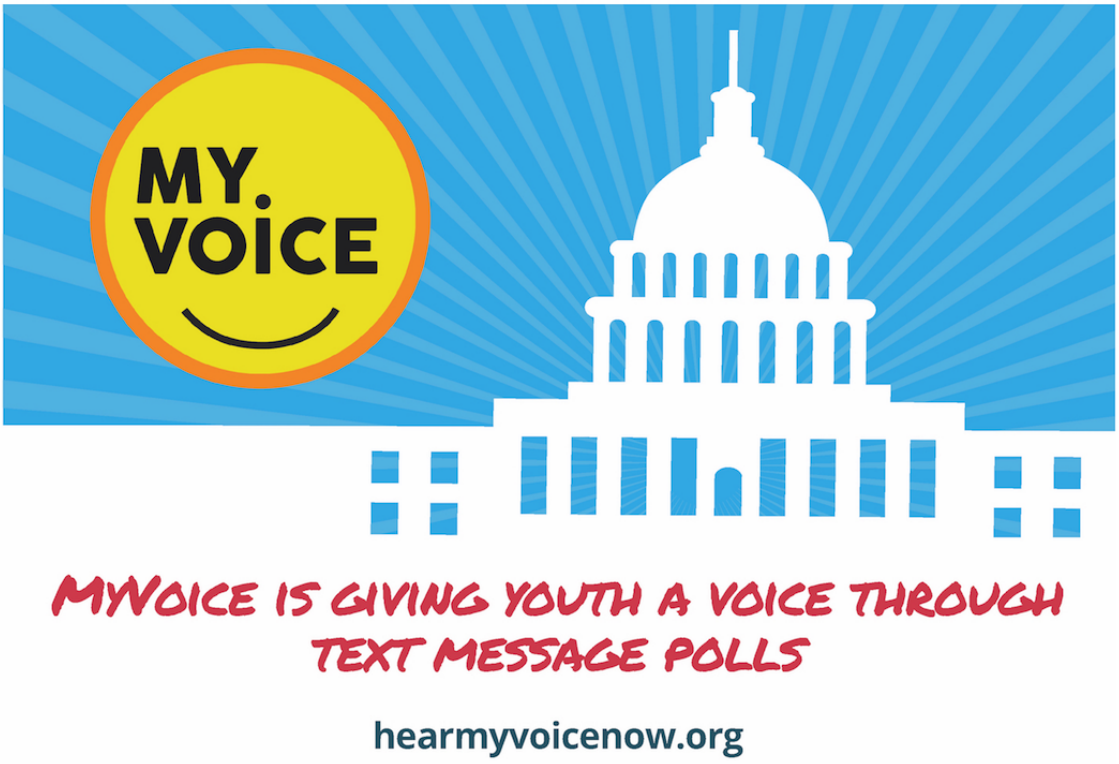


Figure 5. Postcard distributed to lawmakers.



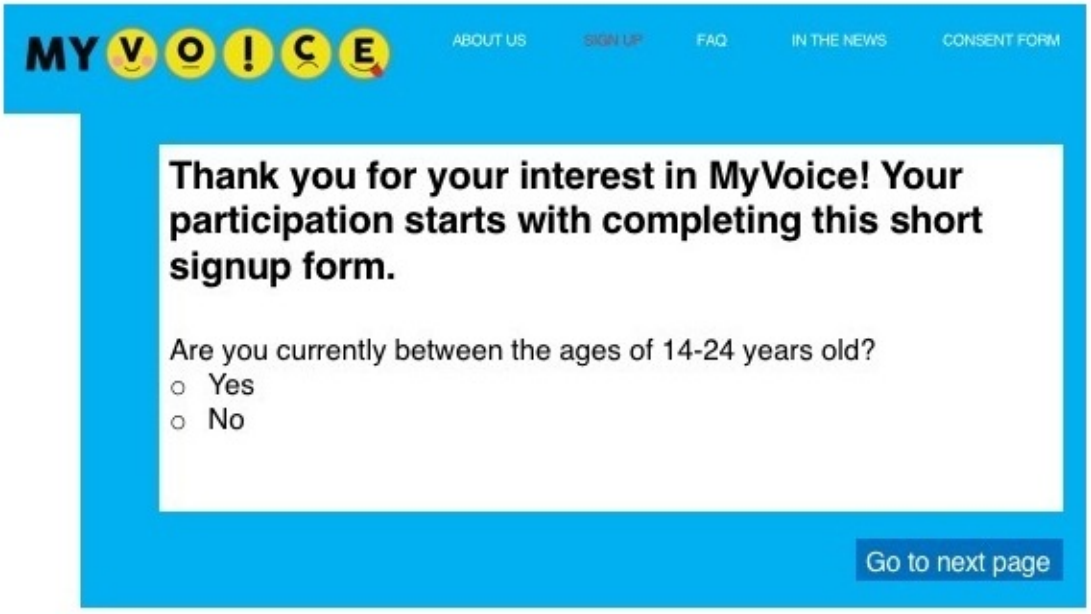
Results

We have launched the national study and are currently recruiting and enrolling participants through in-person and online strategies. The MyVoice website is live and enrollment (including consent) and demographic questionnaires are embedded (see Figures 6 and 7). Question development, weekly data collection, data analysis, and dissemination are in progress.

Through the first two phases of pilot testing, we have collected 56 weeks of data from 114 participants. See Textbox 1 for a selection of topics and corresponding question sets sent to participants.

Figure 6. Screenshot of home page for MyVoice website.

Figure 7. Embedded enrollment (including consent) form in MyVoice website.



Textbox 1. Examples of MyVoice topics and questions.

Police

Intro: *Hi, it's MyVoice! Some people feel safer when police officers are around. Some people feel less safe. How do you feel when police officers are around you?*

Q1: *There has been news of unarmed people being shot by police. On a scale of 1 to 5 how big of a problem is this? (1=not a big prob; 5=a very big prob)*

Q2: *Why?*

Q3: *What are some things that police could do better to keep people safe?*

Q4: *What have your experiences with police been like?*

Q5: *Rate this week's questions (1 through 5)! 1=one star, 5=five stars*

Outro: *That's all for this week. Thank you!*

Sexually transmitted diseases

Intro: *Hi, {{name}}. We are interested in your thoughts about sexually transmitted infections (STIs). If you had an STI, would you tell your sexual partner(s)?*

Q1: *Why or why not?*

Q2: *Would it be hard for you to get TESTED for an STI? Why or why not?*

Q3: *Would it be hard for you to get TREATED for an STI? Why or why not?*

Q4: *Rate this week's questions (1 through 5)! 1=one star, 5=five stars*

Outro: *You're done for the week, {{name}}! Talk to you next week.*

Student debt

Intro: *Hi {{name}}! This week's questions ask your thoughts about college. Whether you are in school or not, we want to hear your opinion. Type "next" to continue.*

Q1: *What are three things that might make it hard for you to go to college?*

Q2: *How much student loan debt is ok to have for a college education? Why?*

Q3: *Should college be free? Why or why not?*

Q4: *How much do you expect to earn per year in your first full-time job?*

Q5: *Rate this week's questions (1-5)! 1=one star, 5=five stars*

Outro: *Alright, you are finished and made another dollar! We'll talk to you next week! :)*

Limitations

The MyVoice sample is not nationally representative; however, quota sampling allows MyVoice to recruit using a variety of methods while meeting national benchmarks for important demographic characteristics.

Question sets typically only include three to five questions per week and may require repeat longitudinal sampling to get in-depth knowledge (ie, fielding several weeks of questions on the same topic). However mixed methods techniques that integrate qualitative and quantitative data allow us to collect data with a deep understanding of context not attainable in traditional surveys of youth and are collected in a manner that may elicit more truthful responses [30].

Discussion

This study represents a novel example of strategic science that collects youth thoughts and opinions in real time with a goal of disseminating to appropriate change agents at the pace that policy decisions are being made [36].

This study protocol describes a youth-centered method of gathering the beliefs, attitudes, and behaviors of youth in their own words. We know that sustainability of interventions, programs, and policies is dependent on the buy-in of its users. Understanding youth perspectives can allow for the development of youth-centered policies that build on the needs, priorities, and recommendations of those who will be directly affected.

The Department of Health and Human Services Office of Adolescent Health currently lists no ongoing longitudinal qualitative or mixed methods study of youth [41]. As a result, our study is expected to make several methodological contributions. First, we will engage a national population-based sample of youth in a longitudinal mixed methods study of youth that includes voices that are traditionally excluded from research (ie, populations) and policy recommendations.

Second, we have developed a strategy to engage youth over time. Including youth in longitudinal research has been difficult, yet essential, to understanding the health problems we face today [1]. We employ text messaging as an inclusive, comfortable, low-burden mechanism for participation [42,43].

Third, our use of text messaging and NLP allows for real-time data collection, analysis, and dissemination of research findings. The timeline of research (months to years) is typically misaligned with the timeline of policy decision making (weeks to months) [44]. MyVoice bridges this gap by creating a method that better matches the needs of policy makers at all levels with the goal of informing youth-centered policies at all levels.

Finally, our project adds to the growing evidence that participation of advisory groups, peer leaders, and community researchers enhances the quality and reach of research [45-47]. Youth play an active role on our research team. They have an ongoing role in the development of the study, recruitment of participants, data collection and analysis, and dissemination to diverse audiences. Alongside academic researchers, community organizations, and clinicians, youth are encouraged to participate in decision-making processes and take on leadership roles.

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Conflicts of Interest

None declared.

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Abbreviations

NLP: natural language processing

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Original Paper

Development of an Index of Engagement in HIV Care: An Adapted Internet-Based Delphi Process

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Abstract

Background: Improving engagement in medical care among persons living with human immunodeficiency virus (HIV) is critical to optimizing clinical outcomes and reducing onward transmission of HIV. However, a clear conceptualization of what it means to be engaged in HIV care is lacking, and thus efforts to measure and enhance engagement in care are limited.

Objective: This paper describes the use of a modified online Delphi process of consensus building to solicit input from a range of HIV and non-HIV researchers and providers, and to integrate that input with focus group data conducted with HIV-infected patients. The overarching goal was to generate items for a patient-centered measure of engagement in HIV care for use in future research and clinical practice.

Methods: We recruited 66 expert panelists from around the United States. Starting with six open-ended questions, we used four rounds of online Delphi data collection in tandem with 12 in-person focus groups with patients and cognitive interviews with 25 patients.

Results: We recruited 66 expert panelists from around the United States and 64 (97%) were retained for four rounds of data collection. Starting with six open-ended questions, we used four rounds of online Delphi data collection in tandem with 12 in-person focus groups with patients and cognitive interviews with 25 patients. The process resulted in an expansion to 120 topics that were subsequently reduced to 13 candidate items for the planned assessment measure.

Conclusions: The process was an efficient method of soliciting input from geographically separated and busy experts across a range of disciplines and professional roles with the aim of arriving at a coherent definition of engagement in HIV care and a manageable set of survey items to assess it. Next steps are to validate the utility of the new measure in predicting retention in care, adherence to treatment, and clinical outcomes among patients living with HIV.

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KEYWORDS

HIV; AIDS; engagement in care; Delphi method; retention in care

Introduction

In 2011, researchers estimated that only 19% of individuals living with human immunodeficiency virus (HIV) in the United States achieve virologic suppression [1]. This finding led to renewed efforts to improve the steps leading up to this critical health outcome, including linkage to antiretroviral therapy initiation to ongoing retention in care [2-6]. Researchers and clinicians frequently use the term “engagement in care” to describe these steps; however, little clarity exists on what defines the engaged patient with respect to HIV care and treatment. For example, appointment attendance does not necessarily equal being invested in one’s care, although it is certainly a prerequisite. In addition, the benchmarks of the care cascade are not necessarily what is meaningful to patients as they move through the trajectory of care and treatment, and thus definitions

of engagement must account for patient perspectives [7-9]. Finally, patients experience challenges in maintaining consistent involvement with HIV care and treatment over the life course, and patients may experience events that cause them to participate inconsistently or drop out altogether. A broader conceptualization of engagement in HIV care can guide the identification and measurement of relevant components of engagement in care. This, in turn, can permit the prediction of who is at risk for poor outcomes.

The literature describes a rich but dispersed set of factors likely related to engagement in care. For example, researchers have long established the importance of patient involvement in clinical decision making [10,11], with the conclusion that greater patient participation leads to greater satisfaction and adherence to care [10,12]. Studies have linked patient-provider relationship constructs to a wide range of proximal (eg, adherence to treatment and keeping appointments) [13] and distal outcomes (eg, virologic suppression and survival) in HIV care [12,14]. Moreover, patient reports of satisfaction, trust, perceived competence of providers, and the belief that a provider knows them as a person [15] associate with better HIV treatment adherence, retention in care, adaptive use of health care resources, and clinical outcomes over time [16-22]. Accordingly, such constructs may be critical components in the development of a patient-centered index of engagement in care. Acknowledging the value of patient, provider, and researcher perspectives on engagement in care, we designed a study to solicit and synthesize these points of view.

In this paper, we describe the use of an online Delphi method of consensus building [23-25], integrated with focus groups and cognitive interviews with patients, to identify content for a patient-centered measure of engagement in HIV care. The Delphi approach to consensus building has a long history in behavioral and health services research [26-30]. In this method, a group of experts complete a series of iterative questionnaires over multiple rounds, which begin with open-ended questions and conclude with more closed-ended items. Participants access the study materials for all rounds via a secure Web portal that maintains respondents' confidentiality. Reponses from the first round of open-ended questions form the basis of the second round of questions, which are more specific and closed ended. This process is repeated, allowing respondents to review feedback on the collective responses of the group, until the group achieves consensus or agreement on the topic under investigation. Key elements of the process include protocols to maintain anonymity of the respondents' identities and responses, multiple iterations of data collection, rapid analysis of responses, and feedback of the group's collective responses at each successive round.

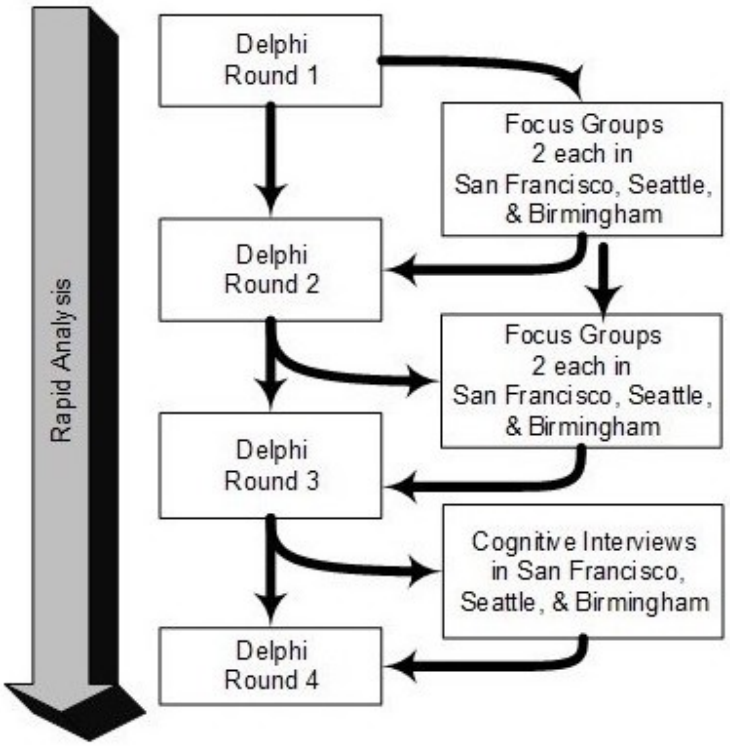
In this report, we describe the process used to identify key elements, components, and indicators of engagement in care to inform the development of a self-report measure of engagement in care to be administered to HIV-infected patients who are receiving HIV primary care. Specifically, we highlight the innovative use of Internet-based recruitment and data collection, coupled with in-person patient focus groups, to solicit input on a current challenge in HIV research. To our knowledge, this use of Internet-based Delphi methods, integrated with in-person focus groups with patients, is the first of its kind in the Delphi literature. A resulting definition of engagement in care along with specific items to assess it will offer a framework for greater understanding of engagement in care. This understanding can, in turn, provide guidance for interventions and policies to optimize engagement in HIV care with the added opportunity to apply the lessons learned and successful procedures learned during this investigation in future studies.

Methods

Design

We used four rounds of online Delphi data collection integrated with face-to-face patient focus groups that were conducted before Delphi rounds 2 and 3 in San Francisco, CA; Seattle, WA; and Birmingham, AL (see Figure 1 for the sequence of data collection procedures). Focus groups were conducted with patients having a range of retention in care profiles. Focus group participants were recruited through provider referral at a HIV specialty clinic in each of three cities: San Francisco, CA; Birmingham, AL; and Seattle, WA. Half of the groups in each city included only patients with optimal retention in the prior year (ie, no missed visits, no large gaps between visits) and the other half were less well-retained (ie, having any missed visits or greater than 6-month gaps between visits). Results from the focus group discussions were fed back into subsequent Delphi rounds. Specifically, patient perspectives that did not emerge from the Delphi process were integrated into subsequent Delphi rounds. The second round of focus groups also included an opportunity for patients to provide input on topics and candidate items generated up to that point. Between rounds 3 and 4, we conducted cognitive interviews with patients of the candidate survey items at the three primary research sites. Specific findings from the focus groups are forthcoming; this paper focuses on the Delphi process. All Delphi procedures, patient focus groups, and cognitive interview procedures were approved by the Committee for Human Research at the University of California, San Francisco. In addition, focus group and cognitive interview procedures were approved by our partnering institutions' institutional review boards at the University of Washington in Seattle, WA, and the University of Alabama at Birmingham in Birmingham, AL.

Figure 1. Interaction of Delphi, focus group, and cognitive interview methods.



Identification, Recruitment, and Enrollment of Delphi Panel Members

We identified three subgroups of experts to include in the Delphi panel (20 each for a target total of 60). We identified group 1 (HIV researchers) by using NIH Reporter, PubMed, and Patient-Centered Outcomes Research Institute (PCORI) grantee lists to identify investigators who had published on HIV care and treatment engagement in the past 5 years or were currently funded to work in the area. Using a range of keywords (eg, retention in care, engagement in care), we identified a diverse group of investigators with regard to geography and training background (eg, clinical, behavioral, and epidemiological scientists). We recruited group 2 (HIV providers with at least half-time clinical practice) through email invitations from our partners in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a cohort of more than 30,000 patients at eight HIV care sites in the United States. For this group, we sought a range of providers, including physicians, nurse practitioners, physician assistants, nurses, and social workers. For group 3 (non-HIV providers and researchers), we sought to broaden input beyond HIV by enrolling panelists who were working outside of HIV, both in research in the area of engagement in care and clinical care delivery in high-volume primary care. We located these respondents through a similar approach as group 1: searching for publications on the topic of engagement in care in other chronic conditions and through local contacts. We used these resources and referrals from those recruited to groups 1 and 2 to identify clinicians (with at least half-time clinical practice) working outside of HIV with high volumes of patients.

While maintaining approximately equal proportions across these three groups, potential panelists were approached via an email from the principal investigators of the study (cosigned by the NIH Program Officer), which briefly explained the purpose of the study, the expected time commitment, and the compensation for participation. We directed those who agreed to a secure website, where the instructions guided them through the consent process and a brief survey to collect information to characterize the participants (eg, age, race, ethnicity, gender, academic discipline, clinical practice characteristics, years since completing degree/training). Once we achieved the targeted sample size, we initiated the first round of data collection. To incentivize enrollment and improve retention among the panelists, we offered a US $50 per round electronic gift card payment with a bonus of an additional US $50 to panelists who completed all four rounds.

Delphi Survey Procedures

We used Qualtrics (Provo, UT, USA), a software program that allows the building, distribution, and analysis of online surveys for administration of the online Delphi surveys. Participants were sent a unique URL directing them to each round of the survey, and reminder emails were sent as the deadlines approached. Each round was open for 3 weeks with some extensions (up to a week) provided when requested. We chose four rounds on Delphi data collection because this was in line with the most common number of rounds identified in the Delphi literature [23-25].

Content of the Delphi Surveys

The objectives of the online Delphi surveys were to solicit patient-centered constructs that are relevant to engagement in care and to review and comment on patients' perspectives on

engagement in care. The survey began with demographics and six open-ended items to encourage a wide range of responses (round 1). These included:

1. How would you describe patients who are well engaged in health care?
2. How would you describe patients who are not well engaged in health care? Please elaborate as much as possible and feel free to use examples.
3. What clinic, provider, and other factors influence patient engagement in health care?
4. Overall, what factors do you think are not emphasized enough with regard to patient engagement in health care?
5. The HIV research and treatment field generally defines the well-engaged patient as a someone who comes to all medical appointments and takes HIV medications on a consistent basis, meaning not missing doses. Please discuss your thoughts about this definition.
6. What else should we be considering with regard to patient engagement in health care (that we haven't already covered in the preceding questions)? Why?

Each subsequent round of Delphi included increasingly specific content, such that round 2 had all items that were identified as potentially relevant to engagement in HIV care. We then asked Delphi panelists to rate each of them along a scale created for this study with anchor points from 0 (not at all important to engagement in care) to 100 (extremely important to engagement in care). Round 2 also allowed panelists the opportunity to offer comments or wording recommendations for the items.

Prior to round 3, analysis focused on two general goals: (1) to develop a working definition of the concept of engagement in care, and (2) to reduce the number of items for the planned new self-report measure (see subsequent Delphi Analysis section). In round 3, we asked experts for feedback on the definition of engagement in care and whether we should include each item in the planned self-report survey instrument to be administered to patients. Panelists rated the items along the following scale from 0 to 100: 0 (absolutely do not include), 50 (maybe include if you have space), 100 (absolutely include). We then again solicited suggestions for wording revisions.

Prior to round 4, we took the most important topics from round 3 by creating items through intensive team discussion, identifying response choices, and conducting individual cognitive interviews with patients at each of the three sites (25 patients total). A resulting small number of items were retained and shared with the panelists in round 4. In that final round, panelists were asked how much they thought each item might predict three key outcomes (adherence to medications, retention in care, virologic suppression) using a five-point Likert scale (not at all, a little, a moderate amount, a lot, and a great deal). Round 4 also included an opportunity to provide feedback on the Delphi study methodology from the panelists.

Delphi Analysis

The investigative team conducted qualitative data analysis of the round 1 Delphi results and the focus groups under the direction of an experienced qualitative researcher. We analyzed responses to the Delphi rounds using content analysis, a standard qualitative technique for cataloging open-ended survey questions [31,32]. This technique is useful for analysis of qualitative data when some a priori domains are defined based on the research questions of interest. In this case, the a priori domains originated from the primary research questions as framed in the six round 1 items. Initial coding of the data consisted of reading the responses and identifying sections of the text that correspond to the a priori domains and developing new domains as needed. A primary analyst reviewed and cataloged each response. A secondary analyst reviewed the cataloged data and inserted commentary throughout, providing a second perspective and additional input. The qualitative team resolved discrepant coding through discussion. The qualitative team then distributed a summary of these results to the larger research team for further input. The broader research team agreed on the final set of domains after thorough review and debate. The team shared these domains with both the focus group participants and the Delphi panelists in the subsequent rounds. We describe the details of the focus group discussions elsewhere (forthcoming) including the use of digital recordings, transcription, coding, and memoing procedures.

Between rounds 1 through 3, the investigative team discussed the data and combined redundant topics, split multifactored topics, and eliminated topics. Typically, eliminated topics included those that the team agreed were correlates of engagement in care (eg, substance use, depression) or that the team had framed as outcomes of engagement in care (ie, retention in care, adherence to medications, viral suppression) rather than aspects, facets, or dimensions of engagement. Our a priori goal was to identify universal elements of engagement in care so that a set of items that are applicable to all patients would result. Therefore, we removed items that would not be applicable to all patients (eg, childcare needs) so that all patients would be able to complete the subsequent measure.

Results

A total of 108 experts were identified and invited to participate as Delphi panel members, which resulted in our exceeding the target of 20 for two of the three groups. Overall, 66 agreed to participate and enrolled (61.1% acceptance rate). The enrollment rate was higher for group 1 than the other groups, which is likely because those individuals had a documented interest in the topic, as evidenced by their publications and grant funding in the area. Of the 66 who began, 64 completed all four rounds (97%) with one person each in groups 1 and 2 failing to respond beyond the second Delphi round. See Table 1 for breakdown by Delphi group. Although we did not formally seek geographic variability in our recruitment of panelists, Figure 2 demonstrates that we had widespread geographic representation in the panelists. There was a mean of 7.75 (SD 1.54) patients in each of the 12 focus groups (N=93). Table 2 documents the characteristics of patients who participated in the focus groups as per the design in Figure 1. The time between Delphi rounds, focus groups, and cognitive interviews varied depending on the amount of analysis and logistical demands required for each task, with the overall data collection spanning 25 months concluding in June 2016.

As per our a priori design, the three groups reflected a range of research and clinical perspectives. See Table 3 for characteristics of the Delphi panelists overall and within each of the three groups.

As noted previously, we started with six broad questions in round 1. This led to 120 candidate topics, identified via Delphi panelists and patients in the focus groups, which formed the basis of round 2. We reduced these to 32 candidate items for round 3 and down to a final set of 13 items for round 4. The working definition of "engagement in care" that was developed prior to round 3 was as follows:

> *Engagement in care is the ongoing interaction of patients, their providers, and care settings that is characterized by a patient's sense of connection to and active participation in care.*

Panelists gave positive comments when asked about the process. Examples of comments included: "It has been a pleasure to be a part of such a meaningful project. Thank you for the opportunity!" and "This was an excellent process. As someone who works on the administering side of HIV research it was great to be a participant for a change. Each step was very clear and interesting," and "Thanks for the great work! I'm excited to apply the findings from your study to my practice!"

Table 1. Response rates of participants.

Variable	Group 1: HIV engagement in care researchers	Group 2: HIV providers	Group 3: Non-HIV providers & researchers	Total
Invited, n	33	39	36	108
Enrolled, n (acceptance rate)	24 (73)	22 (56)	20 (56)	66 (61)
Completed round, n (%)				
Round 1	24 (100)	22 (100)	20 (100)	66 (100)
Round 2	24 (100)	22 (100)	20 (100)	66 (100)
Round 3	23 (96)	21 (96)	20 (100)	64 (97)
Round 4	23 (96)	21 (96)	20 (100)	64 (97)

Figure 2. Geographic distribution of Delphi panelists.

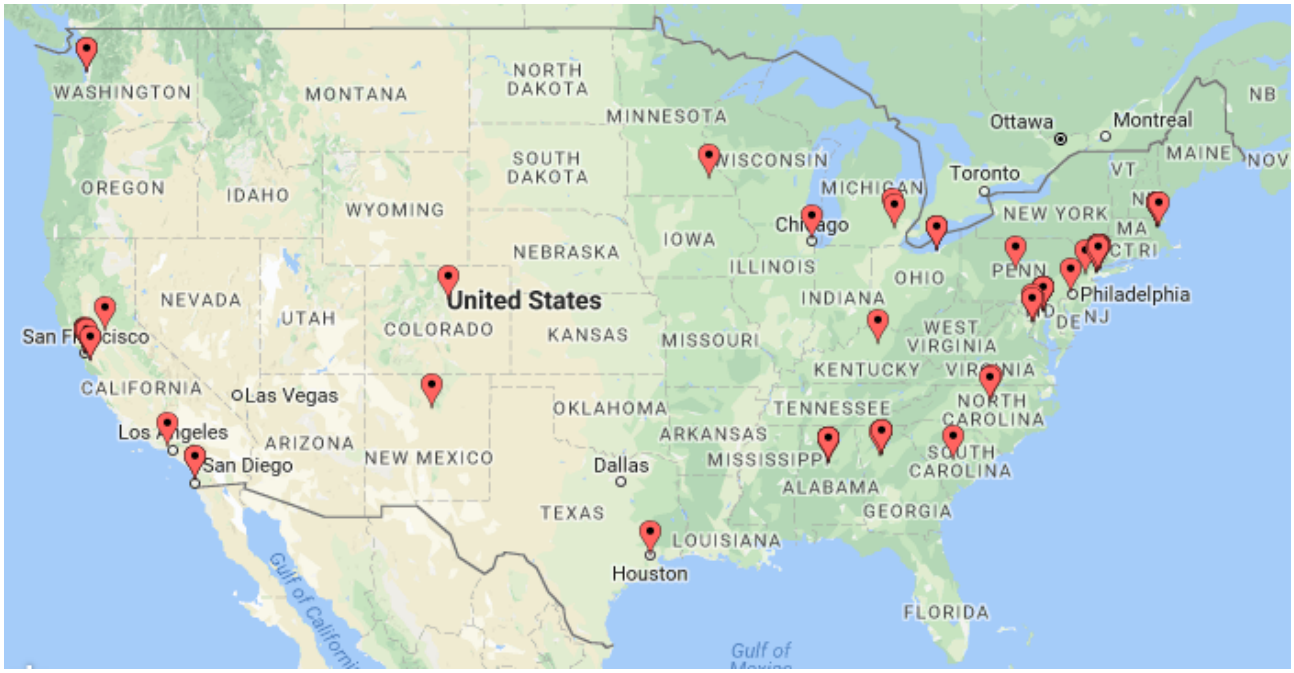


Table 2. Focus group patient characteristics (N=93).

Variable	Participants
Site, n (%)	
Birmingham	27 (29)
San Francisco	30 (32)
Seattle	36 (39)
Age in years (n=92), median (range)	49 (23-71)
Years since HIV diagnosis (n=92), median (range)	16 (1-38)
Gender, n (%)	
Male	56 (60)
Female	33 (35)
Transgender	4 (5)
Race, n (%)	
African American	41 (44)
White	41 (44)
Mixed race/other	11 (12)
Ethnicity, n (%)	
Hispanic	10 (11)
Non-Hispanic	83 (89)
Injection drug use in past 12 months, n (%)	
No	76 (82)
Yes	17 (18)
Sexual orientation [a], n (%)	
Bisexual	12 (14)
Heterosexual	36 (41)
Homosexual	40 (45)
Currently on antiretroviral therapy [b], n (%)	
No	11 (13)
Yes	76 (87)
Ever on antiretroviral therapy [c], n (%)	
No	5 (5)
Yes	87 (95)
Detectable viral load [d], n (%)	
No	55 (82)
Yes	12 (18)

[a]Missing n=5 due to data collection oversight.

[b]Missing n=6 due to data collection oversight.

[c]Missing n=1 due to data collection oversight.

[d]Missing n=26 due to data collection oversight.

Table 3. Delphi panel characteristics.

Variable	Group 1: HIV engagement in care researchers (n=24)	Group 2: HIV providers (n=22)	Group 3: Non-HIV providers & researchers (n=20)	Total sample (N=66)
Gender, n (%)				
Female	16 (67)	15 (68)	15 (75)	46 (70)
Male	8 (33)	7 (32)	4 (20)	19 (30)
Not disclosed	0	0	1 (5)	1 (2)
Age in years, mean (SD)	46.1 (7)	46.1 (9)	46.9 (10)	46.4 (8)
Race and ethnicity, n (%)				
Hispanic/Latino(a)	1 (4)	0	2 (10)	3 (5)
African American	2 (8)	3 (14)	2 (10)	7 (11)
Asian	1 (4)	2 (9)	1 (5)	4 (6)
White	20 (83)	15 (68)	13 (65)	50 (71)
Native Hawaiian or other Pacific Islander	0	1 (5)	0	1 (2)
Other or not specified	0	1 (5)	2 (10)	3 (5)
Primary discipline, n (%)				
Medicine	10 (42)	12 (55)	12 (60)	34 (52)
Social or behavioral science	8 (33)	0	6 (30)	16 (24)
Public health	6 (25)	0	0	6 (9)
Nursing	0	6 (27)	1 (5)	7 (11)
Social work	0	4 (18)	1 (5)	5 (8)
Other	0	0	0	5 (8)
Academic rank, n (%)				
Instructor	1 (4)	1 (5)	1 (5)	3 (5)
Assistant professor	3 (13)	3 (14)	9 (45)	15 (23)
Associate professor	11 (46)	2 (9)	1 (5)	14 (22)
Professor	4 (17)	3 (14)	7 (35)	14 (22)
Other	2 (8)	6 (27)	1 (5)	9 (14)
Not applicable (no academic appointment)	3 (13)	7 (32)	1 (5)	11 (17)
Primary work setting, n (%)				
University	20 (83)	3 (14)	13 (65)	36 (54.6)
Hospital/Clinic	0	19 (86)	4 (20)	23 (34.9)
Government or public health dept.	3 (13)	0	0	3 (4.5)
Other	1 (4)	0	3 (15)	4 (6.0)
Direct patient care, n (%)	9 (38)	22 (100)	15 (75)	46 (69)
Among those with patient care				
Outpatient only, n (%)	2 (22)	14 (64)	6 (40)	22 (48)
Inpatient and outpatient, n (%)	7 (78)	8 (36)	9 (60)	24 (52)
Patients with HIV seen per week, mean (SD)	10.6 (4.4)	52.4 (32.2)	1.0 (1.4)	27.4 (32.5)
Patients without HIV seen per week, mean (SD)	1.3 (2.3)	4.0 (10.4)	15.7 (12.1)	7.3 (11.4)
Total patient load (patients with HIV), mean (SD)	118.0 (96.9)	269.7 (126.9)	7.9 (12.5)	154.6 (150.5)
Total patient load (patients without HIV), mean (SD)	11.9 (18.9)	41.0 (122.6)	198.2 (176.4)	85.6 (150.2)

Discussion

The modified Delphi method of consensus used in this study emerged as an efficient method of gathering input across a group of experts separated by geography, discipline, expertise, and professional roles. This feature of the Delphi method allowed the solicitation of perspectives from busy professionals, whose schedules and competing demands would likely have limited their participation in more time-intensive research procedures. Sampling clinicians and researchers within and outside of HIV allowed a diverse set of complementary perspectives that enabled a comprehensive exploration of factors potentially relevant to engagement in HIV care. Researchers and clinicians are a rich source of information on topics such as engagement in care, but they may work in isolation or in closed networks; with the exception of presentations, case conferences, and specific publications often appearing in niche journals, the field may not systematically seek and integrate their perspectives. Bringing together experts through this Delphi process encouraged a wide range of complementary perspectives that served to illuminate many aspects of the construct in question that might otherwise have not been formally encouraged. For example, some participants prioritized clinical outcomes (eg, virologic suppression) as the only meaningful indicator of engagement in care, whereas others emphasized the importance of a strong patient-provider relationship as key to engagement in care. The process was relatively easy and input from panelists suggests that they found it to be engaging and interesting. Moreover, the online panel provided a way to obtain expert opinion that was less resource intensive than hosting an in-person meeting to convene geographically dispersed participants.

Our decision to include focus group discussions and cognitive interviews with patients reflects a departure from traditional use of the Delphi process, which typically seeks to restrict input to the members of the panel only. However, deliberately integrating patient perspectives into the process allowed for a more diverse set of perspectives than if patient data not been used. For example, it ensured that some topics that did not emerge from the experts were considered during analysis and transmitted to the Delphi panelists for their reactions. Indeed, we found patient perspectives critical to the success of our overarching objective to develop a patient-centered measure. Our design results in an innovative integration of Internet-based data collection procedures with in-person data collection that provides a convergence of perspectives that otherwise would be difficult to achieve.

The process allowed for a rich broadening and expanding of content in response to open-ended questions in round 1 and then a subsequent reduction and refining of content in later rounds. The final set of 13 items reflects the input of all 66 Delphi experts from around the United States and patients in three cities. Illustrative examples of the final items include the following two items: “How much of a role do you have in making decisions about your HIV care?” and “How comfortable do you feel asking questions during your HIV care appointments?” We intend to make the full-item list available once we have completed the initial validation of the index.

Although we did careful searching to identify members of the panel for the Delphi process, it is possible that some expertise areas, geographic regions, and disciplines were not as well represented as others. Although there are no standard metrics for enrollment in Delphi studies, the response rates to our invitations were varied across the three groups of experts. Similarly, we only conducted patient focus groups in three cities, which may limit the breadth of content than had we conducted focus groups in a larger number of geographic areas. Because we only included Delphi panelists and patients in the United States, findings may have limited generalizability to other countries and regions, where the array of factors associated with engagement in HIV care are likely different. Finally, because we chose to focus on universal aspects of engagement in care that would be relevant to all patients, we elected to exclude potential items relevant only for some subgroups, such as childcare and substance use treatment. Although this may improve the applicability across all patients, it may sacrifice some precision for specific groups for whom these targeted topics may be salient.

We are currently administering the final Index of Engagement to patients in care at seven HIV clinics across the United States. We anticipate collecting survey data from approximately 3000 patients, for whom we will be able to validate the index. This validation will include how well scores relate to factors we hypothesize would be correlated with engagement (eg, depression, HIV stigma, substance use) and outcomes/consequences of engagement (eg, self-reported medication adherence, retention in care, virologic suppression). As part of the process, we will distribute findings directly to the Delphi panelists; these will be in the form of reports, published papers, and slides from presentations. Depending on the outcomes of those validation analyses, we will explore developing interventions that target the predictive factors from the Index of Engagement to improve outcomes for people living with HIV.

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Conflicts of Interest

None declared.

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Abbreviations

HIV: human immunodeficiency virus

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Protocol

Implementing a Mental Health Care Program and Home-Based Training for Mothers of Children With Autism Spectrum Disorder in an Urban Population in Bangladesh: Protocol for a Feasibility Assessment Study

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Abstract

Background: Mothers of children with autism spectrum disorder (ASD) have reported a higher level of depression than mothers of children with other neurodevelopmental disorders in both developed and developing countries. Mothers are the lifetime caregivers of children with ASD, and a high burden of depression can negatively impact their ability to provide care. However, access to mental health services in primary care is limited, given the scarcity of qualified providers in Bangladesh.

Objective: We aim to pilot the feasibility of integrating mental health services for the mothers of children with ASD attending schools offering ASD care and improve skills of mothers for child care through a home-based training program.

Methods: The study will be conducted in two selected schools in Dhaka in Bangladesh that have been offering services for ASD for more than 10 years. A female psychologist will be deployed at the schools to offer nonpharmacological services for all mothers having a depressive episode. Referral for pharmacological treatment will be made at the discretion of supervising psychiatrists. An ASD special educator will provide training to the mothers for enhancing their child care skills at home on a monthly basis. The proposed intervention package will be implemented over a period of 4-6 months, and the feasibility of the intervention will be assessed through a pre- and postintervention evaluation by obtaining the perspectives of various stakeholders involved in the implementation of mental health services and maternal training. The primary outcome will include assessment of acceptability, adaptability, demand, practicality, implementation, and integration of the package intervention in the school

settings. The secondary outcomes will include assessment of: 1) the prevalence of maternal depression; 2) children's behavioral, social, and communication skills; and 3) the intervention participation costs incurred by institutions and families.

Results: Between February and March 2017, 188 mothers of children with ASD were screened for depression following a written informed consent. Based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), the Structured Clinical Interview for the DSM-IV (SCID-1) was administered to 66 mothers. In-depth interviews were conducted with 10 mothers and 8 various stakeholders. Between January-June 2017, the team finalized a draft psychosocial counseling module and a maternal training module. Between April-May 2017, mental health services were provided by psychologists to 41 mothers who attended the counseling centers at each school. Three special educators have been trained in June 2017 to initiate training of the participating mothers.

Conclusions: This is the first study of a mental health intervention for mothers of children with ASD to reduce their burden of depression and improve the outcomes of their children. The findings will inform the provision of services for children with ASD and their mothers in Bangladesh and similar settings.

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KEYWORDS

depression; psychosocial; counseling; autism spectrum disorder; mothers; training

Introduction

Background

The global burden of depression accounts for 2.5% of the Disability Adjusted Life Years (DALYs). In the South Asia region, the proportion of burden due to depression is 5-times higher at 13.3% of DALYs per 100,000 populations [1]. The prevalence of maternal depression in the South Asian countries, ranging between 23% and 32% [2-4], is also higher than the estimate in other low- and middle-income countries (15.6 %) [5]. There is a dearth of information on the specific burden of depression in individual South Asian countries, including Bangladesh [6].

The prevalence of autism spectrum disorder (ASD), a neurodevelopmental disorder, has increased exponentially worldwide, including Bangladesh [7-9]. The global burden of ASD accounts for 53 DALYs per 100,000 population [7]. A review of ASD prevalence in Asian countries suggests a range between 1.9 and 14.8 per 10,000 [10]. Mothers of children with ASD have reported higher level of depression than mothers of children with other neurodevelopmental disorders in both developed and developing countries [11], for example, 48% versus 38% in Pakistan and 8% versus 4% in Sweden. Research has documented that parenting a child with ASD can have significant negative impact on the parents' quality of life [12,13]. In Bangladesh, according to a national survey conducted in 2013, the prevalence of ASD was 15.5 per 10,000 children, and higher prevalence was reported in urban areas (300 per 10,000 children) than the rural areas (6.8 per 10,000 children), although the report did not provide an explanation of this regional variation [14]. To our knowledge, there has been little scholarly research published on the burden of maternal depression among children with ASD in Bangladesh.

In 2015, Naheed and colleagues at the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) estimated that 45% of the mothers of ASD children and adolescents aged 3-17 years, who were enrolled in a special school for ASD, had suffered an episode of major depressive disorder (MDD), half of whom reported a current major depressive episode (MDE) [15,16]. Remarkably, most mothers (70%) had a college degree or a higher level of education [14,15].

The high impact of depression among mothers of children and adolescents with ASD therefore underscored the dire need for provision of better quality of mental health care to support them in caring for their children with ASD. Mothers are the lifetime caregivers of children with ASD, and a high burden of depression is likely to negatively impact their ability to care for their children at home [17,18]. Regrettably, like many other countries in South Asia, there is a scarcity of human resources in Bangladesh to provide mental health services. Furthermore, within the mental health departments at the teaching hospitals and specialty hospitals such as the National Mental Health Institute, Bangladesh, many mothers of children with ASD do not prefer receiving care at a mental health facility due to their fear of stigmatization coupled with lack of anticipated support for them in the hospital environment (*personal communication with Aliya Naheed, June 2015*). Indeed, the ASD care programs in Bangladesh are largely limited to institutions based mostly in urban areas [15,19]. These services often are not geared to address the needs of the mothers in caring for their children at home and do not provide any long-term rehabilitation guidance for families.

An important shift for development of future ASD services has been recommended at a Bangladesh-sponsored Global Panel on ASD during the World Autism Day on April 2, 2016, held at the United Nations. There is an impetus in the country to address ASD as a major public health problem [20]. There is a strong political commitment of the Prime Minister of Bangladesh for creating a long-term rehabilitation opportunity for children with ASD and other neurodevelopmental disabilities (as interlinked by the World Health Assembly) under the stewardship of the government [21]. The Bangladesh Government has been taking steps in recent years to develop programs to meet the needs of ASD in the community, including capacity development of parents in ASD care [22]. Nonetheless, to date, the proposed programs have been heavily institution-focused services that primarily target ASD children. Training programs targeting parents have been limited in few schools in select areas. They have involved customized sessions

on awareness building for mothers to better inform about the children's needs, behaviors, and activities for daily living. They have not targeted comprehensive programmatic and training needs of the mothers to improve their ability to care for their children with ASD at home (*personal communication with Aliya Naheed, June 2015*). Furthermore, these parent-oriented programs have not been integrated with mental health services [20,23,24].

The parent-focused services for ASD require a high number of well-qualified educational psychologists with special training in ASD and neurodevelopment disorders (special educators), which is scarce in Bangladesh. Such parent-focused programs cannot be delivered by the community health workers who traditionally support basic maternal and child health services [25]. The deployment of such a trained workforce of special educators requires substantial resources, and the approach is likely to be time-consuming and expensive. An alternative proposal is to bring the mothers of children with ASD under a structured formal training program within specialized schools to which their access can be facilitated. These umbrella programs can enhance maternal skills for child care at home through organized training deploying a more limited cohort of special educators at schools. Furthermore, these educators can engage mothers to develop enhanced home-based services, thus leading to improved child performance and greater satisfaction by mothers at home [24]. Since maternal depression may be attributable to multitude of factors other than ASD in their children, introducing mental health services in the schools where mothers have access to institutional supports for their special needs children, is also likely to create a conducive environment for the mothers to avail mental health services. Creation of a mental health support system combined with the capacity building of mothers for supporting the care needs of their children has not been previously attempted. Furthermore, integrating mental health services in school-based program targeting ASD is an innovative approach and can provide wider outreach for mothers of children with ASD in the community in a low-resource mental health setting.

Cost is one of the key barriers to adopting new interventions in the existing programs in low- and middle-income countries, and cost parameters are often estimated through recall [26-28]. The proposed research will capture the direct cost of the intervention based on actual activities involving the intervention in real time and estimate all possible realistic costs that would be incurred by both the schools (provider cost) and the participating families (out of pocket cost) due to integrating the proposed combined intervention. Due to infeasibility of estimating indirect cost to families related to productivity loss, only the real-time direct cost estimates will be used to help researchers, policy makers, and institutions to design a large-scale trial or scale-up this intervention in the future. A further goal of the research is to assess the barriers to integrating the pilot intervention package with other types of facility-based services as well as prospect for scaling up of the intervention in other institutional settings in urban Bangladesh.

Objectives

The primary objective of the study is to assess the feasibility of the proposed intervention at special schools for children with ASD that would provide mental health services and training to mothers suffering from a concurrent MDE. The secondary aim of the project is to assess the change in the prevalence of MDE among mothers and any improvement in the degree of individual performance of the children with ASD. Additional project aims include assessment of incremental direct institutional costs incurred at schools and out of pocket direct costs incurred by the families following the introduction of mental health services in combination with the maternal training program in the schools.

Methods

Design

This is a mixed-method feasibility study with a pre-post design.

Study Setting

There are about 40 special schools providing variety of services targeting children with ASD and other neurodevelopmental disorders in Bangladesh. The majority of the schools are located in Dhaka centrally with 9 suburban schools. The study will be conducted in two selected schools in Dhaka city that have been providing high quality services for ASD over 10 years. On average, about 100 to150 children with ASD are registered in each school, and services offered at the schools for children with ASD are more or less similar in nature.

Eligibility Criteria

The mothers of children with ASD, aged 18 years and older, with a child aged 3 to 17 years, registered in one of the two study schools, and given written voluntary consent will be recruited in the study. The mothers who are being treated for a severe behavioral or medical comorbid condition or who themselves are mentally or cognitively compromised or too ill to commute will be excluded from the study.

Intervention Phase

The intervention package is planned with the following two components: (1) mental health care services at schools targeting the mothers diagnosed as having depression that have consented to participate in the study and (2) organized training sessions for supporting enhanced child care at home.

Implementing Mental Health Care Services at School

We will set up a counseling center at each school by deploying one trained female psychologist who would provide counseling to the intervention mothers. Currently, there is no structured counseling module available at the National Institute of Mental Health, Bangladesh (NIMH,B) or other institutions in Bangladesh. We will compile the documents available at NIMH,B and develop a counseling module with the help of an Expert Working Group (EWG) represented by psychiatrists, psychologists, and other relevant experts in Bangladesh (Table 1).

Table 1. Content of the psychosocial management module.

Module	Content
Psychoeducation	Psychoeducation refers to the education offered to individuals with a mental health condition and their families to help empower them and deal with their condition in an optimal way. Psychoeducation will be given by trained psychologists under the guidance of a senior psychologist to increase the self-esteem of the mothers, which will include the brief concept on depression, the probable etiology, how to mitigate the symptoms, compliance to the therapeutic process, and the consequences
Assessment of the strength and weakness of the mothers	The psychologists will assess the strengths and weaknesses of the mothers and discover their personal obstacles, issues that might hinder their progress in terms of social context, family support, financial state, educational qualification, and empowerment
Sharing the management plan with the mothers	The psychologists will share the whole management processes with the mothers, and any opinion from the mother could be a part of the management. The goal is to empower mothers and include them as a part of the management team counseling other mothers
Reconstruction of the cognition	Cognitive restructuring is a psychotherapeutic process of learning to identify and dispute irrational or maladaptive thoughts known as cognitive distortions. It is a core part of cognitive behavioral therapy (CBT). CBT is one of the most effective psychological treatments for common problems like depression, anxiety disorders, and so on. The process involved in CBT identifies the cognitive distortion, tracks the accuracy of thinking process, tests the thoughts, evaluates the evidence against the distorted thoughts, and assesses mindfulness and self-compassions, which are the core features of cognitive restructuring
Behavior therapy-graded activity	Graded activity is a principle of therapeutic intervention in which tasks are classified and gradually presented according to the client's level of function and the challenge or degree of skill (physical, social, or cognitive) required by the task. The graded activity starts from personal care, daily household activities, child care, engagement in small and easy tasks, and complex and productive tasks. In this study, after assessing the strengths and weaknesses of the mothers, we will monitor and try to increase their graded activity.
Developing a mother's community and engaging mothers in community-related activities	The psychologist will arrange a workshop in each participating school at 2-month intervals for enabling mothers to meet other mothers in the intervention program and create a common platform where they can share their experiences and success stories and encourage a positive reinforcement from depressed mothers. The mothers will be encouraged to participate in the social awareness or other activities arranged by the schools so that the mothers refrain from social isolation and rebuild their self-esteem

A psychologist will decide on the number of sessions and intervals between consecutive sessions based on the need of a mother. All eligible participants would provide voluntary consent (Multimedia Appendix 1). Before every session the psychologist will assess the mental health state by applying Beck Depression Inventory (BDI), which has been validated in Bangladesh [29]. Every month, a psychiatrist from NIMH,B will visit each school and review the records maintained by the psychologist and provide necessary advice regarding the need for any additional care of the mothers identified with MDE. The psychiatrist will reassess the additional need of a mother with MDE following face-to-face consultation if suggested by the record review or clinically identified by the psychologist. The medical care will therefore focus on management of depression with varying degrees of severity. The care will follow the management guidelines including referral to the National Institute of Mental Health for advanced mental health care if necessary (Table 2). All mothers referred to the NIMH,B for providing advanced mental health care will be eligible to receive free antidepressant, anxiolytic, and antipsychotic medications as deemed clinically appropriate.

Organized Training for Mothers With MDE in the Schools for Supporting Child Care at Home

One special educator will be deployed at each school who will organize structured training sessions for the intervention group of mothers following a training module developed by icddr,b in 2015 titled "Bangladesh Parent Empowerment Program (BPEP)" (*personal communication with Aliya Naheed, June 2015*). The training module will be customized according to the local context under the guidance of a group of experts on ASD. The BPEP module was piloted with 56 parents and validated for its *application* in the local setting (*personal communication with Aliya Naheed, June 2015*). Before training, the special educator will interview the mothers for validating children's ASD diagnosis and rate the ASD. The educator will also interview the mothers to assess the individual performance of their children by using a standard ASD Diagnostic Check-List (ADCL) [30]. The ADCL will provide an assessment on individual performance of the ASD children of the mothers with MDE enrolled in the intervention activities (Multimedia Appendix 2, study activity flowchart). ADCL is a standard tool applied by ASD experts in Bangladesh to track improvement in performance in children with ASD. This tool comprises 60 items focusing on 6 major domains: (1) General Observation (13 items); (2) Cognition (10 items); (3) Emotion (8 items); (4) Social/Self-Help (8 items); (5) Communication (12 items); and (6) Sensory deficiency (9 items). ADCL will be applied to assess the degree of ASD in children at baseline and also in end-line to assess any potential change in the performance of the children following the BPEP training.

Table 2. Participant timeline.

Activities	Prestudy	Q[a]1	Q2	Q3	Q4	Q5
Institutional Review Board	X[b]					
Customization of the training module and development of the training materials		X				
Development of the psychosocial counseling module		X				
Setting up the counseling centers		X				
Staff training		X				
Recruitment of study participants		X				
Preintervention survey at two schools		X				
Preintervention feasibility interviews		X				
Provide mental health services at schools			X	X		
Home-based maternal training by special educators at the schools			X	X		
Monthly home-based refreshers training			X	X		
Postintervention survey at two schools					X	
Postintervention feasibility interviews						
Data entry and management		X	X	X	X	
Data analysis and report writing						X
Dissemination						X
Final project report submission						X

[a]Q: one-quarter of a year (3-month period).

[b]X: accomplishment of an activity.

The special educator will conduct multiple group sessions (with 5-8 mothers in each group) for covering the nine modules over a 4-week timetable following the module that will be developed by the local experts (Table 3). The special educators will follow-up with mothers at home every month for conducting refresher training and document the need for additional training supports for a child. The special educator will consult the icddr,b coinvestigators about the additional training need of a child and incorporate necessary training as advised, if required.

Outcome

The primary outcome of the study is to determine the feasibility of integrating mental health care services at special schools for the mothers suffering from current MDE combined with the maternal training program for supporting child care at home [31]. The facilitators and barriers of the multi-component intervention at different levels will be assessed by conducting focus group discussions with the recipients and those who were involved in the delivery of the services and evaluated through pre-post qualitative interviews to assess the outcome parameters following the standard feasibility guideline [32,33]. The indicators will include acceptability, demand, implementation, practicality, integration, and adaptation (Table 4). The following aspects will also be assessed through in-depth interview (IDI) and key informant interview (KII) at various stakeholders' levels:

- Knowledge, attitude, and practice about depression and management of depression for mothers of children with ASD
- Barriers for mothers for accessing institutional care for mental health and training at home (logistic, cost, family supports, time, etc)
- Community supports required for complying with the intervention
- The barriers of setting up intervention at an institution (administrative, logistics, cost, policy, etc)
- Additional supports that would be required for implementing mental health services at schools for ASD and for continuing the training program at home

The secondary outcomes of the study will assess the potential of the combined interventions' impact based on the following measurable parameters as listed below through pre- and postintervention surveys:

1. Change in the prevalence of MDE among the mothers of children with ASD enrolled in the two selected schools: assessment of MDE in mothers of all children who have been recruited in the study before and after the intervention to evaluate change on the burden of MDE due to the combined intervention. This assessment will be done irrespective of the presence of depression status or other mental health conditions at the baseline to assess any spillover effect of the intervention on mothers in general.
2. Change in the degree of individual behavioral, social, and communication skills of ASD children whose mothers have received the intervention: the goal is to assess if the mental health service that mothers would have access to might influence any positive change in child's behavior, communications, and social skills irrespective of providing

additional training to mothers for child care at home. Individual performance of the children will be assessed before and after intervention to assess change in individual performance of their children following the combined intervention.

3. Incremental costs incurred to the selected schools following introduction of mental health services in combination with the maternal training program: the project will estimate the overall direct costs that would be incurred by an individual institution due to the introduction of the combined services at the school. As such, cost of mental health services will be tracked throughout the intervention period of 6 months which will include counseling sessions, psychiatrists' visits, cost of services obtained at the mental health care facility, or any other costs that might be potentially borne by the institutions for providing mental health care at their schools. The cost of maternal training program will include costs of conducting training of mothers at school over a 4-month period, cost for training sessions, salary of the special educators, training materials for mothers, and any other cost that might be potentially borne by the institutions for supporting this training.
4. Incremental costs incurred to the families (out of pocket cost) for supporting mental health services for participating mothers and child care at home following maternal training: the goal is to assess the additional direct costs incurred by a family to support mental health services for a depressed mother and costs incurred in order to enhance the child's overall performance following adoption of the proposed training program for mothers. As such, we will track out of pocket costs of mental health services throughout the intervention period of 6 months and cost of conducting training of mothers at the school over a period of 4 months. Out of pocket costs borne by the study participants will include travel to health care facility or specialized institution for ASD care, medicines for treating both mother and child, teaching aids for supporting maternal training, fee for visiting an autism expert or other providers, recreational activity of the child with ASD, and any other costs relevant to the intervention that may be incurred by the mother during the intervention period.

Any potential positive change in MDE or child performance would indicate acceptability of the programs by both the stakeholders for its adaption in to the existing school services. Such changes would also indicate demand for the services, practicality for its implementation in the current setting, and potential for integrating in to a broader program for rendering a sustainable service to the target community. In case the proposed comprehensive and multilevel mental health service for addressing depression among mothers of children with ASD is feasible but not affordable by either the schools or families due to a high incremental costs, it would indicate that the proposed intervention would not be feasible for its integration in the existing services of ASD. The threshold for affordability will be determined in consultation with the EWG.

Sample Size

This is a feasibility study; therefore, statistical power calculation was not carried out. The two selected schools would have at least 100-150 children with ASD registered in a given year. On the basis of the previous study findings, we anticipate that about 26% mothers would be diagnosed as having MDE, and we would find a total of 52 to 78 mother-child pairs from two schools for study recruitment [15].

For the qualitative surveys, we will conduct 15-20 key informant interviews including two respondents from each of the following categories: psychologists, psychiatrists, managers at schools, mothers without depression, family members of the depressed mothers, principals, special educators and relevant policy makers, and pediatric neurologists to assess the feasibility of the intervention.

Recruitment

All eligible mothers will be contacted over phone with the permission of the school authorities and sent invitation to participate in the study. The invitation letters will briefly describe depression and its complications in general terms and the importance of early management. The letter will also provide information about the nature of the intervention, the evaluation process, and the purpose of the study in improving ASD care in schools and at home. The parents who would respond positively will be invited to attend an orientation session for discussing the project in detail and will get an opportunity to ask questions for any clarification. A group of trained research staff will individually contact each eligible mother either at home or a convenient location and recruit in the study following a written informed voluntary consent (Multimedia Appendix 1).

The trained research staff will apply a tool (Patient Health Questionnaire, PHQ-9) to screen depression in all recruited mothers based on nine criteria on DSM-IV (*Diagnostic and Statistical Manual of Mental Disorder*, 4th edition) using a Likert scale within a possible range of 0-27 (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day) [34,35]. On the basis of PHQ-9, the levels of depression on screening will be defined as None=0, Minimal=1-4, Mild=5-9, Moderate=10-14, Moderately Severe=15-19, and Severe=20-27. Those who will be defined as having a level of depression more than minimal (score >4) will be further assessed by a trained psychologist using the standard diagnostic tool (SCID-I Research Version) for confirmatory diagnosis of depression [36]. Mothers who would have MDE will be recruited in the intervention following additional consent (Multimedia Appendix 1). Additionally, we will select various stakeholders for conducting key informant interviews following a written informed voluntary consent (Multimedia Appendix 1).

Table 3. Summary of the content of the BPEP (Bangladesh Parent Empowerment Program) training.

Number and name of the module	Components included	Topics covered	Process of delivery
Session 1			
1. Understanding autism	• PowerPoint slides • Video • Feedback and experience sharing	• What is autism? • Characteristics of autism • Prevalence, diagnosis, treatment, cause, and risks of autism • Developmental milestone of ASD[a] and normal child • Myth and impact of autism • Guidance and homework for mothers	1. Group session (5-6 mothers) (60 min) 2. Practical demonstration 3. Role play
2. Communication	• PowerPoint slides • Uses of flash cards • Individual activities • Feedback and experience sharing	• What is communication? • Communication ability of ASD and normal children • Techniques to develop communication ability of ASD children • Techniques to increase eye contact and picture exchange communication system • Guidance and homework for mothers	1. Group session (5-6 mothers) (60 min) 2. Practical demonstration 3. Role play
Session 2			
3. Teaching your child language	• PowerPoint slides • Uses of flash cards with real objects • Feedback and experience sharing	• Language developmental stage of ASD children • Techniques to develop language stage • Guidance and homework for mothers	1. Group session (5-6 mothers) (60 min) 2. Practical demonstration 3. Role play
4. Social communication	• PowerPoint slides • Feedback • Checklist of social communication • Uses of flash card • Feedback and experience sharing	• What is social communication? • Social communication problems of ASD children • Techniques to develop social communication ability • Imitation and playing techniques for ASD children • Guidance and homework for mothers	1. Group session (5-6 mothers) (60 min) 2. Practical demonstration 3. Role play
Session 3			
5. Regulating your child's behavior	• PowerPoint slides • Group discussion • Feedback and experience sharing	• Behavior of ASD children • Techniques to manage ASD child's behavior • Guidance and homework for mothers	1. Group session (5-6 mothers) (60 min) 2. Practical demonstration 3. Role play
6. Setting up your home for success routine and structure	• PowerPoint slides • Uses of flash card on home routine • Feedback and experience sharing	• Preparing work environment for ASD children • Techniques to select toys and play with ASD children • Techniques to teach to follow instruction • Increasing child's participation toward home activities • Guidance and homework for mothers	1. Group session (5-6 mothers) (60 min) 2. Practical demonstration 3. Role play
Session 4			
7. Community living	• PowerPoint slides • Feedback and experience sharing	• Society living techniques for ASD children • Guidance and homework for mothers	1. Group session (5-6 mothers) (60 min) 2. Practical demonstration 3. Role play
Session 5			
8. Sensory regulation	• PowerPoint slides • Group discussion • Feedback and experience sharing	• Sensory difficulties of ASD children • Techniques to reduce sensory difficulties • Guidance and homework for mothers	1. Group session (5-6 mothers) (60 min) 2. Practical demonstration 3. Role play

Number and name of the module	Components included	Topics covered	Process of delivery
9. Food and nutrition	• PowerPoint slides • Group discussion • Feedback and experience sharing	• Food and diet chart for ASD children	1. Group session (5-6 mothers) (60 min) 2. Practical demonstration 3. Role play

[a]ASD: autism spectrum disorder.

Table 4. Feasibility assessment (qualitative).

Indicator	Target	Method	Outcome
Acceptability	• Mother • School managers/administrators • Psychologist • Special educators • Psychiatrist	• IDI[a] • KII[b]	• Satisfaction • Intent to continue to avail services • Perceived appropriateness of the intervention • Fit within the existing goal and culture of the special schools • Perceived positive or negative effects on the mothers, providers, and institutions
Demand	• Mother • School manager/administrators • Psychologist • Special educators • Psychiatrist	• IDI • KII	• Perceived need of the interventions • Intention to use the services
Implementation	• Mother • School manager/administrators • Special educators • Psychologist • Psychiatrist	• IDI • KII	• Process of execution/evaluation • Actual usage by the recipients • Barriers and opportunities during implementation • Amount and type of resources needed to implement the services from every stakeholders' perspective (mothers, providers and school managers, etc) • Success of the implementation
Practicality	• Mother • School manager/administrators • Special educators • Psychologist • Psychiatrist	• IDI • KII	• Efficiency (speed and quality) of the programs • Positive/negative effects on participants and also on the institutions • Ability to carry out every activity of the intervention by every stakeholder • Cost analysis of the overall program
Adaptation	• Psychologist • School manager/administrators	KII	• Degree to which similar outcomes are obtained in a new context • Modifications that are required to accommodate programs in the new context
Integration	• School manager • Policy makers	KII	• Perceived fit with the current infrastructure • Perceived barriers and opportunities to integrate the program • Perceived sustainability • Scope and challenges to scale up • Cost to the organization and policy bodies • Fit with organization goal and culture • Effects (positive/negative) on organization

[a]IDI: in-depth interview.

[b]KII: key informant interview.

Data Collection

Preintervention Survey (Baseline)

A group of trained research staff will conduct preintervention surveys with all eligible mothers at two schools to obtain information on sociodemographic characteristics, child information, school information, and other relevant data. Quality of life will be assessed by using Euro-Qol five dimensions questionnaire (EQ-5D) [7].

All the above tools have already been validated in Bangladesh by previous icddr,b researches (Naheed et al, 2016, unpublished data). A mother identified with any MDE with suicidal ideation, intent or plan, or a prior history of suicide attempt will urgently be referred for hospital-based mental health services in the community and will not be included in the study (standard of care in Bangladesh).

Additionally, we will identify various stakeholders to conduct key informant interviews following a qualitative guideline We

will select stakeholders involved in the following categories: psychologists, psychiatrists, the family members of the depressed mothers, school administrators, management at the referral hospitals, special educators, and pediatric neurologists to assess the feasibility of the intervention, as well as a randomly selected group of mothers without any depression (PHQ-9 score, 0-4). The trained qualitative researchers will conduct the interviews following a written consent. All the interviews will be digitally audio-recorded and transcribed. The interviews will be reviewed by an independent qualitative researcher at various stage of data collection to check validity and reliability of the data for further verification of the missing data.

Postintervention Survey (End Line)

After completion of the intervention, an end-line qualitative survey will be carried out in a subset of the study participants and various stakeholders to assess the indicators of the feasibility of the study. This will include 2-3 interviews with each of the following categories: psychologists, psychiatrists, managers at schools, mothers without depression, family members of the depressed mothers, principals, special educators and relevant policy makers, and pediatric neurologists. The end-line qualitative survey will assess views of various stakeholders about the directions for institutionalizing the proposed intervention based on their experiences in the intervention, particularly the barriers they have encountered during the intervention period.

Data Management and Quality Assurance

This research protocol includes Data Safety Monitoring Plan (DSMP). The purpose of the DSMP is to provide a framework for appropriate oversight and monitoring of the data collection and management to ensure the privacy of the participants and the validity and integrity of the data. The data collection tools will be pretested and checked for validity and reliability before going for data collection. All the study staff will be trained to promote standardized and objective collection and recording of participant's information. A code number will be used against each name, and personal information would not be published or shared with anyone other than the research team. Data would be entered into a computerized database and would also be imported into a password-protected database that is backed through a secure offsite connection.

The principal investigator (PI) will be responsible for carrying out periodic data checking and would also ensure the systematic patterns, errors, scheduling problems, or overall data integrity. The PI will visit the field sites at least once monthly and monitor the data collection. For the qualitative part, transcribed data will be cross-checked with the field notes. Also, to validate translation (from Bangla to English), the research investigation staff will randomly check the transcribed interviews. No one other than the investigators of the research project will have access to information and data collected from the participants.

Data coding, quality control, and data entry will be done following established procedures at icddr,b. Precoded questionnaire will be used. All data forms will be checked for errors, and necessary corrections will be made before data entry. Quantitative data will be entered using SPSS data entry program (version 20) with built-in range and consistency checks. Frequency distributions will be run to identify outliers. Qualitative data will be entered in MS Word and MS Excel for creating a matrix.

Statistical Analysis

Qualitative Analysis

Qualitative data will be analyzed using a framework approach. After familiarization with the data by listening to tapes, transcribing interviews, reading transcripts, and studying notes to highlight common ideas and recurrent themes, investigators will identify key issues, concepts, and themes by drawing on priority issues and questions raised by the respondent based on the aims of the study. Finally, data will be systematically indexed or coded, synthesized, and interpreted for providing explanations for the findings based on study objectives analyzed under relevant emerging themes and subthemes. Results on the same issues from different types of respondents and areas will be compared to strengthen the validity of the findings.

Quantitative Analysis

Descriptive analyses and frequencies of all variables for data visualization will be performed followed by an analytical framework to run analyses. Chi-square tests will be used for categorical variable, and nonparametric *t* test will be used for continuous variables to assess comparisons between different groups. A *P* value <.05 will be considered statistically significant. All statistical analysis will be done using the SPSS software (version 20).

Ethics Review

This protocol has been approved by the icddr,b Institutional Review Board (IRB). The study protocol was also reviewed by the Director of Compliance of the IRB at the Boston Children's Hospital in January 2017 with respect to involvement of Boston-based mentors who will not have direct contact with research subjects, will not be involved in subject recruitment or obtaining informed consent, and will not be viewing any data that will have subject identifiers. The study was considered exempt from human subject research review.

All study participants will be recruited following a written informed consent. A trained research staff will explain the nature and purpose of the study, procedures to be followed, potential risks, benefits to be derived, and right to refuse to participate or to withdraw from the study before obtaining consent. All interviews and the sessions would be conducted in a designated private room in one-to-one sessions to ensure participant's privacy, and no one will be asked any sensitive questions.

Psychosocial counseling will be provided to the mothers free of cost by the designated psychologists deployed at each school. Although the mental health services will target participating mothers, the psychosocial counseling services will be made available to any mother whose child is registered in the schools and who willingly attends the counseling center. However, outcome assessment will be conducted only among the mothers who would be recruited in the intervention phase. All information of the participants will be kept confidential, and no information obtained from the participants will be shared with

the school authorities. The interviews would be conducted in a designated private room.

Several mechanisms would be deployed to ensure privacy, anonymity, and confidentiality of data shared by the participants. A unique identification number will be used for tracking each parent and link it to basic addresses for tracking them until data collection and entry are completed. Participant's names, addresses and other identifiers will only be accessed by the national research staff, coinvestigators, and psychologists; no one other than the national investigators of the research project and members of the Ethical Review Committee of icddr,b will have access to information and data collected from the participants.

Dissemination

A dissemination seminar will be held locally inviting representatives of the ministry of health, ministry of social welfare, officials, nongovernmental organization (NGO) representatives, relevant professional bodies, researchers, policy makers, program managers, and media for sharing the preliminary findings. To ensure maximum research uptake and further research opportunities, the findings will be also shared with international agencies and donor organizations. Final results will be published in peer-reviewed journals and will be presented in international scientific conferences.

Results

The trial registration number was obtained in March 2017 (NCT-03025646). Staff training was conducted in January 2017, and the team completed baseline recruitment of 175 mothers by March 2017. We have screened all participants for depression and applied SCID-1 among 65 mothers who had a PHQ-9 score more than 4. We have simultaneously conducted in-depth interviews among 10 mothers and key informant interviews among 8 various stakeholders, including psychiatrists (2), psychologists (2), special educators (2), principals of schools (1), and school managers (1). The remaining surveys will be completed by mid-July 2017. Data entry and data management are ongoing.

Between January and June 2017, the team finalized two intervention modules under the guidance of two different EWGs. A draft Psychosocial Counseling Module (PCM) has been developed by two professional psychologists under the guidance of an EWG (EWG1). Between January and April 2017, the team customized the BPEP training module, and the training module was validated under the guidance of an EWG (EWG2).

In May 2017, counseling centers were set up and psychologists were deployed at the school following training. The school authority helped mothers to fix an appointment if they were interested to meet the psychologists, and the psychologists offered services at the schools between 8:30 AM and 5:00 PM on week days. A total of 41 mothers have attended the counseling centers till the first week of June and participated in two mental health awareness workshops held at each of the schools. Three special educators have been trained in June 2017, and the group initiated training of the participating mothers in July 2017.

Discussion

Summary

To our knowledge, this will be the first combined mental health and ASD support intervention for mothers of children with ASD to reduce their burden of depression. The project integrates mental health services and school-based programs targeting ASD. If the proposed intervention strategy is found feasible and effective, the project is likely to significantly improve care for ASD at a low cost in a low-resource country context where the burden of maternal depression is high.

Cost is one of the key barriers to adopting new interventions in the existing programs in low- and middle-income countries. The proposed research will capture the direct cost of the interventions based on actual activities involving real-time tracking of estimate of all possible realistic costs that would be incurred to both the schools (provider cost) and the participating families (out of pocket costs). Due to infeasibility of estimating indirect costs due to productivity losses by parents, only the real-time direct cost estimates are expected to help researchers, institutions, and policy makers to design a large-scale trial for scaling up the intervention in Bangladesh.

Limitations

The study will only be conducted in urban settings; therefore, we cannot generalize the findings to rural areas of Bangladesh. However, the burden of ASD is likely to be higher in urban areas, and thus, the study will meaningfully contribute to identifying challenges of supporting mental health among a larger group of mothers who have children with ASD. The proposed study only intends to assess the feasibility of the proposed survey; hence, it would not have enough power to estimate the effect of the intervention on maternal depression and performance of children with ASD.

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Expert Working Group for developing psychosocial counseling module: Mehtab Khanam, PhD, University of Dhaka; Dr Shaheen Islam, University of Dhaka; Dr Helal Uddin Ahmed, National Institute of Mental Health; Dr MM Jalal Uddin, National Institute of Neurosciences and Hospital; Mr Kamal Uddin Ahamed Chowdhury, University of Dhaka; Dr Akibul Huque, University of

Dhaka; Ruma Khondaker, Centre for Mental Health and Care, Bangladesh (CMHC); Chanda Mahjabeen, Haal Chhero Na Bondhu; Syeda Munira Islam, RBengal Media Conportaiton Ltd; Umme Kawser Lata, University of Dhaka; Mita Rani Roy Chowdhury, ACF International Bangladesh Mission; Mostak Ahamed Imran, University of Dhaka; Safina Binte Enayet, BRAC University; and Monzia Mushtaq, BRAC University.

Expert Working Group for customizing the BPEP module: Dr Helal Uddin Ahmed, National Institute of Mental Health; Dr MM Jalal Uddin, National Institute of Neuroscience and Hospital; Prof Dr Shaheen Akhter, IPNA, BSMMU; Dr Shamim Matin Chowdhury, Beautiful Mind; Dr Basana Muhuri, Chittagong Medical College and Hospital; Dr Rownak Hafiz, Autism Welfare Foundation; Ms Sabina Hossain, Society for the Welfare of Autistic Children; Dr Muzharul Mannan, Shuchona Foundation; Sajida Rahman Danny, Parents Forum for Differently Able; Marufa Hossain, School for Gifted Children (Tauri Foundation); Ms Mamtaz Sultana, Beautiful Mind; Manna Chowdhury, Autistic Children Development Foundation Chittagong; Nurjahan Dipa, Parents Forum; Ms Nazneen Akhtar Chaman, parent of a special child; Tanmi Akhter, IPNA, BSMMU; Tamanna Sharmin, Nutrition and Autism Research Center; and Roksana Haque, Center for the Rehabilitation of Paralyzed; Isteaque Ahmed, Salt Communication.

Authors' Contributions

AN is the PI of the study and has developed the concept; designed the methodology, intervention procedures, and implementation plan; and also developed the manuscript for protocol publication. KM is the Co-PI (mentor) provided guidance for the PI in methodology, intervention procedures, implementation plan in terms of mental health and home-based training components. He has also contributed in reviewing and provided feedback to draft the manuscript. KNK is the team leader and co investigator has designed the methodology, intervention procedures, and implementation plan, and also developed the manuscript for protocol publication. SC contributed towards protocol development including study design and methodology. Other co investigators have provided insights in development and finalization of the two intervention modules and planning the modalities of service provision, as well as revisions of the manuscript for protocol publication. AN and KNK drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Consent forms.

[PDF File (Adobe PDF File), 59KB - resprot_v6i12e251_app1.pdf]

Multimedia Appendix 2

Study activity flowchart.

[PDF File (Adobe PDF File), 36KB - resprot_v6i12e251_app2.pdf]

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Abbreviations

ADCL: ASD Diagnostic Check-List
ASD: autism spectrum disorder
AWF: Autism Welfare Foundation
BCC: behavioral change communication
BDI: Beck Depression Inventory
BPEP: Bangladesh Parent Empowerment Program
CBT: Cognitive Behavioral Therapy
DALY: disability-adjusted life year
DSM-IV: Diagnostic and Statistical Manual of Mental Disorder, 4th edition
DSMP: Data Safety Monitoring Plan
EQ-5D: Euro-Qol five dimensions questionnaire
EWG: Expert Working Group
icddr,b: International Centre for Diarrheal Disease Research, Bangladesh
IRB: Institutional Review Board
MDD: major depressive disorder
MDE: major depressive episode
NGO: nongovernmental organization
NIMH,B: National Institute of Mental Health, Bangladesh
PHQ-9: Patient Health Questionnaire
PI: principal investigator
SCID: Structured Clinical Interview for DSM-IV

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Proposal

Exploring Advance Care Planning in Taiwanese Indigenous Cancer Survivors: Proposal for a Pilot Case-Control Study

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Abstract

Background: Research on Taiwanese indigenous cancer survivors' end-of-life (EOL) planning is still in its infancy, despite recent government and societal efforts to promote quality EOL care. Previous national studies in Taiwan have characterized indigenous peoples as a socioeconomically disadvantaged minority group. Compared with their mainstream cohorts, these remote residents are vulnerable to multiple social welfare problems, receiving and accessing little in the way of health care in rural mountain areas. Although advance care planning (ACP) has been shown to help patients achieve better quality of dying, very little is known about indigenous intentions for such interventions. Relevant studies are scarce in Taiwan, and programs for cancer survivors have been based almost entirely on nonindigenous populations. Since there has been no research on Taiwanese indigenous people's aims for ACP, there is a need to understand the impact of survivorship on ACP readiness among those who are currently living with, through, and beyond cancer.

Objective: We aim to identify differences in ACP intent and readiness among indigenous peoples with and without cancer diagnoses. We will identify the impact of factors such as tribal cultural beliefs and quality of life along with cancer exposure on the outcome of ACP readiness differences. In particular, we will examine the effects of ACP knowledge from previous ACP participation, EOL care experiences, and personal registry status of Do-Not-Resuscitate (DNR) in the national database. A secondary objective is to describe indigenous people's intent to participate in public education related to EOL planning.

Methods: A descriptive case-control study (N=200) is proposed where controls are matched to cases' attributes of age, gender, and cancer diagnosis. This matching analysis allows assessment of cancer as an exposure while taking into account age and gender as confounding variables. We are currently in the process of training personnel and extracting clinical and administrative information from the health care system of collaborating facilities. This carefully designed study provides a unique opportunity because for the first time in Taiwan, cancer survivorship and ACP readiness for EOL planning will be examined among difficult-to-reach indigenous peoples.

Results: We plan to complete this study in approximately 3 years.

Conclusions: In this study, we expect to survey palliative care usage in the remote indigenous group, understand factors that influence ACP readiness, and later foster culturally appropriate ACP public participation and policies in order to facilitate collaboration between cancer health care providers in various Taiwanese subcultures.

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KEYWORDS

Taiwanese indigenous peoples; advance care planning; cancer survivors

Introduction

Evidence has shown that successful interventions promoting advance care planning (ACP) have helped patients achieve their end-of-life (EOL) care goals [1], increase satisfaction [2], reduce chances of over- or undertreatment at EOL [3], and minimize conflicts between family members and health care providers during EOL discussions [4].

Despite the national emphasis on minority health and palliative care in Taiwan [5], research on terminal indigenous patients' EOL treatment and care options is still premature [6]. Our understanding of their ACP knowledge and intentions remain unclear, as well as their cultural attitudinal preferences and behavioral engagement [6]. In the most recent Taiwanese Indigenous Health Report [7], there were approximately 530,000 indigenous peoples represented by 16 distinctive tribes, accounting for 2.3% of the overall population. With regards to the geographical distribution, nearly 70% of the indigenous peoples do not dwell in metropolitan cities. The majority of Taiwanese indigenous peoples reside in rural townships or remote mountain areas. A large portion of older women inhabits these isolated, difficult-to-reach locations.

Previous national studies have shown that indigenous peoples in mountainous communities are socioeconomically disadvantaged, receiving and accessing little in terms of health care [8]. Compared with mainstream Taiwanese society, the indigenous group is highly vulnerable to multiple social welfare problems associated with poverty, substance abuse, alcoholism, low literacy, and low life expectancy [9-11]. Over the past 30 years, indigenous peoples had nearly 70% higher mortality than the general Taiwanese population [12]. Among remote indigenous peoples, malignant tumors caused the highest death rate, and the total number of indigenous cancer survivors has increased annually to approximately 15-20%, regardless of age and gender [7]. Survivors are those who have cancer diagnoses and are receiving or completed their cancer treatment.

In the past two decades, culture has been found to be an important factor influencing EOL planning [13], and ethnic differences during EOL treatment decision making have been widely documented [14-18]. Studies relevant to ACP and Taiwanese cancer survivors have been based almost entirely on nonindigenous populations and mainstream culture, such as the white racial majority in the United States.

According to recent studies published during national ACP campaigns in Taiwan, less than 5% of the entire Taiwanese population has been involved in ACP [19-22]. It is also unclear to what extent these findings, based on mainstream culture, could be generalized beyond the majority of Taiwanese people that are in the cities. Historically, individuals with limited health care access and low literacy have reported greater discomfort and less EOL participation than their counterparts in mainstream society [23-25]. Indigenous people's traditional values may contradict basic values of patient autonomy and/or truth telling that underlie ACP, making their cultural needs distinct from the contemporary standard of EOL care [26-29].

In addition, searching for appropriate assessment of indigenous cancer patients' ACP readiness is extremely challenging given the scarce literature [6,30]. Studies relevant to ACP of Taiwanese cancer survivors have been based almost entirely on non-indigenous population in mainstream culture, such as "the white racial majority" in the United States. Current national cancer studies in Taiwan have sampled less than 1% of the mountain indigenous cohort [7]; results are based on the majority of nonindigenous (Han tribe) plain residents. Reported percentages of cancer cohorts have been too small to use for examination of ACP readiness issues for all indigenous peoples.

In addition, studies related to indigenous peoples' death and dying have been limited to epidemiological reports [9,31,32], funeral rituals, and/or local surveys [8,32]. Only one focus group attempted to address healthy indigenous teenagers' cultural view of death [33], and one qualitative study explored Zhou tribes' dilemmas of "a good death" [11]. However, neither included any ACP element. Only a few workshops have been held to introduce the principles of palliative care for this cultural group by the Hospice Foundation of Taiwan [34]. There has been little research to explore Taiwanese indigenous people's intent to find public EOL education. It is likely that as a minority group, their tribal beliefs conflict with the values that underlie ACP [14,15,18,35-40], which ultimately influences their participation in public education.

As a result, the impact of cancer and tribal values on decisions regarding life-sustaining treatment and care remains understudied among Taiwanese pan-indigenous peoples. This cultural group's intent and preference to participate in EOL and palliative care related interventions require extensive study, especially for those terminal cancer patients who will soon face difficult EOL decisions. Research specific to Taiwanese indigenous peoples is needed, in particular those who are geographically inaccessible, to understand how a terminal illness like cancer may change their EOL planning, and how their unique cultural beliefs, values, knowledge and attitudes about ACP differ, if at all, from indigenous peoples who have not had cancer.

Similarly, there has been little research to explore Taiwanese indigenous people's intent to find public EOL education. It is likely that as a minority group their beliefs conflict with values associated with ACP [24,37,40-43]. Even though several studies were published after ACP became the subject of national campaigns [19-22], it is unknown to what extent these findings may be generalized beyond mainstream Taiwanese society.

The purpose of this study is to determine the possible impact of cancer as a life-threatening disease on Taiwanese indigenous peoples' ACP readiness. Comparisons will be made between Taiwanese indigenous groups with and without existing cancer diagnoses; the hypothesis is that cancer survivors' experiences before or during cancer treatment (or with no treatment) may differ. Issues specific to ACP can then be examined between groups similar in age and gender. In addition, this study will assess the impacts of obtained ACP knowledge, in relations to several conditions, including previous self-learning, earlier participation in any forms of ACP education, the registration

of advance directives on the National Health Insurance Care, and prior care providing to dying family members.

This proposed study offers a unique opportunity to examine EOL-related decision making among mountain-residing indigenous cancer survivors who are geographically difficult to reach. For the first time, their current palliative care and hospice usage may be extensively surveyed. In addition, this study will be theoretically driven by the conceptual model of "Stage of Readiness for Change" [44,45] to explore facilitators and inhibitors affecting indigenous cancer survivors' intentions. Specific intervention strategies may be discovered that are extremely helpful for developing a pioneering intervention that facilitates ACP public education participation for this cultural group.

Methods

Study Design

This descriptive study has a case-control design, in which a group of at least 100 Taiwanese indigenous cancer survivors will be compared with another 100 Taiwanese indigenous controls that have not had cancer. The survivor sample will consist of survivors of several common types of cancer, including malignant tumors and leukemia, and will be recruited from referral lists of oncological and family physicians of collaborative institutions from remote areas where indigenous populations reside. Controls will be selected from the same collaborative facilities in this study and will be matched to the survivor group in age and gender. Cancer diagnoses will be matched maximally so that comparisons may be made consistent across cancer types. Both cancer survivors and cancer-free controls will be surveyed for their willingness to participate in further public education in ACP. This also allows us to examine the effects of cancer as an exposure and also registry (and non-registry) of Do-Not-Resuscitate (DNR) status for these cancer types, which may have an influence on ACP readiness.

In the first year, the major research activities for this descriptive study will be gathering, preparing, and developing a valid and short questionnaire of readiness through in-depth interviews from a group of 10-20 indigenous cancer survivors. Interview guides will be developed in order to use phenomenological methods to describe indigenous cancer survivors' EOL decision making, including their concerns, ACP knowledge, self-efficacy, and intent for ACP. Their preferred strategies whether to participate in a culturally appropriate intervention program will be explored.

In the second year, the main efforts will be in two dimensions: (1) case-control screening to reach an accrual goal of 100 subjects, in particular the identification of indigenous cancer survivors in remote, rural Taiwanese areas, and (2) partial data collection through face-to-face or telephone interviews to understand their ACP situations. Some data collection and analysis of the outcome variables (stages of readiness and intent) may be completed. Primary findings may be reported regarding associations among indigenous identities, demographic information, physical functioning, knowledge related to ACP, and an outcome of readiness according to the Theoretical Model.

Time and resources spent in the third year will be mostly on comparisons between factors such as knowledge related to ACP, their self-efficacy, and previous participation in ACP education, and the national registry status related to EOL planning. The complete results will be reported in the final year. The following section details sampling, recruitment, setting, data collection procedures, statistical considerations, and analytic methods.

Sampling and Recruitment Setting

The potential cancer survivor pool was drawn through co-investigator physicians' referral lists of participating sites and cancer registries of a few affiliated institutions where large Taiwanese indigenous populations reside and from areas where the most remote indigenous populations reside. Although this study was open to all large hospitals and affiliated institutions with substantial numbers of Taiwanese indigenous cancer survivors, it is expected that indigenous peoples are aggregated in certain Taiwanese rural areas. Four institutions and community branches of a teaching hospital in Northern, Western, and Eastern Taiwan have agreed to participate in the study and allowed access to cancer patients in the medical database.

The databases from which survivors were sampled were updated annually to include their current contact information. In the first year of the study, an effort was made based on the investigator's judgment to recruit an interview sample varying in age, level of acculturation, socioeconomic status, and readiness for ACP. After discussing with two qualitative investigator experts, a minimum of 10 subjects (5 males and 5 females) was recommended for the in-depth interviews. However, because these 10 interviews might not provide sufficient saturation, the final qualitative sample size might be as large as 20 subjects (n=20). Saturation of data will be determined for each gender separately for this study. The inclusion criteria for interviewed cancer survivors were self-identified adult Taiwanese indigenous peoples above 20 years old, legally competent for advance care planning, fluent in Mandarin and/or Taiwanese, and currently treating or following up cancer at least 1 month prior to participation in this study. Excluded were those critically ill and legally incompetent for ACP during the data collection period. The investigator would contact potential subjects, and the study goal with the recruitment process will be explained in a room reserved for subjects' convenience.

Cancer Survivors

Taiwanese indigenous cancer survivors who have been treated for various types of malignant tumors or leukemia will be recruited for participation in the second year of the survey study. The inclusion criteria for cancer survivors are self-identified Taiwanese indigenous peoples (n=100) residing in mountain areas (non-plains), currently treating or following up cancer at least 1 month prior to participation in this study. They must be legally competent for their own medical decisions without any predictable imminent medical crises. The cancer survivor sample will be drawn from physicians' referral lists of affiliated institutions in areas of large Taiwanese indigenous populations.

Four institutions and community branches of the same teaching hospital mentioned above have agreed to participate in the study,

provided ethical support, and allowed access to their cancer registry patients. If there are significant clusters of Taiwanese indigenous cases and survivors at other institutions, who meet the other criteria for study eligibility, we will add them and select controls from those areas proportionate to their representation in the survivor sample. However, based on the data received from these institutions, we are confident that this study can be completed at the four institutions that have agreed to participate.

Data recruitment will begin when the number of potential, eligible participants treated at each participant site is identified; survivors from the referral lists of each site will be conveniently selected later to create a matched case-control group within the study site. Names of survivors who are known to be at participating study sites will be drawn from database records. Efforts will be made in selection of cases to ensure, as much as possible, a balanced distribution across groups, for example, equal numbers or female and male for each cancer type. The four participating sites from which survivors will be sampled include updates of current contact information. The accuracy of the contacting information will be checked in this study, as well as to confirm that potential participants are still capable of participating in this study.

Controls

Several concerns must be considered in selecting controls. We chose the control sample from the same registry source as the cases to ensure both cancer cases and control survivors are representative of similar experiences, such as geographical areas, hospitals receiving treatment, and tribal identities. For this study, the cases will be drawn from several participating sites in geographically diverse areas in rural Taiwan. Since drawing controls from all other patient regions or the hospital census may be inefficient and costly, we have chosen to conveniently draw the controls from the same hospital base where the cancer survivors reside.

In order to avoid overmatching, the commonly used method of "frequency matching" on key variables will be used to ensure the equality of cancer survivors and controls among indigenous populations. The controls will be selected from the areas served by the participating institutions. They will be first oversampled to ensure a sufficient pool to allow frequency matching with cases/survivors, and later screening interviews will be conducted to identify eligible controls, that is, indigenous Taiwanese who have not had cancer. The inclusion criteria for the control group (n=100) are nonindigenous Taiwanese who are similar to the cancer survivors as a group in age and gender, but have not been diagnosed with any type of cancer. We will exclude participants who are not legally competent in executing ACP and are unable to be reached by the research team. During the screening interview, questions designed to classify controls by age and gender will be asked, and over the course of data collection, this information will be used to ensure the distribution of key variables so that the case/survivor group and control group may be sufficiently comparable.

Instruments

Table 1 lists the instruments that will be developed and used to measure the variables for this study. Those valid instruments have been extensively used with minority ethnic populations. All of the instruments have been used successfully in telephone interviews, with the exception of one newly developed instrument (Stage of Readiness for Advance Care Planning), which has been used successfully in face-to-face interviews. The same instruments will be used for indigenous controls (who do not have cancer); however, the word "cancer" or any experiences relevant to cancer will be changed to "your health" wherever necessary. Medical characteristics, such as cancer stage at diagnosis, treatment received for cancer, and other related information will be obtained from medical files or cancer registry records at participating sites. Data regarding survivors' and controls' present health and ACP status will be obtained from the medical database as well.

Table 1. Constructs/components, variables, and measures.

Constructs/components	Variables	Quantitative measures
Readiness for ACP[a] (outcome variable)	ACP Stage of change	Stage of change for ACP (based on an item algorithm)[a]
Physical functioning	General health status	Short Form-12 v2 Health Surveys Taiwan (Chinese) – Standard Recall (12 items) [46]
Quality of life	Life satisfaction	Life satisfaction subscale (33 items) of Quality of Life Index [47]
Demographics	Tribe, Age, Gender, Life-partnered, Income, Education, Employment, Preferred religion	Tribal identity, Age, Gender, Marital status, Income, Education, Work status, Religion
Knowledge obtained related to ACP	Knowledge about life-sustaining treatment and ACP; previous experiences related to EOL[c]	Knowledge of ACP scale (10 items)[a]; previous EOL experiences scale (6 items)[a]
Intent of Taiwanese indigenous peoples for ACP intervention	Preferred ACP program contents, settings and frequencies, learning methods, possible facilitators, and barriers.	Questions developed for soliciting subjects' preferred strategies

[a]ACP: advance care planning.

[b]Quantitative measures included in the survey questionnaire were developed by Hsiung and Ferrans [28] based on the Transtheoretical Model of Health Behavioral Change [44] and previous ACP studies.

[c]EOL: end-of-life.

Data Collection Procedures

The procedure used to collect data from both the cancer survivor cases and non-cancer controls are similar. The Principle Investigator will contact potential participants to describe the study and invite them to participate, and a telephone call will be scheduled to explain the study in detail and arrange a time for consecutive interviews. Interview schedules/questionnaires will be sent to their homes before the telephone interview, and both cases and controls are anticipated to complete the interviews by phone no more than two times. Telephone interviews with cases/survivors will continue only until the target sample size is reached.

Statistical Considerations and Analytic Methods

Accrual Goals

A total of 200 Taiwanese indigenous peoples will be interviewed, including 100 indigenous cancer cases/survivors and 100 indigenous peoples who have not had cancer with key characteristics matched, similar to the survivor group. Required sample size depends on several parameters, such as desired power, alpha level, expected effect size, and a number of predictors. Normally, a power analysis is performed and effect size (f^2) would be estimated to achieve this goal [48]. However, information needed for a power analysis and the effect size is not available from previous studies that have examined this phenomenon. A few instruments developed for this study have not been largely used across cultural groups. Therefore, Pedhazur and Schmelkin's [49] recommendation of approximately 10 subjects per predictor for a reliable regression equation will be used in this pilot descriptive study. To understand the effect size that may then be used in a subsequent analysis for the categorical dependent variable with four levels, this pilot study would need a minimum number of at least 100 subjects of four groups each for the quantitative survey.

In addition, because there have been no such studies before, we could only provide a power estimate from the Quality of Life (QOL) Index. Previous studies have reported an average standard deviation of 4.5 for the QOL Index, with a difference of 2-3 points being a clinically meaningful difference. A difference of 2-3 points in the total score of the QOL Index has been associated with significant improvement in overall quality of life, self-image, physical symptoms, and general health in studies assessing change in quality of life. If the comparison in this study is based on 100 survivors and 100 control subjects, then there is approximately 80% to detect a 1-point difference in the QOL Index with a 2-tailed test conducted at the .015 level of significance. Our current size number for each group is greater than 99% power to detect a 2-point difference in the QOL Index. In comparing the survivor and control populations, the outcome of primary interest is Stage of Readiness for Advance Care Planning. In order to adjust for comparison, a type I error level of 0.05 will be used in the examination of power for this outcome.

Analytic Methods

To address selection biases, comparisons will be made between participants and those who fit the inclusion criteria yet decline to participate. In particular, we are interested in the differences in their demographic profiles and clinical characteristics. Basic patient descriptors will be described using *t* tests, Wilcoxon tests, and chi-square tests to make comparisons between eligible subjects who eventually do and do not participate in this study. Descriptive statistics stratified by survivorship status (subjects who are survivors or controls) will be used to describe the physical, psychological, social, economic profile of Taiwanese indigenous peoples, as well as the quality of life differences and the prevalence of readiness. Multiple regression models will be used to analyze the exposure effect of cancer, as an independent variable, on ACP readiness, as a dependent variable. While both are continuous measures, they will be analyzed using linear regression, unless a severe departure from normality is observed. If a highly skewed distribution is observed, an attempt will be made to analyze an appropriate transformation using linear regression, or ordinal categories will be defined and analyzed using the proportional odds logistic regression model. The coefficient for the effect of cancer will be tested against zero, adjusting for age and gender by including them in the model as additional independent variables.

In a second phase, potential mediating variables will be added to the model. Mediating variables will be considered in two blocks: (1) obtained knowledge related to ACP and (2) individual characteristics, including tribe identity. For each block, a model will first be fitted including all variables in that block. Second, a backward selection procedure will be used to remove insignificant variables according to the liberal criteria of $P<.10$, in order to capture potential changes in the effect of interest while still maintaining efficiency.

Ethical Considerations

Before collecting data from subjects, permissions and ethical support to conduct this study have been obtained from the four affiliated institutions. The researcher has sought approval from the Institutional Review Board at Mackay Memorial Hospital, Taipei, in 2015. Careful attention will be paid to the sensitive nature of this study, and efforts will be made to ensure the protection of human subjects throughout the whole course. Upon recruitment, all potential participants will be given a written description of the purpose and data collection procedure of the study. This is to ensure that all potential participants understand the scope and purpose of this study. An opportunity will be provided during the informed consent process to allow clarification by participants. Although the research topic may be somewhat culturally sensitive, the probability and magnitude of harm or discomfort anticipated in this type of research is no greater than those risks ordinarily encountered in daily life. All documents related to participants' responses are to be kept in a locked file cabinet accessible only to the researcher. All quantitative data will be kept for at least 5 years before being shredded or destroyed. When the results of this study are published or discussed in any conference and/or workshop, no information will be included that would reveal participants' identities.

Results

This study is expected to be completed within a 3-year timeframe, with results expected to be published in 2018.

Discussion

Principal Considerations

Since there has been no research on Taiwanese indigenous people's aims for ACP, there is a need to understand the impact of survivorship on ACP readiness among those who are currently living with, through, and beyond cancer. This carefully designed study provides a unique opportunity because for the first time in Taiwan, cancer survivorship and ACP readiness for EOL planning will be examined among difficult-to-reach indigenous peoples. We expect to survey palliative care usage in remote indigenous groups, understand factors that influence ACP readiness, and foster culturally appropriate ACP public participation and policies in order to facilitate collaboration between cancer health care providers in various Taiwanese subcultures.

Limitations

The greatest challenge of this cross-cultural case-control study is the identification, recruitment, and data collection of Taiwanese indigenous cancer survivors and controls in difficult-to-access areas. Connections have been made with physicians and cancer nurse case managers in rural Taiwanese areas where most indigenous peoples reside. Local assistants may be hired to foster case identification and control matches. In addition, while the influence of a stigma or fear related to death for cancer survivors and their comparatively healthy control cohorts is still unknown, the Principal Investigator will carefully deal with sensitive interview questions in order to explore death-related cultural beliefs and concerns. The use of small incentives has proved effective in the past to encourage participation and increase response in studies. The incentive value (<US $3) was determined after consulting a panel of indigenous leaders and cultural experts. As much as we want to believe that this incentive value may not be coercive enough as an inducement to create bias in the study, we are not entirely certain if providing any incentives would be an obvious limitation, considering poverty might be an issue among Taiwanese indigenous cancer survivors.

Conclusion

This study will provide a better understanding of Taiwanese indigenous people's cultural beliefs, current planning regarding their EOL medical and care preferences, and future projections of public ACP education participation in mainstream society. This will be of great use for health policy and resource allocation for Taiwan. Collaboration among affiliated hospitals in the Northern, Eastern, and rural areas will also facilitate consistent quality palliative care practice in Taiwan. All research personnel will be trained to obtain professional academic skills in data managing, data collection, and statistical analysis specifically for indigenous peoples. In addition, clinicians participating in this study will also obtain up-to-date information and resources about ACP, which is currently promoted at a national level in Taiwan.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Funding report from the Ministry of Science and Technology of Taiwan, Grant No: MOST 104-2511-S-715-002.

[PDF File (Adobe PDF File), 105KB - resprot_v6i12e238_app1.pdf]

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Abbreviations

ACP: advance care planning
DNR: Do-Not-Resuscitate
EOL: end of life
QOL: quality of life

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Original Paper

Daily Activity Measured With Wearable Technology as a Novel Measurement of Treatment Effect in Patients With Coronary Microvascular Dysfunction: Substudy of a Randomized Controlled Crossover Trial

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Abstract

Background: Digital wearable devices provide a "real-world" assessment of physical activity and quantify intervention-related changes in clinical trials. However, the value of digital wearable device-recorded physical activity as a clinical trial outcome is unknown.

Objective: Because late sodium channel inhibition (ranolazine) improves stress laboratory exercise duration among angina patients, we proposed that this benefit could be quantified and translated during daily life by measuring digital wearable device-determined step count in a clinical trial.

Methods: We conducted a substudy in a randomized, double-blinded, placebo-controlled, crossover trial of participants with angina and coronary microvascular dysfunction (CMD) with no obstructive coronary artery disease to evaluate the value of digital wearable device monitoring. Ranolazine or placebo were administered (500-1000 mg twice a day) for 2 weeks with a subsequent 2-week washout followed by crossover to ranolazine or placebo (500-1000 mg twice a day) for an additional 2 weeks. The outcome of interest was within-subject difference in Fitbit Flex daily step count during week 2 of ranolazine versus placebo during each treatment period. Secondary outcomes included within-subject differences in angina, quality of life, myocardial perfusion reserve, and diastolic function.

Results: A total of 43 participants were enrolled in the substudy and 30 successfully completed the substudy for analysis. Overall, late sodium channel inhibition reduced within-subject daily step count versus placebo (mean 5757 [SD 3076] vs mean

6593 [SD 339], *P*=.01) but did not improve angina (Seattle Angina Questionnaire-7 [SAQ-7]) (*P*=.83). Among the subgroup with improved angina (SAQ-7), a direct correlation with increased step count (r=.42, *P*=.02) was observed.

Conclusions: We report one of the first studies to use digital wearable device-determined step count as an outcome variable in a placebo-controlled crossover trial of late sodium channel inhibition in participants with CMD. Our substudy demonstrates that late sodium channel inhibition was associated with a decreased step count overall, although the subgroup with angina improvement had a step count increase. Our findings suggest digital wearable device technology may provide new insights in clinical trial research.

Trial Registration: Clinicaltrials.gov NCT01342029; https://clinicaltrials.gov/ct2/show/NCT01342029 (Archived by WebCite at http://www.webcitation.org/6uyd6B2PO)

(JMIR Res Protoc 2017;6(12):e255) doi:10.2196/resprot.8057

KEYWORDS

angina; coronary microvascular dysfunction; physical activity

Introduction

Mobile wireless devices and connected wearable biosensors have the potential to provide new insights into chronic medical conditions and help clinicians develop personalized treatment strategies. One potential application of digital wearable device technology is the real-time evaluation of change in daily activity as a clinical outcome. Patient activity level is traditionally assessed using surrogate measures such as exercise testing or patient questionnaires. However, these tools are limited to point-in-time observation and questionnaires provide subjective information that is retrospective. Furthermore, although patient questionnaires correlate with exercise stress testing [1], they may fail to correlate with wearable pedometer-measured daily activity [2], which along with research-grade accelerometer-measured daily activity, have generated physical activity outcome variables for clinical trials in the general population as well as patients at risk for coronary artery disease (CAD) or diagnosed with CAD [3-6]. Commercially available, digital wearable devices are capable of accurately [7-11] measuring daily activity (step count) continuously and objectively, including in patients with cardiac disease [10]. Compared to pedometers and research-grade accelerometers [7-11], digital wearable devices are novel because they generate daily activity data in real time via synchronization to a connected computer or mobile device, which allows for new insights into treatment response and, in particular, how treatments may impact patients in their daily lives.

One area for such potential is the management of angina pectoris, a chronic medical condition with symptoms that decrease exercise capacity, decrease quality of life (QoL), and lead patients to limit physical activities in daily life [12-15]. In treating angina, therapeutic goals include optimizing level of physical activity, functional capacity, and QoL by eliminating ischemic symptoms [16]. Fortunately, treatment of angina with antianginal pharmacologic therapy, cardiac rehabilitation, or psychological intervention has been shown to improve QoL and increase level of physical activity [17-19]. However, until recently, evaluation of the response to antianginal therapies among patients with obstructive CAD has focused on laboratory exercise testing, nitroglycerin utilization, or retrospective QoL and daily activity data capture using patient diaries and questionnaires. It is now recognized that a significant portion of patients with angina are women without obstructive CAD. Many of these women have coronary microvascular dysfunction (CMD) that is their major mechanism for myocardial ischemia. It is estimated to affect at least 2 to 3 million Americans, most frequently women, and has been found to not only decrease QoL and lead to limitation of physical activities, but also increase the risk of death and other cardiovascular events, including heart failure (diastolic dysfunction), myocardial infarction, and stroke [12-15,20-22]. Although specific pathophysiological mechanism(s) of CMD are not fully understood, when evidence of ischemia is present, CMD is treated with conventional antiischemic, antianginal pharmacologic therapies such as beta blockers, calcium channel blockers, and nitrates with the intention being to relieve anginal symptoms so that QoL improves, including allowing for increased exercise capacity, QoL, and physical activity [20]. Unfortunately, these traditional therapies were developed and approved over past decades largely in patients with obstructive CAD and “reproducible” exercise test electrocardiogram (ECG) results. Patients without obstructive CAD often do not have these “reproducible” exercise test results and also do not reliably respond to these traditional antianginals. So these patients continue to have angina, which decreases their ability to be physically active in their daily lives and, as such, they become sedentary as they continue to suffer from symptoms that diminish their QoL and daily activity with no readily available therapy or novel methods to evaluate their responses to treatment, representing an important knowledge gap [12-15,20].

Late sodium channel inhibition (ranolazine) is an antiischemic pharmacologic therapy indicated for the treatment of angina due to CAD that has been demonstrated to improve physical activity, exercise duration, and QoL [17,23,24]. However, there is very limited knowledge about its efficacy and safety in the treatment of CMD [23-27]. A pilot study with ranolazine versus placebo in 20 women with CMD suggested that ranolazine improved angina [28]. Similarly, results of two small studies [17,29] (58 and 46 participants with no obstructive CAD) also supported ranolazine efficacy for increasing coronary flow reserve (CFR) with one study demonstrating improved QoL and physical activity [17]. However, in a much larger (N=128) randomized, placebo-controlled crossover trial of patients with CMD, which aimed to mechanistically test if angina symptoms were related to cardiac magnetic resonance imaging (MRI)

myocardial perfusion reserve index (MPRI), late sodium current inhibition with ranolazine did not improve angina, QoL, ischemia, or diastolic function [30]. These discordant findings were likely related to small sample sizes, differences in participant characteristics (typical male "effort" angina vs female nontypical angina), and evaluation methodologies (exercise vs pharmacological testing, directly vs indirectly measured CFR), as well as severity of CMD [30].

Angina clinical trials have used exercise laboratory testing, 6-minute walk, ECG monitoring, cardiac imaging, QoL questionnaires, and pedometers to determine if treatment of ischemia with antianginal therapy relieves symptoms and results in improved physical activity, functionality, and QoL. The totality of evidence suggests that treatment of angina can relieve symptoms and that no one therapy is more effective than the other. However, beyond larger modern studies that have used questionnaires or historical small studies that used pedometers, our understanding of how treatment with antianginal therapy affects daily activity is limited. As such, data generated by digital wearable devices has the potential to provide new insights into the efficacy of antianginal therapies as it relates to physical activity in daily life in patients with angina, particularly in the CMD population.

To further explore use of digital technology in a therapeutic cardiovascular trial, we conducted a substudy within a randomized, double-blinded, placebo-controlled, crossover trial of patients with angina and CMD and no obstructive CAD [30] to assess within-subject change in daily activity measured by mean daily step count using the Fitbit Flex wireless activity monitor. Specifically, the objective of this study was to determine if treatment of angina with ranolazine in patients with CMD would provide symptomatic relief sufficient to allow patients to increase their levels of daily activity. We hypothesized that those treated with ranolazine compared to placebo would have a higher mean daily step count, and that those with greater antianginal responses would have greater step count increases.

Methods

Patient Population

Participants were recruited from the two-site parent trial [30], which was conducted at both Cedars-Sinai Medical Center and the University of Florida, Gainesville, FL. Patients enrolled in the parent trial had symptoms and signs of myocardial ischemia, no obstructive CAD, and CMD as measured by invasive CFR or noninvasive cardiac MRI-determined MPRI. Inclusion and exclusion criteria were the same as the parent trial [30], with the additional exclusion criteria of immobility and/or physical inability to wear the wristband. Patient characteristics and demographics were collected at baseline and included classification of patients with typical angina or nontypical angina on screening and enrollment. Typical angina was defined as substernal chest pain precipitated by physical exertion or emotional stress and relieved with rest or nitroglycerin; nontypical angina was defined as symptoms that did not meet criteria for typical angina. In addition, participants who underwent invasive CFR were classified as CFR either less than 2.5 or 2.5 and greater. Institutional Review Boards at Cedars-Sinai Medical Center and the University of Florida approved the study, and all participants gave written informed consent before participation.

Study Design

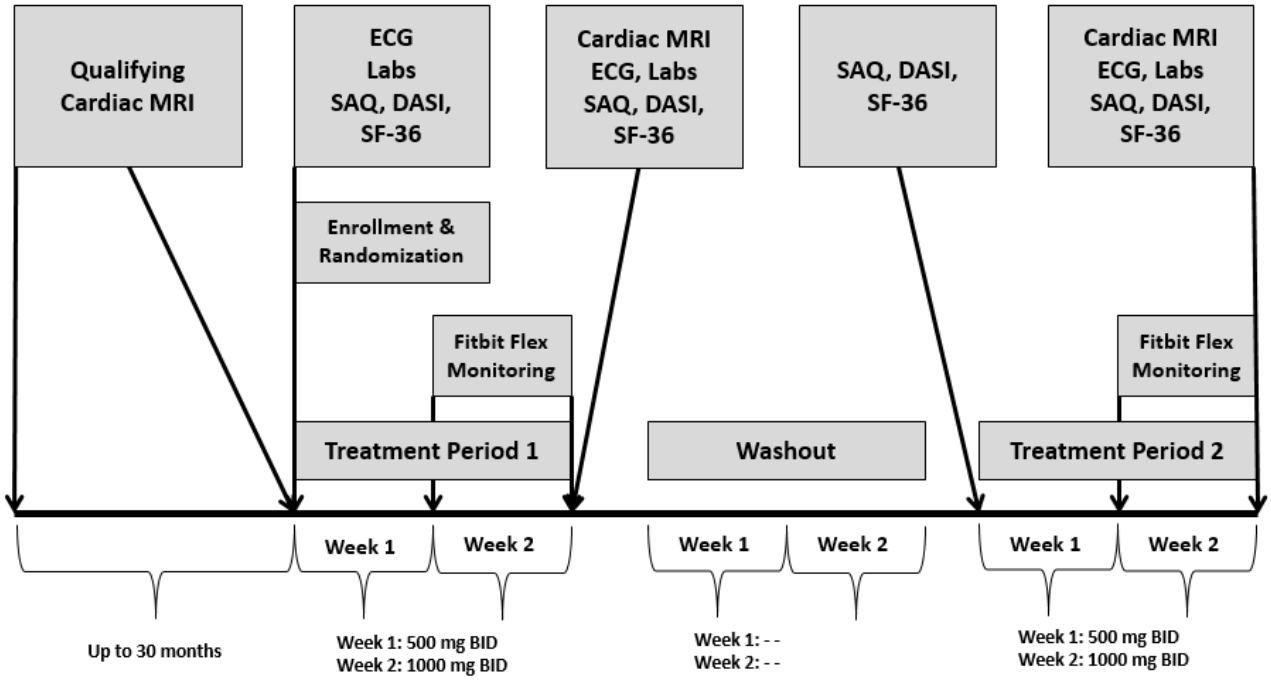
The parent trial was a double-blind, placebo-controlled, crossover trial with short-term (2 week treatment periods; week 1: ranolazine or placebo 500 mg twice a day, week 2: ranolazine or placebo 1000 mg twice a day) ranolazine-placebo exposure (order randomly assigned to a sequence of ranolazine or placebo first followed by a 2-week washout and subsequent crossover to placebo or ranolazine or vice versa) [30]. The substudy design included daily activity monitoring with a digital wearable device performed during week 2 of both treatment period 1 and 2 (ranolazine 1000 mg twice a day or placebo 1000 mg twice a day) (Figure 1) [30].

The duration of daily activity monitoring was designed for 1-week duration to account for daily activity that occurs in real life. In addition, it was previously demonstrated that ranolazine increases exercise performance in patients with angina-limited exercise after 1 week of treatment [23]. Daily activity monitoring occurred during week 2 of each 2-week treatment period instead of during week 1 because low-dose study treatment (500 mg twice a day) was initiated during week 1 and titrated to high-dose study treatment (1000 mg twice a day) during week 2, such that daily activity monitoring during week 2 of each treatment period would assess daily activity under the maximal therapeutic effect of ranolazine or placebo. Daily activity was quantified as step counts and categorized by pedometer-determined indexes of physical activity in healthy adults as follows: (1) sedentary lifestyle index: less than 5000 steps per day; (2) low active: 5000 to 7499 steps per day; (3) somewhat active: 7500 to 9999 steps per day; (4) active: 10,000 or more steps per day; and (5) highly active: greater than 12,500 steps per day [31].

Digital Wearable Device

The wearable accelerometer was the Fitbit Flex, which continuously measures daily physical activity that is reported as step count [8]. The Fitbit Flex has a battery life of 5 days and generates data that includes steps, distance covered (miles), and calories burned [8]. At the time of study design, prior versions of the Fitbit device had been reported to have an accuracy of 95% to 97% for measuring activity (steps) when worn correctly, and accuracy was evaluated by direct observation and by comparison to other activity monitors [7,9]. The Fitbit Flex has since been validated for measuring physical activity, including in patients with cardiac disease [10,11]. The Fitbit Flex was selected so that the wearable accelerometer would be encased in a wristband with the assumption being that this would decrease the risk for loss of device.

Figure 1. Substudy design flow diagram, participant screening, enrollment, and randomization flow diagram. Treatment period 1 and 2 with daily activity monitoring during week 2 of each treatment period: randomized to sequence of ranolazine first followed by crossover to placebo or vice versa. BID: twice a day; DASI: Duke Activity Status Index; ECG: electrocardiogram; MRI: magnetic resonance imaging; SAQ: Seattle Angina Questionnaire; SF-36: 36-item Short Form Survey.



Before randomization, each participant was provided with a Fitbit Flex, a dongle for wireless synchronization, a USB cord, and a wall charger. Participants were instructed regarding the device placement and the daily physical activity monitoring protocol, which included scheduled monitoring dates, device charging, wrist placement, and device synchronization. Participants were encouraged not to modify their daily activity or achieve any specific step count goal or daily activity level. The device was worn by the participant on the nondominant wrist continuously each day during week 2 of both the active treatment and placebo periods. All days with step count data were considered a valid day of wear as long as the participant did not report any violations of the protocol in that they continuously wore the Fitbit per protocol during the entirety of the monitoring period. Research coordinators verbally confirmed that participants complied with the protocol after completion of each monitoring period. Per protocol, the device could only be removed temporarily for bathing or swimming, but otherwise removal was not allowed unless a participant was instructed to remove the device by the research coordinator (ie, adverse device reaction, device failure, or device charging while sleeping if indicated).

Digital wearable device data were uploaded regularly by participants via computer synchronization using the "Sync Now" function in the Fitbit Connect software, which was installed on each participant's personal computer or device and aggregated by research coordinators for analysis. Each device was accompanied by a unique account that was password protected and accessible only to research coordinators; therefore, participants were not able to view their own step count data. They were able to view the Fitbit Flex indicator lights, although they were not instructed as to what the specific meaning of the light patterns indicated. During the clinical trial, participants received reminder telephone calls regarding device charging, placement, and synchronization. In the case that a research coordinator determined that a device needed to be charged, the participant was instructed to remove the device during sleep and place the device on the nondominant wrist immediately on waking. Research coordinators monitored device synchronization and intervened if the device failed to upload data during monitoring periods. To assure participant safety and equipment integrity, participants were also instructed about allergic reactions, exposure to liquids, and device cleaning. In total, 15 Fitbit Flex's purchased between 2013 and 2015 were used throughout the duration of the study.

Angina and Quality of Life Questionnaires

Patient questionnaires were administered as described [30] to assess angina (Seattle Angina Questionnaire [SAQ] and SAQ-7), functional capacity/status, and QoL (Duke Activity Status Index [DASI] and the 36-item Short Form Survey [SF-36]). Angina was also assessed by an angina and nitroglycerin use diary as previously described in the parent trial [30].

Cardiac Magnetic Resonance Imaging

The cardiac MRI protocol was performed as previously described and was conducted under identical conditions and timing, dosing, and settings, approximately 4 hours after the morning study drug dose [30,32-35]. A cardiac MRI MPRI of 1.8 or less was considered abnormal [33] and correlates with invasive coronary reactivity testing [34] and risk factors [35]. MPRI data were obtained to evaluate CMD, and left ventricular peak filling rate (PFR) and time to PFR (tPFR) data were obtained to evaluate diastolic function [36].

Invasive Coronary Reactivity Testing

Clinically indicated invasive coronary reactivity testing [21,30,37] measured coronary microvascular and macrovascular endothelial and non-endothelial-dependent function was available for 13 of 30 participants (43%) as previously described [38].

Statistical Analysis

This substudy was planned to enroll 30 participants to achieve 80% power to detect a mean difference in daily step count between a patient's ranolazine and placebo treatments of 1000 using a paired *t* test with the crossover design of the parent study, at a significance level of .05, assuming a standard deviation of 1863 in step count difference. Participants were randomized to two sequences (ranolazine then placebo or placebo then ranolazine) centrally at a 1:1 ratio and blocked by clinical site [39].

The analytic approach was a within-subject comparison (paired) of the difference between a participant's mean daily step count during 1 week on ranolazine and their mean daily step count during 1 week on placebo. The main endpoint of the parent trial was the difference between change in SAQ for ranolazine versus placebo. There were two treatment periods, ranolazine and placebo, giving two measurements per participant for mean step count and cardiac MRI variables. There were a total of four measurements per participant, including treatment baselines and posttreatment values, for SAQ and QoL giving two treatment changes per participants. The primary approach was a standard paired *t* test. Difference in mean daily step count was also evaluated for the subgroups of typical or nontypical angina, CFR of less than 2.5, and "low active" or "sedentary" daily physical activity during placebo. Linear regression models like those used in the parent study [38] were tested using within-subject treatment differences as the outcome (treatment change in step count) to adjust for potential interaction of relevant clinical variables with treatment (examine how other variables influenced the effect the drug had on step count), where data were available, and to explore subgroup effects for angina type (typical angina or nontypical angina). Carryover effects tested the interaction between treatment and period by comparing the within-subject mean with means between the arms [40]. The significance level was set to .05. A participant was included if they had at least 3 days of 7 days of step count data available in each treatment period. If data were missing such that a participant did not have a minimum of 3 of 7 days of step count data, they were not included per protocol in the analysis. A minimum of 3 days of step count data was required in each treatment period based on pedometer daily activity monitoring findings reported by Tudor-Locke et al [41], who determined that 3 days of step count data provide a sufficient estimate of steps per day during a 7-day monitoring period. Analyses were performed using SAS version 9.3 (SAS Institute, Inc, Cary, NC, USA).

Study Oversight

The study was an investigator-initiated, intramurally funded substudy embedded within a parent trial ancillary to the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. The parent trial was funded, in part, by Gilead Sciences and was overseen by the WISE Data Safety Monitoring Committee. Statistical analysis was performed by investigators independent of NHLBI and Gilead, masked to treatment assignment. The decision to submit for publication was made by investigators who had access to all data after the last participant completed the study.

Results

Participant Characteristics

Between February 12, 2014 and June 1, 2016, 43 participants entered the Fitbit pilot study, 31 of whom were also enrolled in the parent trial (29 included in the parent trial analyses), and 12 who were enrolled in the substudy after the parent trial closed enrollment. Among the 43 participants who entered the substudy, 13 participants (30%) could not be analyzed for within-subject change in step count because of dropout before protocol initiation (n=3), incomplete data (n=6), Fitbit Flex not returned (n=1), protocol nonadherence (n=1), and washout dropout (n=2), leaving 30 participants (70%) who adhered to the protocol sufficient to provide adequate data for analysis as an outcome variable (Figure 2).

There was mean 6.5 (SD 1.0) days of digital wearable device monitoring during treatment with ranolazine (independent of randomization sequence) with 7.6% (16/210) days missing data and mean 6.6 (SD 0.9) days of activity monitoring during treatment with placebo (independent of randomization sequence) with 6.2% (13/210) days missing data. Pertinent baseline demographics and clinical variables are summarized in Table 1. Overall, the group mean was in the "low active" category of daily physical activity [31].

Compliance and Safety

Compliance to the intervention, measured by returned pill counts, was available for 56 of 60 sessions and was 100% for those 56 sessions overall. Ranolazine and placebo interventions were well tolerated with three (ranolazine) and three (placebo) participants reduced to 500 mg twice daily dosing for adverse effects, as per protocol. No serious adverse events during the ranolazine period occurred. Nonserious adverse events during the ranolazine period occurred in two participants—nausea and lightheadedness (n=1) and excessive sweating (n=1)—and in one participant during placebo—throat swelling (n=1)—as previously reported [30]. No digital wearable device adverse events occurred; compliance to wearing the device and device function were verified at the end of the trial. One participant had very low step counts but was compliant with wearing the device and was kept in the analysis.

Figure 2. Substudy participant screening, enrollment, randomization, and completion flow diagram. Participants were randomized to sequence of ranolazine first followed by crossover to placebo (treatment period 1) or vice versa (treatment period 2). For both treatment periods 1 and 2, daily activity monitoring occurred during week 2.

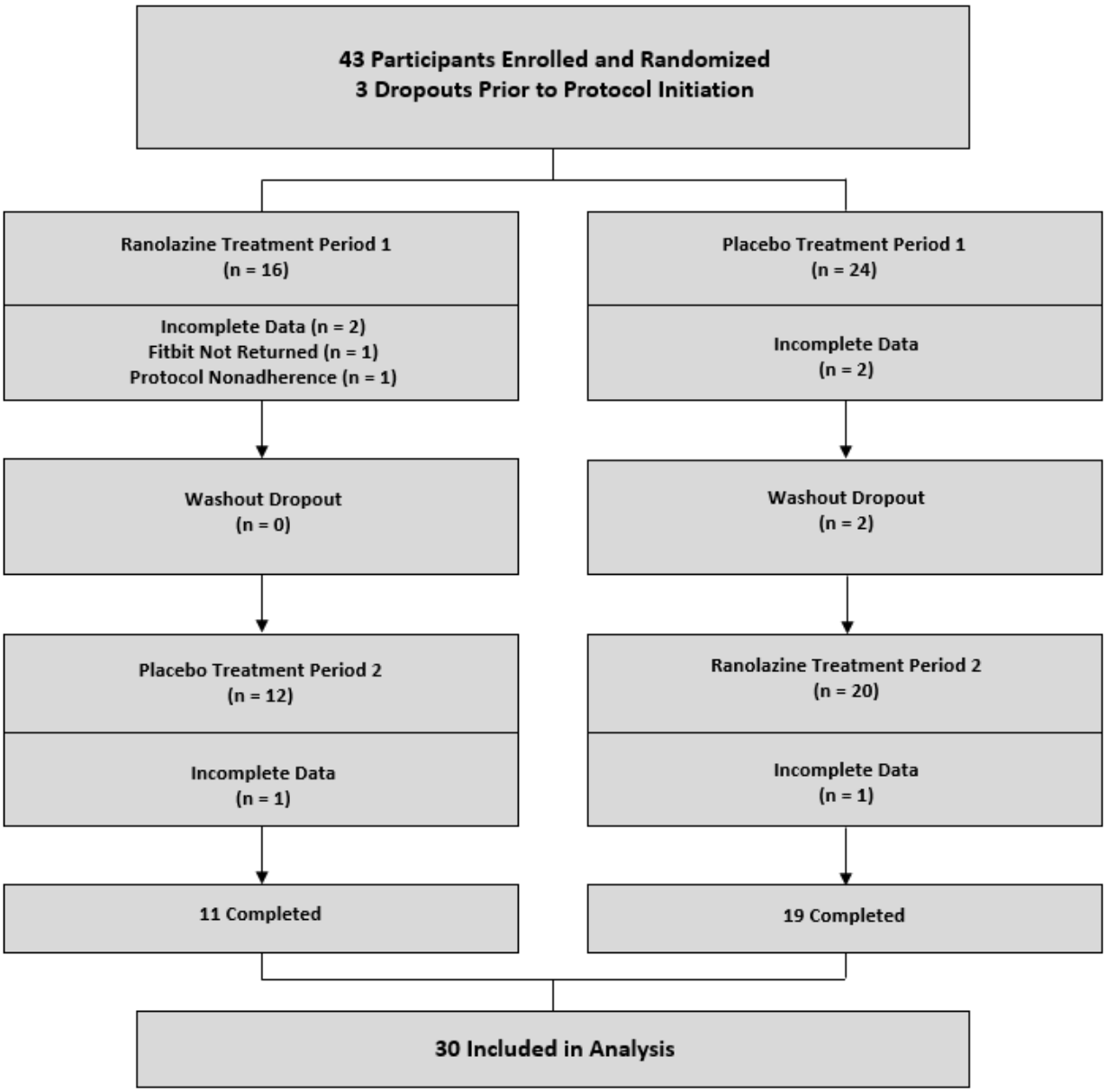


Table 1. Baseline demographics and clinical variables (N=30).

Variables	Analyzed participants
Age in years, mean (SD)	54.03 (10.59)
Female, n (%)	29 (97)
Postmenopausal (n=29), n (%)	20 (69)
Body mass index in kg/m^2 (n=29), mean (SD)	27.71 (6.74)
>30 kg/m^2, n (%)	10 (35)
Race (non-Caucasian), n (%)	25 (83)
Tobacco use, n (%)	
Current	1 (3)
Former	8 (27)
Never	21 (70)
Hypertension, n (%)	16 (53)
Hyperlipidemia, n (%)	13 (43)
Family history of premature coronary artery disease, n (%)	19 (63)
Coronary reactivity testing, mean (SD)	
Qualifying coronary flow reserve (n=13)	2.38 (0.63)
Qualifying coronary blood flow (n=6)	90.82 (71.18)
Qualifying acetylcholine response (n=10)	–0.08 (12.25)
Qualifying nitroglycerin response (n=11)	19.31 (19.55)
Qualifying cold pressor testing response (n=8)	7.94 (12.95)
Left ventricular end-diastolic pressure (n=9)	13.33 (3.57)
Cardiac magnetic resonance imaging, mean (SD)	
Baseline systolic blood pressure (n=28)	123.61 (21.03)
Baseline diastolic blood pressure (n=28)	68.79 (12.38)
Baseline heart rate (n=29)	70.59 (11.38)
Baseline rate pressure product (n=28)	8804 (2284)
Global myocardial perfusion reserve index (n=11)	1.69 (0.20)
Subendocardial MPRI (n=11)	1.52 (0.14)
Subepicardial MPRI (n=11)	1.75 (0.27)
Symptoms, n (%)	
Typical angina	12 (40)
Shortness of breath	24 (80)
Palpitations	15 (50)
Nausea	8 (27)
Medications, n (%)	
Beta blockers	12 (40)
Calcium channel blockers	7 (23)
Angiotensin-converting enzyme inhibitors	2 (7)
Angiotensin receptor blockers	6 (20)
Nitrates	10 (33)
Prior ranolazine	4 (13)
Statins	13 (43)

Variables	Analyzed participants
Aspirin	15 (50)
Diuretic	3 (10)
Hormone replacement therapy (n=19)	4 (21)
Vitamin D	10 (33)

Daily Physical Activity, Angina, Quality of Life, Hemodynamics, and Cardiac Magnetic Resonance Imaging Results

Step counts on individual days ranged from 7 to 19,879 during ranolazine and 25 to 18,110 during placebo. The individual mean across days within the treatment period ranged from 68 to 14,465 during ranolazine and 228 to 13,311 during placebo. During the ranolazine period, participants had significantly lower mean daily step counts compared to placebo (Table 2) with mean daily step count for ranolazine compared to placebo increased in 20% (6/30) of participants, decreased in 57% (17/30), and unchanged in 23% (7/30). The step count result was similar when the one participant with very low step counts was not included (mean change in step counts for the 29 remaining participants was mean –860, SD 1706, 95% CI –1509 to –211, *P*=.01). None of the secondary outcomes, other SAQ subscales, or angina or nitroglycerin use diary differed during ranolazine versus placebo (data not shown), although tPFR was higher on ranolazine (Table 2). Similar to the parent trial, due to a relatively high variance in the baseline-treatment comparison, we also directly compared treatment periods, rather than change from baseline, and observed no difference in within-subject change in SAQ-7 or SAQ subscales (physical limitation, angina stability, angina frequency, treatment satisfaction, QoL), DASI, SF-36 (energy/fatigue), SF-36 (emotional), diary-reported angina frequency or diary-reported nitroglycerin usage change, MPRI, PFR, and tPFR. Consistent with the parent trial, pharmacological stress heart rate and rate pressure product were lower during ranolazine periods versus placebo (Table 2).

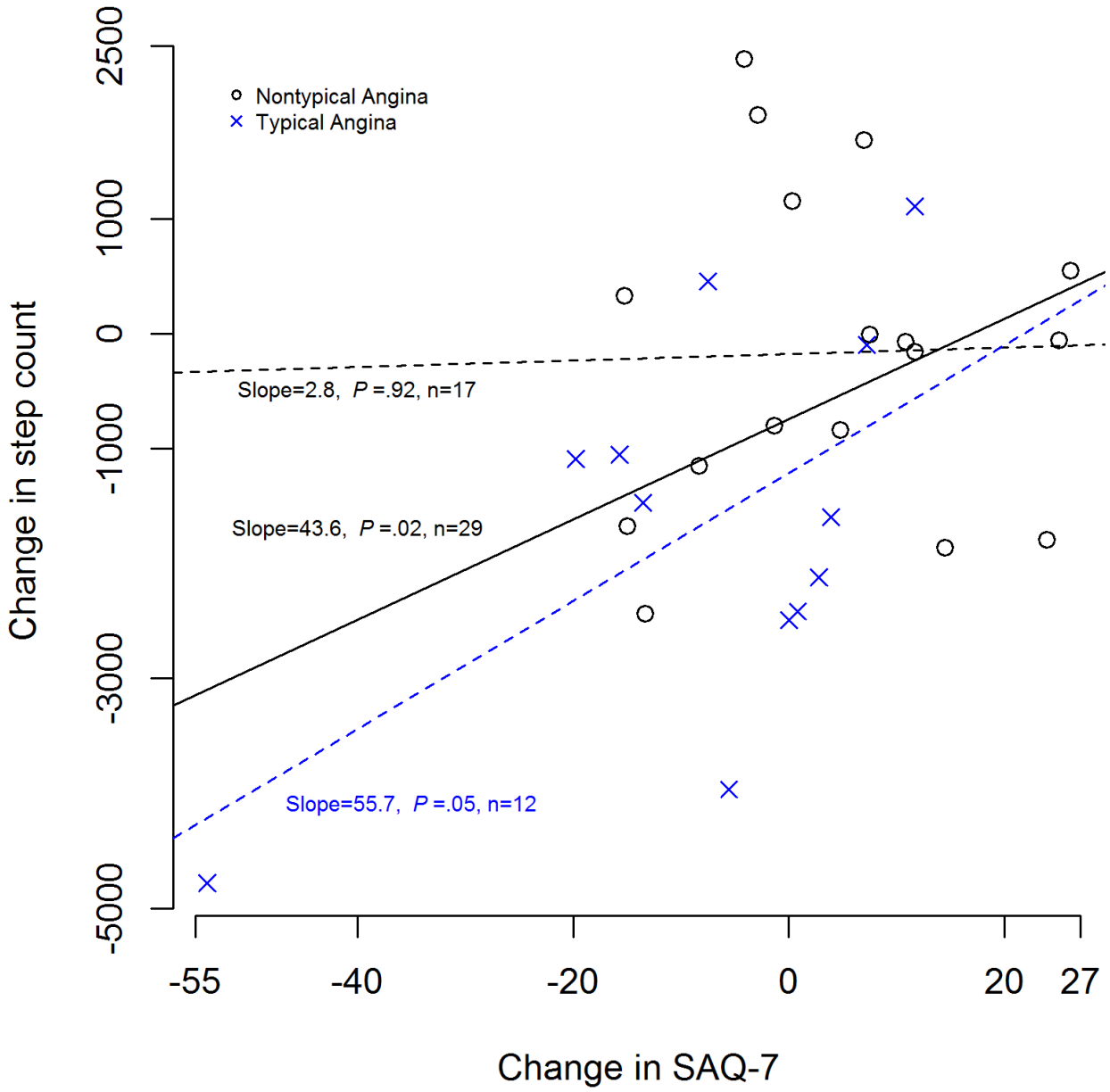
Table 2. Mean daily step count, Seattle Angina Questionnaire (SAQ), hemodynamic, myocardial perfusion reserve, and diastolic filling treatment effect.

Variables[a]	Ranolazine		Placebo		Treatment change		
	Mean (SD)	N	Mean (SD)	N	Mean (95% CI)	N	*P*
Mean daily step count	5756.49 (3075.51)	30	6593.29 (3393.44)	30	–836.8 (–1464.74, –208.86)	30	.01
SAQ							
Physical limitation	69.35 (26.10)	28	65.18 (21.44)	28	2.01 (–4.04, 8.06)	27	.50
Angina stability	55.17 (27.04)	29	54.17 (26.33)	30	–6.03 (–22.63, 10.56)	29	.46
Angina frequency	55.86 (27.32)	29	56.33 (23.56)	30	–4.14 (–13.76, 5.48)	29	.39
Treatment satisfaction	66.31 (23.61)	29	66.81 (23.72)	30	–3.09 (–12.62, 6.44)	29	.51
Quality of life	50.29 (21.76)	29	45.56 (19.54)	30	1.72 (–4.80, 8.25)	29	.59
SAQ-7	58.19 (24.43)	29	55.86 (19.85)	30	–0.64 (–6.74, 5.46)	29	.83
Pharmacological stress [b]							
Heart rate (bpm)	97.6 (14.1)	30	104.4 (16.34)	30	–6.8 (–9.8, –3.7)	30	<.001
SBP (mmHg)	126.37 (24.55)	30	128.23 (20.42)	30	–1.87 (–8.68, 4.95)	30	.58
DBP (mmHg)	58.83 (15.00)	30	60.93 (15.47)	30	–2.1 (–7.5, 3.3)	30	.43
Stress RPP	12275.97 (2745.26)	30	13292.47 (2543.46)	30	–1016.5 (–1860.2, –172.8)	30	.02
Global MPRI	2.09 (0.75)	30	2.16 (0.71)	30	–0.08 (–0.43, 0.28)	30	.67
MPRI Subendocardial midventricular	1.9 (0.9)	30	1.9 (0.7)	30	–0.03 (–0.43, 0.36)	30	.86
Diastolic filling							
PFR (mL/s)	322.8 (128.9)	30	321.35 (116.98)	30	1.5 (–27.6, 30.5)	30	.92
tPFR (ms)	171.75 (43.31)	30	158.41 (39.85)	30	13.34 (0.91, 25.76)	30	.04

[a]DBP: diastolic blood pressure; MPRI: myocardial perfusion reserve index; PFR: peak filling rate; RPP: rate pressure product; SAQ: Seattle Angina Questionnaire; SBP: systolic blood pressure; tPFR: time to peak filling rate.

[b]Pharmacologic Stress=adenosine or regadenoson infusion.

Figure 3. Correlation between change in angina and change in mean daily step count (n=29, *P*=.02). Patients who had higher mean step count on ranolazine are above the zero horizontal line and patients with a higher mean step count on placebo are below the zero horizontal line. Patients who had a larger treatment change under ranolazine are on the right of the vertical zero line and the participants who had a larger treatment change under placebo are to the left of the vertical zero line. The estimated regression line in this plot for all patients had an increasing slope (436 steps per 10 unit increase in SAQ-7 change, *P*=.02), also for the subgroup with typical angina (557 steps per 10 unit increase, *P*=.05).



There were no significant differences in baseline variables among patients who experienced a within-subject mean daily step count increase of 500 steps or greater (n=6), a decrease of 500 steps or greater (n=17), or a change of less than 500 steps (n=7). The change in 500 steps was informally based on the distribution of the step count data and a visual median . Increase in SAQ-7 (decrease in angina) from baseline (measured before initiation of treatment randomization and crossover), regardless of treatment, was directly correlated with a within-subject increase in mean daily step count (*r*=.42, *P*=.02) (Figure 2). This was more evident in participants with typical angina (*r*=.57, *P*=.05) compared to no correlation in participants with nontypical angina (*r*=.03, *P*=.92) (Figure 3).

There were no significant correlations for DASI, SF-36, diary-reported angina frequency and nitroglycerin usage, MPRI, and diastolic function with mean daily step count.

Subgroup analysis among the participants with typical angina (n=12) showed within-subject mean daily step count was lower during ranolazine compared to placebo (mean 5522 [SD 2891] vs mean 7150 [SD 3490], *P*=.007, respectively); however, there was no difference in step count among the participants with nontypical angina (n=18, mean 5913 [SD 3265] vs mean 6222 [SD 3376], *P*=.34, respectively). In participants with CFR less than 2.5 (n=9), mean daily step count trended lower during ranolazine treatment than placebo (mean 5298 [SD 1590] vs mean 6414 [SD 2862], *P*=.10, respectively). Further subgroup

secondary measure analyses were not informative (data not shown).

Due to the relatively small sample size of the substudy and potential confounding variables, linear regression models used individual's change in step count as the outcome between ranolazine and placebo and adjusted for various factors that may be associated with it, including age, body mass index, and typical angina versus nontypical angina. The model adjusting for age, body mass index, and typical angina versus nontypical angina did not identify any of these three factors to be significantly associated with change in step count.

When participants were categorized as "sedentary" daily physical activity [31] during the placebo treatment period of the crossover, observed mean daily step count was not significantly different by intervention during treatment with ranolazine compared to during treatment with placebo (mean 2752 [SD 1275] vs mean 2986 [SD 1384], P=.30, respectively); however, among participants whose daily physical activity level during the placebo treatment period of the crossover exceeded the category of "sedentary" daily physical activity [31], within-subject mean daily step count was lower during treatment with ranolazine compared to during treatment with placebo, but this difference was not statistically significant (mean 7259 [SD 2558] vs mean 8397 [SD 2529], P=.06, respectively).

Discussion

We found in this substudy that late sodium channel inhibition was associated with a decreased step count overall during daily life in these participants, although the subgroup with angina improvement had a step count increase. This suggests that digital wearable device technology may be useful as a clinical variable and outcome in clinical trials research.

These substudy results are consistent with primary findings of the parent trial (eg, late sodium current blockade with ranolazine did not improve overall group angina in participants with CMD). Surprisingly, we observed a significantly lower mean daily step count during late sodium current blockade compared to placebo in our substudy. This finding is new and differs from the previous studies of ranolazine in CMD [28,29,17,30], although previously one clinical trial utilized a wearable accelerometer and demonstrated that treatment of heart failure with preserved ejection fraction with nitrates was associated with decreased daily activity [42]. Although our findings may offer potential insight for identification of patient subgroups who may benefit from antianginal therapies, these results must be considered exploratory given the small sample size of our substudy and do not modify existing clinical practice.

A variety of explanations may have contributed to the finding of reduced step count. The result could be a chance finding; however, it was present in the overall and subgroup analyses. It is possible that in CMD patients, those who are more active may have become less active due to unreported ranolazine side effects (ie, dizziness or gastrointestinal intolerance). In fact, two of the three reported side effects occurred during treatment with ranolazine. It is also possible that the digital wearable device was unable to detect the various types of daily activities participants may have performed, such as swimming or bicycling versus walking, or changes in daily activity intensity. Additionally, our results failed to detect a relationship between change in SAQ angina or QoL and change in step count, although our substudy was underpowered to evaluate this.

The unique attributes of our population and description of their daily activity should be noted. Women comprised 97% of our population, precluding conclusions regarding response in men, who typically are more represented in pivotal chronic angina trials with ranolazine (75%) and suffered from obstructive CAD [23,24,43]. To our knowledge, this report is the first time that levels of daily activity determined by a digital wearable device have been described in a CMD population.

Strengths

The strengths of our substudy include the crossover design, which allowed participants to serve as his or her own control thus negating the effects of daily activity intersubject variability and reducing confounding effects of other antianginal therapies. Participant compliance with study medication is also a notable strength of our substudy.

Limitations

The limitations of our substudy include a small sample size and a mean "low active" [31] cohort of participants. Although it is understandable that highly symptomatic angina patients limit their activity, this may make it more difficult to detect changes in activity. The SAQ has not been validated in CMD patients. Further, the 2-week active intervention duration may have minimized the measurable effect of late sodium channel inhibition (ranolazine) in the second week of monitoring, but this duration has been documented successfully in pivotal and dose-finding trials with ranolazine [23,44]. In addition, although participants verbally reported to research coordinators that they wore the device during the entire monitoring period as instructed per protocol, we did not monitor usage objectively; given randomization, we assumed that it was worn similarly in both groups. Finally, self-reported physical activity data was not collected to compare to data generated by the digital wearable device.

Future Directions

Digital wearable devices have the potential for an expanded role in research as a clinical trial outcome and should be explored in a variety of health conditions.

Conclusions

We report one of the first studies to use digital wearable device-determined step count as an outcome variable in a placebo-controlled crossover trial of late sodium channel inhibition in patients with CMD. Our substudy demonstrates that late sodium channel inhibition was associated with a decreased step count overall, although the subgroup with angina improvement had a step count increase. Our findings suggest digital wearable device technology may provide new insights in clinical trial research.

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Conflicts of Interest

CLS, PKM, LEJT, and CNBM received an investigator-initiated research grant from Gilead, the manufacturer of Ranexa (ranolazine), to support the clinical trial.

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Abbreviations

CAD: coronary artery disease
CFR: coronary flow reserve
CMD: coronary microvascular dysfunction
DASI: Duke Activity Status Index
ECG: electrocardiogram
MPRI: myocardial perfusion reserve index
MRI: magnetic resonance imaging
NHLBI: National Heart, Lung, and Blood Institute
PFR: peak filling rate
QoL: quality of life
SAQ: Seattle Angina Questionnaire
tPFR: time to peak filling rate
WISE: Women's Ischemia Syndrome Evaluation

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Protocol

The Second-Look Procedure for Transoral Videolaryngoscopic Surgery for T1 and T2 Laryngeal, Oropharyngeal, and Hypopharyngeal Cancer Patients: Protocol for a Nonrandomized Clinical Trial

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Abstract

Background: Transoral videolaryngoscopic surgery (TOVS) has been widely applied for early T stage head and neck cancer. The resection is performed with a minimum safety margin for function preservation under a limited surgical field of view, making it difficult to be certain of complete resection.

Objective: Our aim is the evaluation of the completeness of resection by initial TOVS resection, and the possibility of primary control by TOVS alone, allowing for repeat procedures for function preserving treatment in early T stage laryngeal, oropharyngeal, and hypopharyngeal cancer patients.

Methods: Patients are treated by TOVS for the primary site with or without neck dissection. Patients are divided in two groups based on the results of the pathological evaluation of the surgical specimen; the control group in which the resection is considered to be complete, and the intervention (second-look procedure) group in which incomplete tumor resection is suspected. The predictive factors for the possibility of complete resection by TOVS will then be analyzed.

Results: Patient enrollment started on January 1, 2014, and closed on March 31, 2016, with 54 patients. The control group consists of 27 patients, the intervention group is 21 patients, and 6 patients were excluded. There were no clinical differences between the control and intervention groups. The observation period will end on December 31, 2018.

Conclusions: TOVS has potential for both definitive resection and function preservation with minimal invasiveness. Identifying the limitations of TOVS is beneficial to ensure accurate treatment selection in early T stage head and neck cancer patients.

Trial Registration: UMIN Clinical Trials Registry: UMIN000012485; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000014472 (Archived by WebCite at http://www.webcitation.org/6v1b741Iw)

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KEYWORDS

early T stage head and neck cancer; transoral surgery; second-look procedure

Introduction

The treatment of head and neck cancer demands attention be paid both to definitive curability and function preservation, for example, phonation and deglutition. Although most head and neck cancer patients indicate advanced stage at the first visit, the number of early T stage patients has been increasing because of the development of diagnostic instruments, such as positron emission tomography-computed tomography (PET-CT) [1] and narrow band imaging (NBI) endoscopy [2], as well as greater awareness of head and neck cancer among doctors in other fields [3]. With the development of surgical support instruments, there have been many innovations in minimally invasive surgery for the treatment of head and neck cancer, especially with regard to definitive surgery for early T stage patients [4-8]. The local or regional recurrence rates are 13.4% [9] for transoral surgery (TOS) and 24.7% [10] for (chemo)radiotherapy in early T stage laryngeal cancer, 14.4% [11] and 22.8% [12] in oropharyngeal cancer, and 25.4% [13] and 30.2% [14] in hypopharyngeal cancer, respectively. Although these data are from a single institutional retrospective study, TOS has been considered to provide equivalent outcomes to conventional (chemo)radiotherapy or open surgery (eg, total or partial laryngectomy, pharyngectomy [4,6,15,16]). In our department, transoral videolaryngoscopic surgery (TOVS) [6] has been applied to T1 and T2 laryngeal, oropharyngeal, and hypopharyngeal cancer as a local surgery with or without neck dissection. We believe that one of the main problems associated with TOVS is the issue of completeness of resection due to the limited field of view and lack of maneuverability, as well as the minimum safety margin required for maximum function preservation. In this study, we sought to identify the completeness or limitation of TOVS through the application of the second-look procedure in cases of suspected incomplete tumor resection.

Methods

Study Setting

This parallel two-arm open-label nonrandomized trial is taking place at a single institute (ie, an academic hospital).

Endpoints

The primary endpoints are the evaluation of the completeness of resection by the initial TOVS resection, and the possibility of primary control by TOVS alone, allowing for repeat procedures of salvage surgery in cases of suspected incomplete tumor resection at the initial TOVS. The secondary endpoints are overall survival, disease free survival, and function preserving survival.

Eligibility Criteria

Head and neck cancer is classified according to the 7thedition of the TNM classification [17]. Clinical T1 and T2 stage laryngeal, oropharyngeal, and hypopharyngeal carcinoma patients are enrolled.

Inclusion Criteria

Prior to enrollment in this trial, the patients must meet all of the following criteria: pathologically proven carcinoma; primary tumor located in the larynx, oropharynx, or hypopharynx; cT1 and cT2 tumor on visual and endoscopic examinations and imaging examinations (eg, CT and/or magnetic resonance imaging [MRI]); cN stage evaluated by ultrasonic echo [US] and/or PET-CT); primary site assessed as resectable by TOVS and regional lymph node by neck dissection on CT, MRI, and/or US; no distant metastasis on PET-CT (cM0); no prior treatment for any head and neck cancers; aged over 20 years old (regarded as a legal adult in Japan); performance status 0-2 on Eastern Cooperative Oncology Group (ECOG) criteria; sufficient general condition for the operation under general anesthesia; and provision of written informed consent.

Exclusion Criteria

Prior to enrollment in this trial, the patients must not have incurable synchronous malignancies, priority systemic diseases, nor refuse to undergo the second-look procedure.

Patients who had treatment history in the head and neck are excluded because of the possibility of scar formation that can influence submucosal resection by TOVS. The patients who had previous malignancy are included in case these diseases have been cured or well controlled (maintaining complete response condition).

Enrollment

Patient enrollment started on January 1, 2014, for a scheduled period of 2 years. Ethics approval for the study was obtained from Yokohama City University Institutional Review Board (#B131107003). Written informed consent was obtained from the participants in the study and for publication of their data.

Treatment Methods

Surgery

Primary resection is performed using the TOVS technique. The mucosal lesion is confirmed by NBI endoscope and Lugol's solution dyeing. The horizontal safety margin is set at 1-3 mm from the border of the lesion. The vertical resection is performed in the submucosal layer. After resection, rapid pathological margin examination is undertaken for the horizontal and vertical sections. In cases with positive margins as assessed by rapid pathological examination, additional resection is performed until a negative margin is confirmed. The resected specimen is stretched on a cork board to clarify directions and fixed with formalin for permanent pathological diagnosis. The wound is covered with a polyglycolic acid sheet for oropharyngeal and hypopharyngeal cancer patients. In node positive patients, neck dissection is performed at the same time.

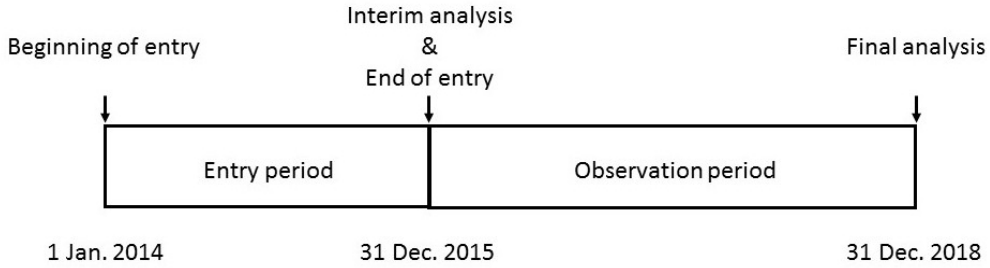
Control Arm

The patients in whom the resection is assessed as complete with negative margins by both rapid and permanent pathological examinations receive no additional therapy for local control.

Intervention (Second-Look Procedure) Arm

The patients in whom complete resection is not unexpectedly confirmed by permanent pathological examination (ie, the presence of positive or close margins) are entered into the intervention arm. Approximately 2-3 months after the first TOVS operation, the second-look procedure (re-TOVS) is performed for these patients.

Figure 1. Study schedule.



The period between first and second TOVS are set as wound repair time for precise observation at the second-look TOVS, and close follow-up is applied during the period for these patients. During the second-look procedure, precise observation by high-vision endoscope, pathological examination from the resected primary site, and additional resection for the tumor remnant are performed.

In cases where the additional resection cannot be completed using the TOVS technique, open surgery and/or (chemo)radiotherapy are administered as alternative definitive therapy.

Follow-Up

All patients are followed up for at least 5 years after patient accrual has been completed. Visual and endoscopic observations of the primary site are performed every month for the first and second years, and every 2-3 months from the third to fifth years. Enhanced cervical CT and/or US for the primary site and regional lymph nodes is performed every 3-6 months for the first and second years, and every 6-12 months from the third to fifth years. PET-CT is performed every year for the first and second years, and enhanced whole body CT is performed every year from the third to fifth years for the evaluation of distant metastasis.

Scheduled Analysis

Target sample size is set at 40-60 patients, based on the average patient number (20-30 patients per year) in our institution and the entry period of 2 years. We plan an interim analysis at the end of the entry period. If the number of patients enrolled has reached the target number at the time of the interim analysis, enrollment will cease. If not, enrollment will be extended until at least 40 patients are enrolled. The final analysis is to be performed 5 years after the first entry. The expected schedule is shown in Figure 1.

Statistical Analysis

For univariate and multivariate comparisons, Fisher's exact test and a Cox proportional hazards model are used, respectively. The outcome variables are completeness of the first TOVS resection, the possibility of local control by TOVS, and survival. The predictive variables are clinical characteristics (ie, age, sex, primary site, primary subsite, TN stage, tumor shape, enhanced CT observation), pathological characteristics (ie, histological type, differentiation, margin study, lymphatic invasion, vascular invasion, nerve invasion), and others (eg, tumor location in glottic cancer and human papilloma virus infection in oropharyngeal cancer). These predictive variables emerge after the initial TOVS. We therefore expect them to be factors predicting outcome.

Results

Trial Status

UMIN Clinical Trials Registry (UMIN000012485) was completed December 14, 2013. Patient enrollment started January 1, 2014, and enrollment closed March 31, 2016, with 54 patients. The observation period will end December 31, 2018.

Patient Characteristics

Patient enrollment began January 1, 2014, and closed March 31, 2016, with 54 patients (Table 1). We placed 27 patients into the control group and 21 patients into the intervention group. Six patients were excluded based on the following: 2 patients had past treatment history in the head and neck, 2 patients had incurable synchronous malignancies, and 2 patients rejected the second-look procedure.

Table 1. Patient characteristics.

	Control group (n=27)	Intervention group (n=21)
Age in years, range (median)	48-85 (67)	55-84 (71)
Sex, n		
Male	25	18
Female	2	3
Primary site, n		
Larynx	9	5
Oropharynx	10	4
Hypopharynx	8	12
TN stage, n		
T		
Tis	4	0
T1	12	7
T2	11	14
N		
N0	22	21
N1	1	0
N2	4	0
N3	0	0
Pathology, n		
Squamous cell carcinoma	26	21
Spindle cell carcinoma	1	0

Discussion

Principal Findings

TOS is considered to be a definitive therapy, comparable to radiotherapy or open surgery, for early T stage laryngeal, oropharyngeal, and hypopharyngeal cancer consistent with organ and function preservation. In the case of early T stage with node-positive patients, TOS is performed with neck dissection. TOS includes TOVS [6,8,16,17], transoral LASER microsurgery (TLM) [9,13,15], transoral robotic surgery (TORS) [4], and endoscopic laryngo-pharyngeal surgery (ELPS) [5,7]. There are advantages and disadvantages associated with all these surgical procedures. Endoscope-assisted surgery (eg, TOVS, TORS, and ELPS) affords precise views that help resection be completed with minimal invasiveness [4-8,16,17]. Straight operation field surgery (eg, TOVS and TLM) provides easy maneuverability in a similar manner to laryngo-microsurgery techniques [6,8,9,13,15-17], while TORS allows a better view and more accurate procedure, especially when working in less accessible areas [4]. Among these techniques, we mainly choose TOVS, as our priorities are precise endoscopic observation and easy access to the target region [6,8,16,17]. On the other hand, one of the common drawbacks to these techniques is the limited view and working field [4-9,13,15-17].

TOVS aspires to definitive resection with minimum safety margins that may contribute to organ and function preservation. However, such an approach increases the risk of remnant tumor. As complete resection is confirmed by pathological evaluation, the actual decision is difficult because the surgical margin is kept to a minimum and the specimen tends to shrink during electrical coagulation and formalin fixation. The can lead to difficulties in identifying positive or close margins. Salvage treatment for remnant and recurrent tumors at the primary site differs by institution. The salvage treatment is selected among a number of options including re-TOS, radical dissection (eg, total or partial laryngectomy and pharyngectomy), and (chemo)radiotherapy, depending on the recurrence status [7,9,18,19]. Radical dissection is considered as the most reliable and effective treatment method, but results in some loss of function (eg, aphonia, dysarthria, and dysphagia). Although (chemo)radiotherapy can preserve the organs, sensory torpor and/or radiation scars cause functional disorders (eg, hoarseness and dysphagia [20,21]). Moreover, radical dissection after (chemo)radiotherapy failure indicates a high incidence of postoperative complications [22]. Taken together, the drawbacks associated with radical dissection and/or (chemo)radiotherapy and the concept of function preservation that underpins TOS lead us to select re-TOVS as our first choice in salvage treatment.

Limitations

There potential limitations to our study. Research is taking place at only a single institute, and recruited numbers are low. This small sample size may affect the generalizability of results.

Conclusions

Early detection of remnant and recurrent tumors is necessary when considering re-TOVS. Recurrence after complete resection is stochastic, and it is considered impossible to absolutely prevent such recurrence. However, we think that second-look TOVS can allow disease control by use of the TOVS technique with function preservation. We hypothesize that one of the causes of remnant tumor is the limited observation and resection that follows from restricted field of view and maneuverability. Second-look TOVS is adapted for high-risk patients with remnant tumor, and precise observation and/or biopsy for confirmation of a pathological negative status is performed for any actual cases of no remnant tumor. Additional resection is performed for truly remnant cases. We hope to identify the predictive factors for complete or incomplete resection by TOVS.

Conflicts of Interest

None declared.

Authors' Contributions

GN and NO collectively drafted the study protocol and ethical approval. GN participated in the central monitoring of data collection, trial management, and data analysis. DS, KY, YA, YC, and TT participated in patient diagnosis, treatment, and follow-up. NO, who is the principal investigator of this study, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read the manuscript draft critically to make contributions, and all authors read and approved the final manuscript.

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Abbreviations

ECOG: Eastern Cooperative Oncology Group
ELPS: endoscopic laryngo-pharyngeal surgery
MRI: magnetic resonance imaging
NBI: narrow band imaging
PET-CT: positron emission tomography-computed tomography
TLM: transoral laser microsurgery
TORS: transoral robotic surgery
TOS: transoral surgery
TOVS: transoral videolaryngoscopic surgery
US: ultrasonic echo

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Original Paper

The National Patient-Centered Clinical Research Network (PCORnet) Bariatric Study Cohort: Rationale, Methods, and Baseline Characteristics

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Abstract

Background: Although bariatric procedures are commonly performed in clinical practice, long-term data on the comparative effectiveness and safety of different procedures on sustained weight loss, comorbidities, and adverse effects are limited, especially in important patient subgroups (eg, individuals with diabetes, older patients, adolescents, and minority patients).

Objective: The objective of this study was to create a population-based cohort of patients who underwent 3 commonly performed bariatric procedures—adjustable gastric band (AGB), Roux-en-Y gastric bypass (RYGB), and sleeve gastrectomy (SG)—to examine the long-term comparative effectiveness and safety of these procedures in both adults and adolescents.

Methods: We identified adults (20 to 79 years old) and adolescents (12 to 19 years old) who underwent a primary (first observed) AGB, RYGB, or SG procedure between January 1, 2005 and September 30, 2015 from 42 health systems participating in the Clinical Data Research Networks within the National Patient-Centered Clinical Research Network (PCORnet). We extracted information on patient demographics, encounters with healthcare providers, diagnoses recorded and procedures performed during these encounters, vital signs, and laboratory test results from patients' electronic health records (EHRs). The outcomes of interest

included weight change, incidence of major surgery-related adverse events, and diabetes remission and relapse, collected for up to 10 years after the initial bariatric procedure.

Results: A total of 65,093 adults and 777 adolescents met the eligibility criteria of the study. The adult subcohort had a mean age of 45 years and was predominantly female (79.30%, 51,619/65,093). Among adult patients with non-missing race or ethnicity information, 72.08% (41,248/57,227) were White, 21.13% (12,094/57,227) were Black, and 20.58% (13,094/63,637) were Hispanic. The average highest body mass index (BMI) recorded in the year prior to surgery was 49 kg/m^2. RYGB was the most common bariatric procedure among adults (49.48%, 32,208/65,093), followed by SG (45.62%, 29,693/65,093) and AGB (4.90%, 3192/65,093). The mean age of the adolescent subcohort was 17 years and 77.5% (602/777) were female. Among adolescent patients with known race or ethnicity information, 67.3% (473/703) were White, 22.6% (159/703) were Black, and 18.0% (124/689) were Hispanic. The average highest recorded BMI in the year preceding surgery was 53 kg/m^2. The majority of the adolescent patients received SG (60.4%, 469/777), followed by RYGB (30.8%, 239/777) and AGB (8.9%, 69/777). A BMI measurement (proxy for follow-up) was available in 84.31% (44,978/53,351), 68.09% (20,783/30,521), and 68.56% (7159/10,442) of the eligible adult patients at 1, 3, and 5 years of follow-up, respectively. The corresponding proportion was 82.0% (524/639), 49.9% (174/349), and 38.8% (47/121) in the adolescent subcohort.

Conclusions: Our study cohort is one of the largest cohorts of patients with bariatric procedures in the United States. Patients are geographically and demographically diverse, which improves the generalizability of the research findings and allows examination of treatment effect heterogeneity. Ongoing and planned investigations will provide real-world evidence on the long-term benefits and risks of these most commonly used bariatric procedures in current clinical practice.

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KEYWORDS

obesity; bariatric surgery; comparative effectiveness; real-world evidence; weight loss

Introduction

As severe obesity has increased in prevalence, the use of bariatric surgery has expanded considerably over the past 20 years. Because of this expansion and the rapid shifts in the types of bariatric procedures performed in recent years—from predominantly Roux-en-Y gastric bypass (RYGB) in the early 2000's, shifting towards greater use of adjustable gastric banding (AGB) by early 2010's, and then to predominantly sleeve gastrectomy (SG) currently [1-3]—long-term data comparing the effectiveness and safety of different procedures on sustained weight loss, comorbidities, and adverse effects are limited. In addition, prior studies have included insufficient numbers of patients to examine differential outcomes within important patient subgroups. More data are needed in larger, more broadly representative samples with long-term follow-up to help inform clinical decisions about bariatric procedure selection in various patient sub-populations (eg, individuals with diabetes, older patients, adolescents, and minority patients).

In 2014, the Patient-Centered Outcomes Research Institute (PCORI) launched the National Patient-Centered Clinical Research Network (PCORnet) to support studies that address questions important to patients [4]. PCORnet is a distributed data network that includes 13 Clinical Data Research Networks (CDRNs) and 20 Patient-Powered Research Networks, making it one of the largest research consortia in the United States. It currently includes electronic health record (EHR) or administrative claims data from more than 100 million individuals and has access to over 40 million patients who could be recruited into pragmatic clinical trials. PCORnet data is stored at individual participating sites in a common data format [5].

Initiated in 2016, the PCORnet Bariatric Study (PBS) is one of the first 2 multi-CDRN observational studies conducted within the network [6]. A group of patients, clinicians, and researchers developed the study aims [7]. The cohort was set up with 2 major goals. The first was to evaluate the comparative effectiveness and safety of AGB, RYGB, and SG, the 3 most commonly performed bariatric procedures in contemporary clinical practice. The second goal was to demonstrate PCORnet's potential as a national resource for evidence generation. Here, we describe the design and early descriptive results of the study.

Methods

Data Sources

A total of 42 health systems from 11 CDRNs participated in this descriptive study (Textbox 1). Of the 2 non-participating CDRNs, 1 outpatient-focused network deferred due to insufficient number of bariatric patients and the other network was not yet founded at the time that the PBS was proposed. The participating health systems are geographically diverse and provide care to demographically heterogeneous populations.

As part of its efforts to facilitate rapid and efficient studies drawing from multiple data sources, PCORnet standardized the EHR data from the participating health systems by implementing a common data model (CDM). Table 1 describes the specific data domains extracted from the EHRs. These domains include patient demographics, encounters with healthcare providers, diagnoses recorded and procedures performed during these encounters, vital signs, laboratory test results, and mortality (obtained from other sources in some CDRNs).

Textbox 1. Eleven participating PCORnet Clinical Data Research Networks and data-contributing sites in the PCORnet Bariatric Study. Johns Hopkins University and Health System, UPMC Health Plan, and Boston HealthNet did not contribute data for this paper but will for future analyses.

Clinical Data Research Network (CDRN) and the corresponding data-contributing sites

- Chicago Area Patient-Centered Outcomes Research Network (CAPriCORN)
  - Loyola Medicine
  - Northwestern Medicine
  - University of Chicago Medical Center
  - University of Illinois Hospital & Health Science System
- Greater Plains Collaborative (GPC)
  - Marshfield Clinic
  - University of Texas Southwestern Medical Center
  - University of Iowa Healthcare
  - University of Kansas Medical Center
  - University of Wisconsin - Madison
  - University of Nebraska Medical Center
- Kaiser Permanente & Strategic Partners Patient Outcomes Research To Advance Learning (PORTAL)
  - Kaiser Permanente Washington Health Research Institute (formerly Group Health Research Institute)
  - HealthPartners Research Foundation
  - Kaiser Permanente Colorado
  - Kaiser Permanente Mid-Atlantic
  - Kaiser Permanente Northwest
  - Kaiser Permanente Southern California
- Mid-South
  - Greenway
  - University of North Carolina
  - Vanderbilt University Medical Center
- New York City Clinical Data Research Network (NYC-CDRN)
  - Mount Sinai
  - New York University
  - Weill Cornell
  - Montefiore/Einstein
- OneFlorida Clinical Research Consortium
  - University of Florida Health
  - Orlando Health
  - Tallahassee Memorial Health System
- PaTH Towards a Learning Health System Clinical Data Research Network (PaTH)
  - Geisinger Health System
  - Johns Hopkins University and Health System
  - Penn State College of Medicine, Penn State Milton S. Hershey Medical Center
  - Temple Health System, Lewis Katz School of Medicine at Temple University
  - University of Pittsburgh and University of Pittsburg Medical Center (UPMC)
  - UPMC Health Plan

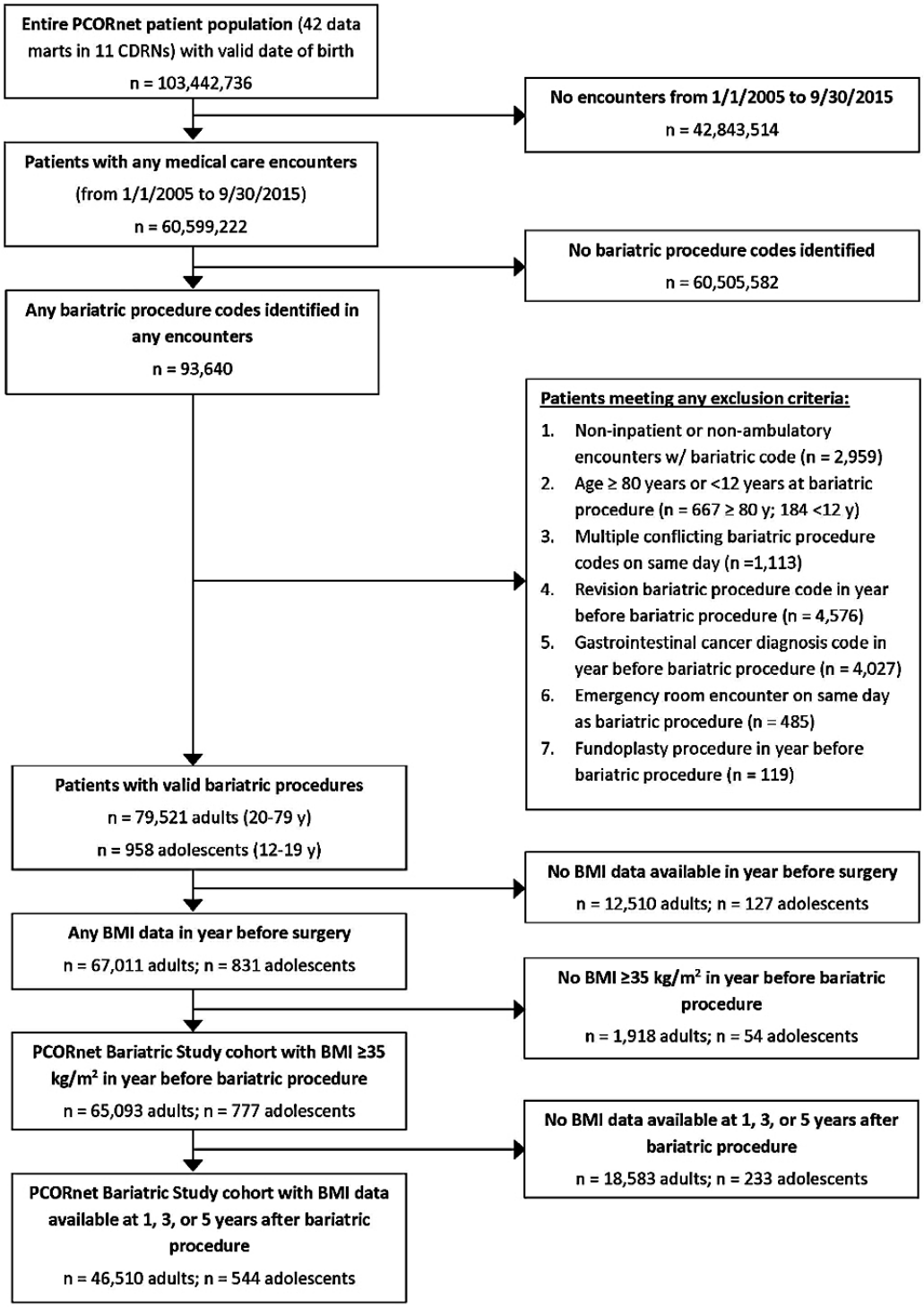
- University of Utah and University of Utah Health Care
- A Pediatric Learning Health System (PEDSnet)
  - Cincinnati Children's Hospital Medical Center
  - Nemours
  - Nationwide Children's Hospital
- Patient-Centered SCAlable National Network for Effectiveness Research (pSCANNER)
  - University of California Irvine
  - University of California Los Angeles
- Research Action for Health Network (REACHnet)
  - Baylor Scott & White Health
  - Ochsner Health System
  - Tulane University
- Scalable Collaborative Infrastructure for a Learning Healthcare System (SCILHS)
  - Beth Israel Deaconess Medical Center
  - Boston HealthNet
  - Partners Health
  - Wake Forest Baptist Hospital

Table 1. Data elements collected by the PCORnet Bariatric Study from the PCORnet common data model.

Domain	Description	Applicability for PCORnet Bariatric Study
Demographic	Contains 1 record per patient with key demographic variables.	Age at surgery, sex, race, and Hispanic ethnicity are captured.
Encounter	Contains 1 record for each time a patient sees a provider in ambulatory setting or is hospitalized; multiple encounters per day are possible if they occur with different providers or in different care settings.	Encounter type are used to identify initial bariatric procedures and all subsequent complications and procedures during the follow-up period. We have captured data from all encounter types including inpatient, outpatient, and emergency room visits.
Diagnosis	Contains all uniquely recorded diagnoses for all encounters. Each diagnosis is associated with a specific patient and encounter.	Diagnosis codes and associated encounter dates are used to establish medical history prior to surgery[a].
Procedure	Contains all uniquely recorded procedures for all encounters. Each procedure is associated with a specific patient and encounter.	Procedure codes and associated encounter dates are used to establish bariatric surgery dates and any re-operations, revisions, or operative complications.
Vitals	Contains 1 record per height or weight result. Multiple measurements per encounter are recorded as separate measures.	Height and weight are captured for body mass index; blood pressure and tobacco use information is also available.
Lab Results	Contains 1 record per laboratory result.	The common data model currently contains a limited number of laboratory tests; glycated hemoglobin (HbA1c) is being collected and is required to identify diabetes outcomes in an ongoing analysis.
Death	Contains 1 record per patient for those who died.	Some health systems have existing linkages to state and national death indices; others will be funded to conduct linkages.

[a]We focused on extracting data on obesity-associated comorbidities and health conditions used to calculate the Charlson-Elixhauser combined comorbidity score.

Figure 1. Flow diagram for identification of the PCORnet Bariatric Study cohort in 11 Clinical Data Research Network (CDRNs). BMI: body mass index.



Cohort Identification

We identified adults (20 to 79 years old) and adolescents (12 to 19 years old) who underwent a primary (first observed) AGB, RYGB, or SG procedure between January 1, 2005 and September 30, 2015 in any of the 42 participating health systems. To be eligible for cohort inclusion, patients must have (1) at least 1 body mass index (BMI) measurement of 35 kg/m^2 or more recorded in their EHRs in the year prior to the surgery (ie, baseline); (2) no prior revision bariatric procedure code during baseline; (3) no recorded gastrointestinal cancer diagnosis or fundoplasty procedure during baseline; (4) no multiple conflicting bariatric procedure codes on the same day; and (5) no emergency room encounter on the day of the index procedure (Figure 1). We excluded patients with missing baseline BMI, insufficient height or weight data to calculate baseline BMI, or baseline BMI less than 35 kg/m^2 because guidelines recommend consideration of bariatric surgery for adult patients with severe obesity (BMI 40 kg/m^2 or greater) or BMI 35 kg/m^2 or greater plus comorbidity [8]. We identified bariatric procedures using

the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes, Current Procedure Terminology codes (CPT-4), and Healthcare Common Procedure Coding System (HCPCS) codes (list available from authors by request). There were relatively few additional eligibility criteria (Figure 1) in order to maximize the representativeness of the cohort.

We extracted information on patient demographics (eg, age, sex, race/ethnicity), height, weight, BMI, blood pressure, and select comorbidities (eg, diabetes, sleep apnea) from the standardized data domains described in Table 1. Comorbidities were identified by ICD-9-CM diagnosis and procedure codes and the Systematized Nomenclature of Medicine (SNOMED) codes. We also calculated a combined comorbidity score that merges the Charlson and Elixhauser comorbidity scores [9]. The score, calculated based on 20 conditions identified by ICD-9-CM and SNOMED codes in the year prior to surgery, was initially developed to predict mortality. It has been shown to be a good proxy for general health status and has been used in prior analysis of bariatric patients [10].

Follow-Up

Patients were followed as part of routine clinical care in each participating health system. We used BMI measurements after the index bariatric procedure as a proxy for follow-up. Because the United States transitioned from the ICD-9-CM coding system to the ICD-10-CM system on October 1, 2015, we ended follow-up on September 30, 2015 to avoid changes related to coding of diagnoses and procedures.

Analysis

The baseline characteristics of the study cohort were compared by procedure type. The temporal trends in bariatric procedures during the study period were also assessed. Within the study cohort, the characteristics of patients with and without a BMI measurement during follow-up were further compared. We also examined the length of follow-up by procedure type. Finally, we compared the study cohort with patients who were excluded from the study due to missing baseline BMI measurement. We performed all the comparisons separately for the adult and adolescent subcohorts.

Stakeholder Engagement

In addition to the extensive clinical data and research infrastructure necessary to collect the data for the study, a unique aspect of the PCORnet Bariatric Study is the engagement of a broad range of stakeholders. As part of our initial work to formulate the proposal, we identified 4 key stakeholder groups that would be critical to the success of our project: patients and caregivers, healthcare providers, healthcare system or organizational leaders, and community and advocacy groups. Each participating network was asked to engage a stakeholder as part of their research team and representatives from each of these groups formed an Executive Stakeholder Advisory Board and advised the scientific investigators on all aspects of the conduct of the study.

Results

Baseline Characteristics of the Study Cohort

Adult Subcohort

There were 65,093 adult bariatric patients in the PBS cohort, more than 10 times the size of the well-established Longitudinal Assessment of Bariatric Surgery study cohort [11]. These adult patients had a mean age of 45 years and were predominantly female (79.30%, 51,619/65,093) (Table 2). Among patients with non-missing race or ethnicity information, 72.08% (41,248/57,227) were White, 21.13% (12,094/57,227) were Black, and 20.58% (13,094/63,637) had an ethnicity of Hispanic recorded in their EHRs. The mean maximum BMI at baseline was 49 kg/m^2, with 37.26% (24,255/65,093) having a BMI measurement of 50 kg/m^2 or more. More than half of the patients (58.83%, 38,297/65,093) had a hypertension diagnosis in their EHRs. Other common conditions recorded in the EHR included sleep apnea (48.83%, 31,785/65,093), dyslipidemia (46.67%, 30,377/65,093), gastroesophageal reflux disease (GERD) (40.94%, 26,650/65,093), diabetes (35.97%, 23,411/65,093), depression (29.69%, 19,324/65,093), anxiety (20.98%, 13,657/65,093), and non-alcoholic fatty liver disease (NAFLD) (20.42%, 13,293/65,093).

RYGB was the most common bariatric procedure in this subcohort (49.48%, 32,208/65,093), followed by SG (45.62%, 29,693/65,093) and AGB (4.90%, 3192/65,093) (Table 2). The SG patients appeared to be slightly younger at the time of surgery while the AGB patients had a lower mean maximum baseline BMI. The frequency of numerous comorbidities differed by procedure type, with RYGB patients typically showing higher prevalence of pre-operative comorbidity than patients with other procedure types. There was racial and ethnic variation in the type of procedures received—the proportion of Black patients ranged from 15.65% (4515/28,845) in the RYGB group to 27.05% (6894/25,485) in the SG group, and the proportion of Hispanic patients ranged from 11.53% (352/3,054) in the AGB group to 24.58% (7144/29,059) in the RYGB group.

Table 2. Baseline[a] characteristics of adult patients aged 20-79 years in the PCORnet Bariatric Study cohort (N=65,093).

Characteristic	AGB[b]	RYGB[c]	SG[d]	All
Number, (%)	3192 (100.00)	32,208 (100.00)	29,693 (100.00)	65,093 (100.00)
Age at surgery, mean (SD)	45.7 (12.35)	45.5 (11.63)	44.3 (11.72)	45.0 (11.72)
Age category, n (%)				
20-44 years	1509 (47.27)	15,146 (47.03)	15,481 (52.14)	32,136 (49.37)
45-64 years	1460 (45.74)	15,357 (47.68)	12,805 (43.12)	29,622 (45.51)
65-79 years	223 (6.99)	1705 (5.29)	1407 (4.74)	3335 (5.12)
Female, n (%)	2524 (79.07)	25,679 (79.73)	23,416 (78.86)	51,619 (79.30)
Baseline maximum BMI, mean (SD)	46.1 (6.80)	49.5 (8.23)	48.8 (8.29)	49.0 (8.23)
Baseline maximum BMI category, n (%)				
35-39 kg/m^2	547 (17.14)	2566 (7.97)	2715 (9.14)	5828 (8.95)
40-49 kg/m^2	1897 (59.43)	16,740 (51.97)	16,373 (55.14)	35,010 (53.78)
50-59 kg/m^2	623 (19.52)	9435 (29.29)	7641 (25.73)	17,699 (27.19)
≥60 kg/m^2	125 (3.92)	3467 (10.76)	2964 (9.98)	6556 (10.07)
Year of surgery, n (%)				
2005-2009	572 (17.92)	4519 (14.03)	481 (1.62)	5572 (8.56)
2010	719 (22.53)	4407 (13.68)	1368 (4.61)	6494 (9.98)
2011	785 (24.59)	5735 (17.81)	3772 (12.70)	10,292 (15.81)
2012	591 (18.52)	5364 (16.65)	4930 (16.60)	10,885 (16.72)
2013	300 (9.40)	4703 (14.60)	6118 (20.60)	11,121 (17.08)
2014	175 (5.48)	4414 (13.70)	7394 (24.90)	11,983 (18.41)
2015	50 (1.57)	3066 (9.52)	5630 (18.96)	8746 (13.44)
Hispanic[f], n (%)	352 (11.53)	5598 (17.76)	7144 (24.58)	13,094 (20.58)
Race category[f], n (%)				
American Indian or Alaska Native	13 (0.45)	186 (0.64)	155 (0.61)	354 (0.62)
Asian	15 (0.52)	225 (0.78)	300 (1.18)	540 (0.94)
Black or African American	685 (23.65)	4515 (15.65)	6894 (27.05)	12,094 (21.13)
Native Hawaiian or Other Pacific Islander	2 (0.07)	98 (0.34)	88 (0.35)	188 (0.33)
White	2031 (70.11)	22,628 (78.45)	16,589 (65.09)	41,248 (72.08)
Multiple race	43 (1.48)	438 (1.52)	321 (1.26)	802 (1.40)
Other	108 (3.73)	755 (2.62)	1138 (4.47)	2001 (3.50)
Missing race, n (%)	295 (9.24)	3363 (10.44)	4208 (14.17)	7866 (12.08)
Systolic BP[g], mean (SD)	128.1 (16.46)	131.0 (18.54)	131.6 (17.26)	131.1 (17.89)
Diastolic BP, mean (SD)	76.7 (11.24)	76.0 (12.43)	75.4 (11.75)	75.8 (12.08)
Missing BP, n (%)	240 (7.52)	1930 (5.99)	1836 (6.18)	4006 (6.15)
Combined comorbidity score[h], n (%)				
<0	1022 (32.02)	10,310 (32.01)	8911 (30.01)	20,243 (31.10)
0	1805 (56.55)	16,672 (51.76)	16,675 (56.16)	35,152 (54.00)
>0	365 (11.43)	5226 (16.23)	4107 (13.83)	9698 (14.90)
No. of hospital days in year before surgery, mean (SD)	0.30 (2.22)	0.46 (4.61)	0.47 (4.28)	0.46 (4.37)
Health conditions[i], n (%)				

Characteristic	AGB[b]	RYGB[c]	SG[d]	All
Anxiety	557 (17.45)	7105 (22.06)	5995 (20.19)	13,657 (20.98)
Depression	799 (25.03)	10,451 (32.45)	8074 (27.19)	19,324 (29.69)
Diabetes	942 (29.51)	13,845 (42.99)	8624 (29.04)	23,411 (35.97)
DVT[j]	20 (0.63)	220 (0.68)	214 (0.72)	454 (0.70)
Dyslipidemia	1373 (43.01)	16,251 (50.46)	12,753 (42.95)	30,377 (46.67)
Eating disorder	158 (4.95)	4441 (13.79)	1722 (5.80)	6321 (9.71)
GERD[k]	1171 (36.69)	14726 (45.72)	10,753 (36.21)	26,650 (40.94)
Hypertension	1820 (57.02)	20,210 (62.75)	16,267 (54.78)	38,297 (58.83)
Infertility	20 (0.63)	215 (0.67)	213 (0.72)	448 (0.69)
Kidney disease	169 (5.29)	2764 (8.58)	1964 (6.62)	4897 (7.52)
NAFLD[l]	429 (13.44)	8148 (25.30)	4716 (15.88)	13,293 (20.42)
Osteoarthritis	58 (1.82)	585 (1.82)	577 (1.94)	1220 (1.87)
PCOS[m]	141 (4.42)	1741 (5.41)	1463 (4.93)	3345 (5.14)
PE[n]	29 (0.91)	402 (1.25)	286 (0.96)	717 (1.10)
Psychotic disorder	70 (2.19)	1098 (3.41)	822 (2.77)	1990 (3.06)
Sleep apnea	1362 (42.67)	17,583 (54.59)	12,840 (43.24)	31,785 (48.83)
Smoking	185 (5.80)	2987 (9.27)	2380 (8.02)	5552 (8.53)
Substance use disorder	31 (0.97)	673 (2.09)	615 (2.07)	1319 (2.03)

[a]Baseline: identified in the year prior to surgery.

[b]AGB: adjustable gastric banding.

[c]RYGB: Roux-en-Y gastric bypass.

[d]SG: sleeve gastrectomy.

[e]BMI: body mass index.

[f]Number and proportion are calculated among patients with non-missing race (or ethnicity) information.

[g]BP: blood pressure.

[h]The combined comorbidity score merges the Charlson and Elixhauser comorbidity scores [9]. It is calculated based on 20 conditions identified by ICD-9-CM and SNOMED codes in the year prior to surgery. The score ranges from –2 to 26, with a higher score generally indicating poorer health status.

[i]Identified by one or more ICD-9-CM or SNOMED diagnosis code in the year prior to surgery.

[j]DVT: deep vein thrombosis.

[k]GERD: gastroesophageal reflux disease.

[l]NAFLD: non-alcoholic fatty liver disease.

[m]PCOS: polycystic ovarian syndrome.

[n]PE: pulmonary embolism.

Adolescent Subcohort

The PBS cohort also included 777 adolescent bariatric patients, more than twice the size of the largest published bariatric study of an adolescent population (Table 3) [12]. The mean age of the adolescent subcohort was 17 years and 77.5% (602/777) were female. Among patients with race or ethnicity information, 67.3% (473/703) were White, 22.6% (159/703) were Black, and 18.0% (124/689) were Hispanic. The mean maximum BMI at baseline was 53 kg/m^2, with 54.3% (422/777) having a BMI measurement of 50 kg/m^2 or more. As in the adult subcohort, the prevalence of having certain comorbid conditions recorded in the EHR was high in the adolescent patients. Sleep apnea (37.1%, 288/777), dyslipidemia (34.0%, 264/777), and hypertension (30.5%, 237/777) each occurred in more than 30% of the adolescent patients. GERD (26.1%, 203/777), depression (26.1%, 203/777), polycystic ovarian syndrome (PCOS) (20.9%, 162/777), NAFLD (19.7%, 153/777), anxiety (17.3%, 134/777), and diabetes (15.7%, 122/777) were also common. The majority of the adolescent patients received SG (60.4%, 469/777), followed by RYGB (30.8%, 239/777) and AGB (8.9%, 69/777). The mean age and baseline BMI were quite similar across the three treatment groups. The RYGB patients appeared to have more comorbid conditions recorded in their EHRs than the other 2 groups, but these prevalence estimates may be less reliable than in the adult subcohort.

Table 3. Baseline[a] characteristics of adolescent patients aged 12 to 19 years in the PCORnet Bariatric Study cohort (N=777).

Characteristic	AGB[b]	RYGB[c]	SG[d]	All
Number, (%)	69 (100.0)	239 (100.0)	469 (100.0)	777 (100.0)
Age at surgery, mean (SD)	17.4 (1.3)	17.7 (1.4)	17.3 (1.6)	17.5 (1.5)
Age category, n (%)				
12 years	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.3)
13-15 years	6 (8.7)	18 (7.5)	68 (14.5)	92 (11.8)
16-17 years	28 (40.6)	56 (23.4)	136 (29.0)	220 (28.3)
18-19 years	35 (50.7)	165 (69.0)	263 (56.1)	463 (59.6)
Female, n (%)	55 (79.7)	191 (79.9)	356 (75.9)	602 (77.5)
Baseline maximum BMI, mean (SD)	51.4 (7.9)	53.2 (9.1)	52.6 (9.0)	52.7 (8.9)
Baseline maximum BMI category, n (%)				
35-39 kg/m^2	1 (1.5)	5 (2.1)	4 (0.9)	10 (1.3)
40-49 kg/m^2	34 (49.3)	99 (41.4)	212 (45.2)	345 (44.4)
50-59 kg/m^2	28 (40.6)	88 (36.8)	163 (34.8)	279 (35.9)
≥60 kg/m^2	6 (8.7)	47 (19.7)	90 (19.2)	143 (18.4)
Year of surgery, n (%)				
2005-2009	21 (30.4)	28 (11.7)	8 (1.7)	57 (7.3)
2010	17 (24.6)	32 (13.4)	36 (7.7)	85 (10.9)
2011	11 (15.9)	50 (20.9)	50 (10.7)	111 (14.3)
2012	10 (14.5)	35 (14.6)	83 (17.7)	128 (16.5)
2013	9 (13.0)	42 (17.6)	92 (19.6)	143 (18.4)
2014	1 (1.5)	28 (11.7)	124 (26.4)	153 (19.7)
2015	0 (0.0)	24 (10.0)	76 (16.2)	100 (12.9)
Hispanic[f], n (%)	4 (6.5)	43 (22.3)	77 (17.7)	124 (18.0)
Race category[f], n (%)				
American Indian or Alaska Native	0 (0.0)	1 (0.5)	4 (1.0)	5 (0.7)
Asian	0 (0.0)	2 (0.9)	3 (0.7)	5 (0.7)
Black or African American	11 (16.7)	38 (17.5)	110 (26.2)	159 (22.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	45 (68.2)	160 (73.7)	268 (63.8)	473 (67.3)
Multiple race	3 (4.6)	8 (3.7)	15 (3.6)	26 (3.7)
Other	7 (10.6)	8 (3.7)	20 (4.8)	35 (5.0)
Missing race, n (%)	3 (4.4)	22 (9.2)	49 (10.5)	74 (9.5)
Systolic BP[g], mean (SD)	125.9 (16.5)	128.6 (15.9)	130.2 (17.0)	129.3 (16.6)
Diastolic BP, mean (SD)	75.2 (11.5)	74.1 (12.2)	70.3 (12.1)	71.9 (12.2)
Missing BP, n (%)	1 (1.5)	13 (5.4)	14 (3.0)	28 (3.6)
Combined comorbidity score[h], n (%)				
<0	1 (1.5)	20 (8.4)	46 (9.8)	67 (8.6)
0	66 (95.7)	148 (61.9)	324 (69.1)	538 (69.2)
>0	2 (2.9)	71 (29.7)	99 (21.1)	172 (22.1)
No. of hospital days in year before surgery, mean (SD)	1.5 (4.4)	0.2 (1.9)	2.4 (12.6)	1.7 (10.0)

Characteristic	AGB[b]	RYGB[c]	SG[d]	All
Health conditions[i], n (%)				
Anxiety	11 (15.9)	44 (18.4)	79 (16.8)	134 (17.3)
Depression	22 (31.9)	68 (28.5)	113 (24.1)	203 (26.1)
Diabetes	5 (7.3)	52 (21.8)	65 (13.9)	122 (15.7)
DVT[j]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyslipidemia	30 (43.5)	71 (29.7)	163 (34.8)	264 (34.0)
Eating disorder	1 (1.5)	23 (9.6)	14 (3.0)	38 (4.9)
GERD[k]	12 (17.4)	74 (31.0)	117 (25.0)	203 (26.1)
Hypertension	29 (42.0)	70 (29.3)	138 (29.4)	237 (30.5)
Infertility	0 (0.0)	4 (1.7)	7 (1.5)	11 (1.4)
Kidney disease	0 (0.0)	3 (1.3)	6 (1.3)	9 (1.2)
NAFLD[l]	2 (2.9)	81 (33.9)	70 (14.9)	153 (19.7)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PCOS[m]	12 (17.4)	61 (25.5)	89 (19.0)	162 (20.9)
PE[n]	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Psychotic disorder	1 (1.5)	7 (2.9)	12 (2.6)	20 (2.6)
Sleep apnea	11 (15.9)	113 (47.3)	164 (35.0)	288 (37.1)
Smoker	1 (1.5)	11 (4.6)	23 (4.9)	35 (4.5)
Substance use disorder	1 (1.5)	1 (0.4)	2 (0.4)	4 (0.5)

[a]Baseline: identified in the year prior to surgery.

[b]AGB: adjustable gastric banding.

[c]RYGB: Roux-en-Y gastric bypass.

[d]SG: sleeve gastrectomy.

[e]BMI: body mass index.

[f]Number and proportion are calculated among patients with non-missing race (or ethnicity) information.

[g]BP: blood pressure.

[h]The combined comorbidity score merges the Charlson and Elixhauser comorbidity scores [9]. It is calculated based on 20 conditions identified by ICD-9-CM and SNOMED codes in the year prior to surgery. The score ranges from –2 to 26, with a higher score generally indicating poorer health status.

[i]Identified by one or more ICD-9-CM or SNOMED diagnosis code in the year prior to surgery.

[j]DVT: deep vein thrombosis.

[k]GERD: gastroesophageal reflux disease.

[l]NAFLD: non-alcoholic fatty liver disease.

[m]PCOS: polycystic ovarian syndrome.

[n]PE: pulmonary embolism.

Temporal Trends in Bariatric Procedures Performed in the Study Cohort

We observed dramatic shifts in the type of procedures performed in adults between 2005 and 2015 (Figure 2). Almost all of the bariatric procedures performed in the health systems contributing to the dataset in 2005 were RYGB. SG became increasingly popular starting in 2010 and was the most commonly performed bariatric procedure by 2013. Although the shifts in the type of procedures performed in the adult subcohort are consistent with other studies, it is worth noting that while all 11 participating CDRNs contribute data to all study years, not all 42 participating health systems within these CDRNs have data in all years. We also found substantial variability in the type of procedures performed in adults across CDRNs during the study period (Figure 3). RYGB was the most commonly performed procedure in 3 CDRNs while SG was the primary procedure in 8 CDRNs. The proportion of RYGB procedure ranged from 16% to 69% across CDRNs.

Figure 2. Shift in choice of bariatric procedure in adults in the PCORnet Bariatric Study from 2005 to 2015.Size of the data point is proportionate to the number of patients at that time point. All 11 Clinical Data Research Network (CDRNs) that participate in the study contribute data to all study years, but not all 42 participating health systems have data in all years. AGB: adjustable gastric banding; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy.

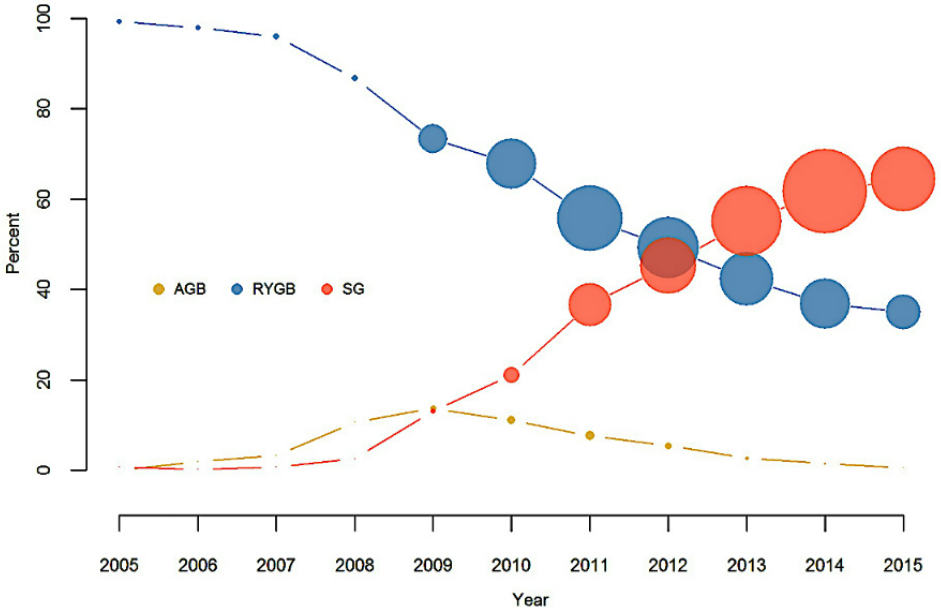


Figure 3. Variability in use of the three most common bariatric procedure types in adults in the PCORnet Bariatric Study, by Clinical Data Research Network (CDRN), 2005-2015. AGB: adjustable gastric banding; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy.

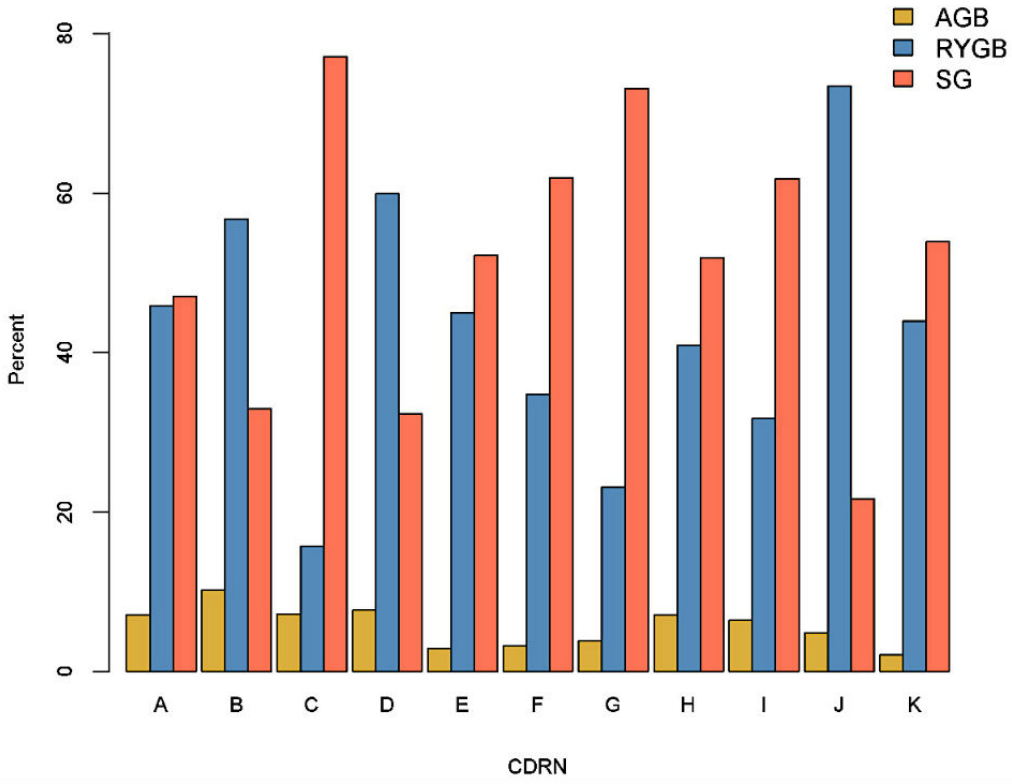


Table 4. Characteristics of adult patients aged 20 to 79 years with or without a body mass index measurement in the electronic health record at baseline[a] and in follow-up.

Characteristic	The Adult PCORnet Bariatric Study cohort			
	All	Patients with BMI[b]≥35 at baseline and a BMI measurement during follow-up	Patients with BMI ≥35 at baseline but missing BMI during follow-up	Patients with missing BMI at baseline (excluded from the study cohort)
Number (%)	65,093 (100.00)	46,510 (100.00)	18,583 (100.00)	12,510 (100.00)
Bariatric procedure, n (%)				
AGB[c]	3192 (4.90)	2567 (5.52)	625 (3.36)	3049 (24.37)
RYGB[d]	32,208 (49.48)	24,982 (53.71)	7226 (38.89)	6621 (52.93)
SG[e]	29,693 (45.62)	18,961 (40.77)	10,732 (57.75)	2840 (22.70)
Age at surgery, mean (SD)	45.0 (11.72)	45.5 (11.60)	43.6 (11.91)	45.8 (12.10)
Age category, n (%)				
20-44 years	32,136 (49.37)	22,075 (47.46)	10,061 (54.14)	5866 (46.89)
45-64 years	29,622 (45.51)	22,042 (47.39)	7580 (40.79)	5782 (46.22)
65-79 years	3335 (5.12)	2393 (5.15)	942 (5.07)	862 (6.89)
Female, n (%)	51,619 (79.30)	37,315 (80.23)	14,304 (76.97)	9535 (76.23)
Baseline maximum BMI, mean (SD)	49.0 (8.23)	49.1 (8.17)	48.8 (8.39)	N/A
Baseline maximum BMI category, n (%)				
35-39 kg/m^2	5828 (8.95)	3865 (8.31)	1963 (10.56)	0 (0.0)
40-49 kg/m^2	35,010 (53.78)	25,123 (54.02)	9887 (53.20)	0 (0.0)
50-59 kg/m^2	17,699 (27.19)	12,870 (27.67)	4829 (25.99)	0 (0.0)
≥60 kg/m^2	6556 (10.07)	4652 (10.00)	1904 (10.25)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	12,510 (100.00)
Year of surgery, n (%)				
2005-2009	5572 (8.56)	5183 (11.14)	389 (2.09)	2532 (20.24)
2010	6494 (9.98)	5819 (12.51)	675 (3.63)	2721 (21.75)
2011	10,292 (15.81)	9015 (19.38)	1277 (6.87)	2518 (20.13)
2012	10,885 (16.72)	8977 (19.30)	1908 (10.27)	2041 (16.31)
2013	11,121 (17.08)	8556 (18.40)	2565 (13.80)	1227 (9.81)
2014	11,983 (18.41)	7951 (17.10)	4032 (21.70)	896 (7.16)
2015	8746 (13.44)	1009 (2.17)	7737 (41.63)	575 (4.60)
Hispanic[f], n (%)	13,094 (20.58)	9612 (21)	3482 (19.49)	876 (8.00)
Race category[f], n (%)				
American Indian or Alaska Native	354 (0.62)	279 (0.68)	75 (0.46)	45 (0.42)
Asian	540 (0.94)	422 (1.03)	118 (0.73)	63 (0.59)
Black or African American	12,094 (21.13)	8526 (20.76)	3568 (22.09)	1586 (14.86)
Native Hawaiian or Other Pacific Islander	188 (0.33)	143 (0.35)	45 (0.28)	9 (0.08)
White	41,248 (72.08)	30,371 (73.95)	10,877 (67.33)	8523 (79.87)
Multiple race	802 (1.40)	465 (1.13)	337 (2.09)	90 (0.84)
Other	2001 (3.50)	866 (2.11)	1135 (7.03)	355 (3.33)
Missing race, n (%)	7866 (12.08)	5438 (11.69)	2428 (13.07)	1839 (14.70)

Characteristic	The Adult PCORnet Bariatric Study cohort			
	All	Patients with BMI[b]≥35 at baseline and a BMI measurement during follow-up	Patients with BMI ≥35 at baseline but missing BMI during follow-up	Patients with missing BMI at baseline (excluded from the study cohort)
Systolic BP[g], mean (SD)	131.1 (17.89)	130.5 (17.08)	132.8 (19.78)	131.1 (16.69)
Diastolic BP, mean (SD)	75.8 (12.08)	75.6 (11.56)	76.1 (13.36)	76.1 (11.41)
Missing BP, n (%)	4006 (6.15)	1801 (3.87)	2205 (11.87)	10,736 (85.82)
Combined comorbidity score[h], n (%)				
<0	20,243 (31.10)	15,488 (33.30)	4755 (25.59)	2845 (22.74)
0	35,152 (54.00)	23,879 (51.34)	11,273 (60.66)	8463 (67.65)
>0	9698 (14.90)	7143 (15.36)	2555 (13.75)	1202 (9.61)
No. of hospital days in year before surgery, mean (SD)	0.46 (4.37)	0.43 (3.74)	0.53 (5.66)	0.79 (9.52)
Health conditions[i], n (%)				
Anxiety	13,657 (20.98)	9917 (21.32)	3740 (20.13)	1837 (14.68)
Depression	19,324 (29.69)	14,339 (30.83)	4985 (26.83)	3370 (26.94)
Diabetes	23,411 (35.97)	17,320 (37.24)	6091 (32.78)	3835 (30.66)
DVT[j]	454 (0.70)	336 (0.72)	118 (0.63)	94 (0.75)
Dyslipidemia	30,377 (46.67)	22,823 (49.07)	7554 (40.65)	5152 (41.18)
Eating disorder	6321 (9.71)	4983 (10.71)	1338 (7.20)	238 (1.90)
GERD[k]	26,650 (40.94)	18,995 (40.84)	7655 (41.19)	4764 (38.08)
Hypertension	38,297 (58.83)	28,017 (60.24)	10,280 (55.32)	7089 (56.67)
Infertility	448 (0.69)	339 (0.73)	109 (0.59)	75 (0.60)
Kidney disease	4897 (7.52)	3824 (8.22)	1073 (5.77)	491 (3.92)
NAFLD[l]	13,293 (20.42)	9646 (20.74)	3647 (19.63)	1380 (11.03)
Osteoarthritis	1220 (1.87)	814 (1.75)	406 (2.18)	165 (1.32)
PCOS[m]	3345 (5.14)	2345 (5.04)	1000 (5.38)	435 (3.48)
PE[n]	717 (1.10)	547 (1.18)	170 (0.91)	96 (0.77)
Psychotic disorder	1990 (3.06)	1471 (3.16)	519 (2.79)	235 (1.88)
Sleep apnea	31,785 (48.83)	22,894 (49.22)	8891 (47.84)	5254 (42.00)
Smoking	5552 (8.53)	4008 (8.62)	1544 (8.31)	618 (4.94)

Characteristic	The Adult PCORnet Bariatric Study cohort			
	All	Patients with BMI[b]≥35 at baseline and a BMI measurement during follow-up	Patients with BMI ≥35 at baseline but missing BMI during follow-up	Patients with missing BMI at baseline (excluded from the study cohort)
Substance use disorder	1319 (2.03)	984 (2.12)	335 (1.80)	199 (1.59)

[a]Baseline: identified in the year prior to surgery.

[b]BMI: body mass index.

[c]AGB: adjustable gastric banding.

[d]RYGB: Roux-en-Y gastric bypass.

[e]SG: sleeve gastrectomy.

[f]Number and proportion are calculated among patients with non-missing race (or ethnicity) information.

[g]BP: blood pressure.

[h]The combined comorbidity score merges the Charlson and Elixhauser comorbidity scores [9]. It is calculated based on 20 conditions identified by ICD-9-CM and SNOMED codes in the year prior to surgery. The score ranges from –2 to 26, with a higher score generally indicating poorer health status.

[i]Identified by one or more ICD-9-CM or SNOMED diagnosis code in the year prior to surgery.

[j]DVT: deep vein thrombosis.

[k]GERD: gastroesophageal reflux disease.

[l]NAFLD: non-alcoholic fatty liver disease.

[m]PCOS: polycystic ovarian syndrome.

[n]PE: pulmonary embolism.

Comparisons Between Study Cohort and Patients Excluded From the Study

Adult Subcohort

We excluded 12,510 adult bariatric patients with missing baseline BMI in the EHR who met the other eligibility criteria of the study and an additional 1918 patients whose baseline BMI were less than 35 kg/m^2. Compared to the 65,093 adult patients in the PBS cohort, patients with missing baseline BMI information were more often White (79.87%, 8523/10,671 versus 72.08%, 41,248/57,227), less often Black (14.86%, 1586/10,671 versus 21.13%, 12,094/57,227), less often Hispanic (8.00%, 876/10,951 versus 20.58%, 13,094/63,637), and more likely to have their procedure performed in earlier study years (Table 4). Fewer of the excluded patients had comorbid health conditions recorded in the EHR, such as anxiety (14.68%, 1837/12,510 versus 20.98%, 13,657/65,093), eating disorder (1.90%, 238/12,510 versus 9.71%, 6321/65,093), NAFLD (11.03%, 1380/12,510 versus 20.42%, 13,293/65,093), and sleep apnea (42.00%, 5254/12,510 versus 48.83%, 31,785/65,093). Not surprisingly, patients without a baseline BMI measurement also had a much higher proportion of missing blood pressure measurements (85.82%, 10,736/12,510 versus 6.15%, 4006/65,093). Ongoing and future analyses will account for the differences in the patient characteristics.

Adolescent Subcohort

We excluded 127 adolescent patients with missing baseline BMI in the EHR who met the other eligibility criteria of the study and an additional 54 patients whose baseline BMI were less than 35 kg/m^2. Compared to the adolescent patients in the PBS cohort, patients with missing baseline BMI information were more likely to have undergone AGB or RYGB procedure and more likely to have their bariatric procedures performed in earlier study years (Table 5). They were also less often female (64.6%, 82/127 versus 77.5%, 602/777), and had lower proportions of comorbid conditions recorded in the EHR, such as depression (15.8%, 20/127 versus 26.1%, 203/777), diabetes (4.7%, 6/127 versus 15.7%, 122/777), dyslipidemia (8.7%, 11/127 versus 34.0%, 264/777), hypertension (12.6%, 16/127 versus 30.5%, 237/777), NAFLD (6.3%, 8/127 versus 19.7%, 153/777), PCOS (5.5%, 7/127 versus 20.9%, 162/777), and sleep apnea (16.5%, 21/127 versus 37.1%, 288/777). The excluded patients spent more days in the hospital, on average, in the year prior to the surgery compared to those in the PBS cohort (6 versus 2 days).

Follow-Up

Adult Subcohort

Within the adult subcohort, 71.45% (46,510/65,093) patients had one or more BMI measurements beyond 6 months of post-operative follow-up. However, follow-up ended on September 30, 2015, so not all patients were eligible to be followed for 1, 3, or 5 full years. For example, only patients who had a bariatric procedure on October 1, 2010 or earlier could be followed for 5 complete years during the study's timeframe. The proportion of eligible patients with at least one BMI measurement in the follow-up windows of interest was 84.31% (44,978/53,351) at 6 to 18 months, 68.09% (20,783/30,521) at 30 to 42 months, and 68.56% (7159/10,442) at 54 to 66 months after surgery (Table 6). Long-term follow-up varied by treatment group, with SG patients being most likely to have a BMI measurement at years 3 and 5, followed by RYGB patients and AGB patients.

Table 5. Characteristics of adolescent patients aged 12 to 19 years with or without a body mass index measurement in the electronic health record at baseline[a] and in follow-up.

Characteristic	The Adolescent PCORnet Bariatric Study cohort			
	All	Patients with BMI[b]≥35 at baseline and a BMI measurement during follow-up	Patients with BMI ≥35 at baseline but missing BMI during follow-up	Patients with missing BMI at baseline (excluded from the study cohort)
Number (%)	777 (100.0)	544 (100.0)	233 (100.0)	127 (100.0)
Bariatric procedure, n (%)				
AGB[c]	69 (8.9)	61 (11.2)	8 (3.4)	36 (28.4)
RYGB[d]	239 (30.8)	177 (32.5)	62 (26.6)	62 (48.8)
SG[e]	469 (60.4)	306 (56.3)	163 (70.0)	29 (22.8)
Age at surgery, mean (SD)	17.5 (1.5)	17.3 (1.6)	17.7 (1.3)	17.7 (1.6)
Age category, n (%)				
12 years	2 (0.3)	2 (0.4)	0 (0.0)	3 (2.4)
13-15 years	92 (11.8)	75 (13.8)	17 (7.3)	11 (8.7)
16-17 years	220 (28.3)	157 (28.9)	63 (27.0)	28 (22.1)
18-19 years	463 (59.6)	310 (57.0)	153 (65.7)	85 (66.9)
Female, n (%)	602 (77.5)	428 (78.7)	174 (74.7)	82 (64.6)
Baseline maximum BMI, mean (SD)	52.7 (8.9)	52.5 (8.5)	53.0 (9.9)	N/A
Baseline maximum BMI category, n (%)				
35-39 kg/m^2	10 (1.3)	5 (0.9)	5 (2.2)	0 (0.0)
40-49 kg/m^2	345 (44.4)	249 (45.8)	96 (41.2)	0 (0.0)
50-59 kg/m^2	279 (35.9)	192 (35.3)	87 (37.3)	0 (0.0)
≥60 kg/m^2	143 (18.4)	98 (18.0)	45 (19.3)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	127 (100.0)
Year of surgery, n (%)				
2005-2009	57 (7.3)	52 (9.6)	5 (2.2)	34 (26.8)
2010	85 (10.9)	78 (14.3)	7 (3.0)	18 (14.2)
2011	111 (14.3)	98 (18.0)	13 (5.6)	24 (18.9)
2012	128 (16.5)	106 (19.5)	22 (9.4)	31 (24.4)
2013	143 (18.4)	105 (19.3)	38 (16.3)	10 (7.9)
2014	153 (19.7)	101 (18.6)	52 (22.3)	6 (4.7)
2015	100 (12.9)	4 (0.7)	96 (41.2)	4 (3.2)
Hispanic[f], n (%)	124 (18.0)	81 (16.8)	43 (20.8)	14 (18.9)
Race category[f], n (%)				
American Indian or Alaska Native	5 (0.7)	3 (0.6)	2 (1.0)	2 (1.8)
Asian	5 (0.7)	5 (1.0)	0 (0.0)	1 (0.9)
Black or African American	159 (22.6)	122 (24.6)	37 (18.0)	26 (23.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	473 (67.3)	330 (66.4)	143 (69.4)	74 (67.3)
Multiple race	26 (3.7)	12 (2.4)	14 (6.8)	1 (0.9)
Other	35 (5.0)	25 (5.0)	10 (4.9)	6 (5.5)

Characteristic	The Adolescent PCORnet Bariatric Study cohort			
	All	Patients with BMI[b]≥35 at baseline and a BMI measurement during follow-up	Patients with BMI ≥35 at baseline but missing BMI during follow-up	Patients with missing BMI at baseline (excluded from the study cohort)
Missing race, n (%)	74 (9.5)	47 (8.6)	27 (11.6)	17 (13.4)
Systolic BP[g], mean (SD)	129.3 (16.6)	128.5 (16.7)	131.3 (16.4)	119.6 (16.3)
Diastolic BP, mean (SD)	71.9 (12.2)	71.3 (12.0)	73.3 (12.7)	68.5 (10.2)
Missing BP, n (%)	28 (3.6)	12 (2.2)	16 (6.9)	111 (87.4)
Combined comorbidity score[h] , n (%)				
<0	67 (8.6)	46 (8.5)	21 (9.0)	2 (1.6)
0	538 (69.2)	365 (67.1)	173 (74.3)	102 (80.3)
>0	172 (22.1)	133 (24.5)	39 (16.7)	23 (18.1)
No. of hospital days in year before surgery, mean (SD)	1.7 (10.0)	1.5 (7.9)	2.1 (13.7)	6.4 (39.6)
Health conditions[i] , n (%)				
Anxiety	134 (17.3)	87 (16.0)	47 (20.2)	18 (14.2)
Depression	203 (26.1)	151 (27.8)	52 (22.3)	20 (15.8)
Diabetes	122 (15.7)	88 (16.2)	34 (14.6)	6 (4.7)
DVT[j]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Dyslipidemia	264 (34.0)	192 (35.3)	72 (30.9)	11 (8.7)
Eating disorder	38 (4.9)	25 (4.6)	13 (5.6)	7 (5.5)
GERD[k]	203 (26.1)	137 (25.2)	66 (28.3)	29 (22.8)
Hypertension	237 (30.5)	175 (32.2)	62 (26.6)	16 (12.6)
Infertility	11 (1.4)	4 (0.7)	7 (3.0)	0 (0.0)
Kidney disease	9 (1.2)	7 (1.3)	2 (0.9)	9 (7.1)
NAFLD[l]	153 (19.7)	103 (18.9)	50 (21.5)	8 (6.3)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
PCOS[m]	162 (20.9)	120 (22.1)	42 (18.0)	7 (5.5)
PE[n]	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
Psychotic disorder	20 (2.6)	14 (2.6)	6 (2.6)	2 (1.6)
Sleep apnea	288 (37.1)	198 (36.4)	90 (38.6)	21 (16.5)
Smoking	35 (4.5)	25 (4.6)	10 (4.3)	4 (3.2)

Characteristic	The Adolescent PCORnet Bariatric Study cohort			
	All	Patients with BMI[b]≥35 at baseline and a BMI measurement during follow-up	Patients with BMI ≥35 at baseline but missing BMI during follow-up	Patients with missing BMI at baseline (excluded from the study cohort)
Substance use disorder	4 (0.5)	2 (0.4)	2 (0.9)	3 (2.4)

[a]Baseline: identified in the year prior to surgery.

[b]BMI: body mass index.

[c]AGB: adjustable gastric banding.

[d]RYGB: Roux-en-Y gastric bypass.

[e]SG: sleeve gastrectomy.

[f]Number and proportion are calculated among patients with non-missing race (or ethnicity) information.

[g]BP: blood pressure.

[h]The combined comorbidity score merges the Charlson and Elixhauser comorbidity scores [9]. It is calculated based on 20 conditions identified by ICD-9-CM and SNOMED codes in the year prior to surgery. The score ranges from –2 to 26, with a higher score generally indicating poorer health status.

[i]Identified by one or more ICD-9-CM or SNOMED diagnosis code in the year prior to surgery.

[j]DVT: deep vein thrombosis.

[k]GERD: gastroesophageal reflux disease.

[l]NAFLD: non-alcoholic fatty liver disease.

[m]PCOS: polycystic ovarian syndrome.

[n]PE: pulmonary embolism.

Table 6. Follow-up information in the PCORnet Bariatric Study cohort.

Cohort	Follow-up window of interest		
	1 year (measured at 6 to 18 months)	3 years (measured at 30 to 42 months)	5 years (measured at 54 to 66 months)
Number and proportion of patients in the adult subcohort having a BMI[a] measurement during follow-up, among patients eligible[b] , n/N (%)			
All	44,978/53,351 (84.31%)	20,783/30,521 (68.09%)	7159/10,442 (68.56%)
AGB[c]	2367/3098 (76.40%)	1507/2519 (59.82%)	609/1111 (54.82%)
RYGB[d]	24,061/28,039 (85.81%)	12,429/18,684 (66.52%)	5257/7824 (67.19%)
SG[e]	18,550/22,214 (83.50%)	6847/9318 (73.48%)	1293/1507 (85.79%)
Number and proportion of patients in the adolescent subcohort having a BMI measurement during follow-up, among patients eligible[b], n/N (%)			
All	524/639 (82.0%)	174/349 (49.9%)	47/121 (38.8%)
AGB	58/69 (84.1%)	21/57 (36.8%)	6/34 (17.6%)
RYGB	165/208 (79.3%)	69/136 (50.7%)	25/52 (48.1%)
SG	301/362 (83.1%)	84/156 (53.8%)	16/35 (45.7%)

[a]BMI: body mass index.

[b]Number of patients who can be followed for a certain follow-up window of interest based on the study timeframe, which ended on September 30, 2015. For example, only patients who had a bariatric procedure on October 1, 2014 or earlier would be eligible for having one complete year of follow-up information. However, the number of eligible patients was an estimate because we did not request actual dates for the analysis for privacy consideration—all patients who had their procedure performed in 2013 or earlier and 3/4 of patients who had their procedure performed in 2014 will be eligible for at least one year of follow-up.

[c]AGB: adjustable gastric banding.

[d]RYGB: Roux-en-Y gastric bypass.

[e]SG: sleeve gastrectomy.

Among the adult patients in the PBS cohort, those without a BMI measurement during follow-up were overall quite similar to those with a measurement (Table 4). However, they appeared to be younger (44 versus 46 years), less often White (67.33%, 10,877/16,155 versus 73.95%, 30,371/41,072), and more likely to have their procedure performed in later study years. These patients generally have lower proportions of comorbid conditions, but the differences were relatively small.

Adolescent Subcohort

Within the adolescent subcohort, 70.0% (544/777) patients had at least 1 BMI measurement beyond 6 months of post-operative follow-up. Of eligible patients, 82.0% (524/639) had a BMI measurement at 6 to 18 months following their index procedure (Table 6). Weight data were available in 49.9% (174/349) of eligible patients at 30 to 42 months, and 38.9% (47/121) of eligible patients at 54 to 66 months. The proportion of patients with a BMI measurement at years 3 and 5 was lowest in the AGB group, and similar between the RYGB and SG groups.

Among the adolescent patients in the PBS cohort, those without a BMI measurement during follow-up were overall quite similar to those with a measurement (Table 5). However, they were less often Black (18.0%, 37/206 versus 24.6%, 122/497), more likely to have undergone SG (70.0%, 163/233 versus 56.3%, 306/544), have their procedures performed in later study years, and have lower prevalence of recorded depression (22.3%, 52/233 versus 27.8%, 151/544) and hypertension (26.6%, 62/233 versus 32.2%, 175/544) than those with a measurement.

Discussion

Principal Findings

In this large, population-based, retrospective cohort study using the national PCORnet data infrastructure, we have identified 65,093 adults and 777 adolescents who underwent 1 of the 3 most common bariatric procedures, AGB, RYGB, and SG, in 42 geographically diverse health systems. Over the time frame of the study (2005 to 2015), we observed a dramatic shift in bariatric procedure use (Figure 2), with a sharp decline in the proportions of patients undergoing RYGB and AGB and increase in the proportion undergoing SG. In particular, the large number of SG patients in this cohort (29,693 adults and 469 adolescents) makes this a valuable resource for comparative effectiveness research. We also observed heterogeneity in bariatric procedure preferences across the 11 participating CDRNs (Figure 3), which underscore the need for better comparative effectiveness research evidence to inform patient and provider decisions about bariatric surgery.

Strengths

The ongoing PBS is one of the largest cohorts of patients with bariatric procedures in the United States. Patients are geographically and demographically diverse, which improves the generalizability of the research findings and allows examination of treatment effect heterogeneity. This, in turn, may result in findings that can more easily be applied to clinical decision-making. The ability to use real-world data collected as part of healthcare delivery not only allows us to collect long-term follow-up data efficiently and at a lower cost but also to learn from the routine practice of medicine.

A unique strength of the PBS study is the depth and diversity of its stakeholder involvement, which includes not only several patients as study team members, but also multiple pediatric and adult bariatric surgeons from different institutions, primary care and specialty physicians, researchers, and leaders of patient-level policy and advocacy organizations. Stakeholders are fully engaged in all stages of the protocol development, including formulating the research questions and the study aims, selecting outcomes that are of interest to the patients, and identifying methods to study these outcomes (eg, prioritization of variables for heterogeneity of treatment effect analyses). They are also actively involved in monitoring study conduct, interpreting data in the context of local patient populations and coding practices, and designing and implementing dissemination plans. This robust engagement strategy helps ensure that the products of this research study are meaningful to patients, clinicians, and policy makers.

By having sites translate source data into the CDM in PCORnet, researchers can distribute one query to all sites and receive back standardized output (eg, identical variable names and categories) from disparate data sources. Using the CDM avoids much of the redundant preparatory work that would otherwise be needed to assemble cohorts or count potential events and other endpoints. Code lists and query programs developed as part of this study can also be used for future studies that leverage the PCORnet CDM. The CDM and distributed data network framework has been shown to improve the efficiency of the conduct of multi-database studies [13-17].

The PBS employs an efficient ethical review process. Adherence to human subjects protections and regulations was addressed at the CDRN level. Some participating networks obtained Institutional Review Board (IRB) approval for the study's protocol using an IRB reliance agreement across their sites; others created and relied on a central IRB [18]. At some CDRNs, individual site's IRB determined that these analyses of de-identified data did not qualify as human subjects research. The Kaiser Permanente Washington Health Research Institute, the lead site of the PBS, obtained IRB approval for overseeing data collection and leading analyses.

Ongoing and Planned Activities

Ongoing and planned investigations in the PBS include head-to-head comparisons of these procedures on long-term changes in weight, rates of diabetes remission and relapse, and incidences of major surgery-related adverse events. These comparisons will be conducted separately in adults and adolescents. Additional evaluations will examine the heterogeneity of treatment effects for important covariates such as age, sex, race, and comorbidities. Furthermore, selected analyses will compare pooled individual-level data analysis with more privacy-protecting analytic approaches that share less granular information [19,20].

Examination of mortality after bariatric surgery is challenging using only EHR data. Deaths are not typically captured in EHRs except if they occur during hospitalization or in the emergency

room, or when a primary care provider becomes aware of a patient's death and the information is entered manually into the EHR. Some sites within the participating CDRNs have linked to state or national death indices. The PBS plans to perform additional linkages to these death registries for a subset of the study population to increase the accuracy and completeness of death information. In addition, a number of pre-specified surgery-related adverse events, including re-hospitalization and re-operation after bariatric surgery, may be incompletely captured in EHRs because patients may get a portion of their care outside of the data-contributing health systems. The PBS study will link the EHR data from select health systems to insurance claims data to improve capture of these events.

Limitations

This study has several limitations. A non-negligible number of bariatric patients had missing BMI data either at baseline or in follow-up, and the reasons for having missing measurements were generally not well-recorded during the study period. Because the PCORnet CDM typically reflects data stored as discrete data elements, it is possible that some EHR data (eg, BMI recorded in a clinician's note instead of in the vital signs table) was not represented in our analyses. Long-term follow-up (eg, 5 years) information was not available in some patients. Relying primarily on routinely collected health data means our data collection process might not be as systematic as in other prospective cohort studies (eg, the Longitudinal Assessment of Bariatric Surgery study [11] and the Teen-Longitudinal Assessment of Bariatric Surgery study [12]). However, it does represent the information that informs patient and provider decisions in routine clinical care. There was also variability in data capture and documentation across health systems during the study period.

We did not validate the algorithms used to identify the comorbidities of interest (eg, sleep apnea). It is possible that these conditions were under-recorded or over-recorded in certain EHRs. However, the implementation of the PCORnet CDM helps standardize a core set of variables expected to be commonly used in research studies. There is currently no plan to conduct analyses using data beyond September 30, 2015. Although the PBS cohort will perform linkages with additional data sources to improve the completeness and accuracy of certain information, these linkages will not be performed in the entire cohort.

Conclusion

Using the data and research infrastructure created by the PCORnet, we have created one of the largest cohorts of patients with bariatric procedures in the United States. The diversity of the patients and the active engagement of the stakeholders enhance the generalizability and relevance of the research findings. The study will produce real-world evidence on the long-term benefits and risks of these most commonly used bariatric procedures in current clinical practice.

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Conflicts of Interest

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Abbreviations

AGB: adjustable gastric banding
BMI: body mass index
BP: blood pressure
CDM: common data model
CDRN: Clinical Data Research Network
CPT: current procedure terminology
DVT: deep vein thrombosis
EHR: electronic health record
GERD: gastroesophageal reflux disease
HCPCS: Healthcare Common Procedure Coding System
ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification
IRB: institutional review board
NAFLD: non-alcoholic fatty liver disease
PBS: PCORnet Bariatric Study
PCORI: The Patient-Centered Outcomes Research Institute
PCORnet: The National Patient-Centered Clinical Research Network
PCOS: polycystic ovarian syndrome
PE: pulmonary embolism
RYGB: Roux-en-Y gastric bypass
SG: sleeve gastrectomy
SNOMED: Systematized Nomenclature of Medicine

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Protocol

Influence of Social Determinants, Lifestyle, Emotional Well-Being and the Use of Unconventional Therapies in Breast Cancer Progression in a Cohort of Women in Barcelona: Protocol for the DAMA Cohort

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Abstract

Background: Breast cancer continues to be the most commonly diagnosed cancer in women. Breast cancer survivors face numerous problems, especially after completing the first year of intense treatment. We present the protocol for an ongoing study to analyze the impact of a series of factors on breast cancer survival related to lifestyle, emotional well-being, and use of complementary and alternative medicine (CAM).

Objective: We aim to analyze the influence of social determinants, lifestyle changes, emotional well-being, and use of CAM in the progression of breast cancer in women diagnosed with breast cancer between 2003 and 2013 in Barcelona, Spain.

Methods: We will perform a mixed cohort study (prospective and retrospective) of women diagnosed with breast cancer, created using a convenience sample in which we study the evolution of the disease (relapse, death, or remaining disease-free). Once identified, we sent the women information about the study and an informed consent form that they are required to sign in order to participate; a total of 2235 women were recruited. We obtained the following information from all participants: sociodemographic profile via a phone interview, and a self-administered survey of information about the study's objectives (lifestyles, emotional

well-being, health care services, and the use of CAM). Lastly, we examined clinical records to obtain data on the tumor at the time of diagnosis, the treatment received, the occurrence of relapses (if any), and the tumor typology. We present data on the women's social profile based on descriptive data obtained from the telephone interview (welcome survey).

Results: Based on the welcome survey, which was completed by 2712 women, 14.42% (391/2712) of respondents were <50 years of age, 45.50% (1234/2712) were between 50 and 65 years of age, and 40.08% (1087/2712) were >65 years of age. A total of 43.69% (1185/2712) belonged to the highest social classes (I and II), 31.27% (848/2712) to the middle class (III), and 23.49% (637/2712) to the working classes (IV and V). Approximately 22.71% (616/2712) lived alone, 38.31% (1039/2712) lived with one person, and 38.97% (1057/2712) lived with two or more people.

Conclusions: We obtained information from a large cohort of women, but this study has limitations related to the convenience sampling strategy, one of which is reduced representativeness. Conversely, being a self-administered survey, the study introduces biases, especially from respondents that answered on paper. However, the information that the study provides will serve as the basis for designing future interventions aimed at improving the knowledge gaps indicated for women with breast cancer.

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KEYWORDS

breast cancer; cohort study

Introduction

Breast cancer continues to be the most commonly diagnosed cancer in women [1]. In 2012, there were more than 25,000 new cases in Spain; in Catalonia, 1 in 9 women will be diagnosed with breast cancer in her lifetime [2]. Due to population aging, early detection, and diagnostic improvements, this trend will increase and the number of new cases is likely to rise by 70% in the coming decades [1]. Diagnostic improvements and treatment have also increased survival; in Catalonia the mortality rate has declined by 2.1% each year since 1993, such that current survival at 5 years is 82.8% [2].

Breast cancer survivors face numerous problems, especially after completing the first year of intense treatment. These problems keep survivors closely tied to hospitals, and they become aware that the physical and emotional consequences not only continue, but sometimes worsen. Survivors experience physical changes [3] that result in changes in their intimate life [4,5] and employment [6], as well as fatigue and pain associated with the disease that is detrimental to their mental health and quality of life [7]. The environment and social networks of survivors are vital to their quality of life and survival, and recent studies have shown that the biological mechanisms triggered in socially isolated individuals increase their risk of poorer results in terms of survival [8].

Depression and anxiety are the mental illnesses that most commonly affect women, and signs of these diseases are observed in 20-30% of breast cancer patients within the first year after diagnosis; in comparison, the general population prevalence of depression and anxiety are just 8% and 6%, respectively, according to studies in Switzerland and the United States [9]. According to the *European Study of the Epidemiology of Mental Disorders - Spain* study carried out in 2001-2002, the prevalence/year (new and old cases cases) of depression and anxiety were 5.6% and 1.18%, respectively [10].

Lifestyles factors such as diet, physical activity, tobacco usage, and alcohol consumption are directly or indirectly related to breast cancer, and to the general health of any person. In this sense, one of the basic principles of the European Code Against Cancer [11] is to maintain a healthy life in terms of a balanced diet and physical activity, and to reduce or avoid toxic habits.

To cope with secondary side effects, improve quality of life, and feel better, people often resort to complementary and alternative medicines (CAMs). In the United States, an estimated 28-73% of breast cancer survivors use one or more of these therapies [12]. Such therapies are also used in in Spain [13], although to our knowledge there is currently no data on the frequency of use. Acupuncture is an effective treatment for nausea and pain, and recent studies in patients undergoing hormone treatment have demonstrated that these therapies reduce hot flashes, anxiety, depression, and somatic and vasomotor symptoms [14].

However, since these strategies are not included in cancer follow-up protocols, their use depends on each woman's own resources, which may lead to important inequalities. According to the Wisconsin Longitudinal Study, overall health status and the appearance of a particular breast cancer can be influenced not only by the status of the individual herself in the present moment of her life, but also by the history of her family [15]. Socioeconomic status and the environment both influence quality of life among women with breast cancer. Both of these factors are linked to the emotional stress caused by the disease and the difficulties added to job loss, lack of support in housework, lack of support in changing lifestyles, and lack of information and financial resources to adopt and maintain habits [16]. Some of these habits are a healthy diet that may involve dietitian visits, or access to certain types of foods, exercises, or therapies [17].

For this reason, it is important to analyze the needs and problems related to breast cancer patients' lifestyles (tobacco and alcohol consumption, eating habits, physical exercise), emotional well-being (quality of life, social networks, mental health, relationship with health services, employment situation), and use of CAM, and how these factors can influence survival. Thus, we designed the *Dones Amb Càncer de Mama* (DAMA) Cohort of women diagnosed with breast cancer, and in this paper we present the protocol that was followed to gather information and construct the profile of the women in this cohort.

Objectives

The main objective of the study is to analyze the influence of social determinants, lifestyle changes, emotional well-being, and use CAM in the progression of breast cancer in women diagnosed with breast cancer between 2003 and 2013 in Barcelona. Specific objectives include: (1) retrospectively describing lifestyles before and after breast cancer, according to socioeconomic status; (2) describing emotional well-being and use of CAM among women diagnosed with breast cancer, according to socioeconomic status; (3) describing patients' clinical progression from the time of breast cancer diagnosis to the start of the study; (4) evaluating whether lifestyle, emotional well-being, and the use of CAM are associated with tumor progression, according to socioeconomic status; and (5) analyzing the influence of contextual determinants on breast cancer progression according to lifestyles, emotional well-being, and the use of CAM.

Methods

Study Population

We included women aged >18 years who were diagnosed with and/or treated for breast cancer in the four most important hospitals in the Barcelona Public Hospital Network (Hospital Clínic, Hospital Vall d'Hebrón, Hospital de Sant Pau, Parc de Salut Mar) between January 1, 2003 and December 31, 2013. Subjects were women from the Minimum Basic Data Set who, at the time of admission in the hospital, coded with any of the codes between 174.0 and 174.9 of the 9th revision of the International Classification of Diseases (ICD-9). Inclusion criteria were: (1) aged >18 years, (2) admitted to hospital with a main diagnosis of breast cancer, and (3) diagnosed or treated at any time during the study period. Exclusion criteria were: (1) died from any cause before the start of the study, (2) diagnosed with any other type of cancer before being diagnosed with breast cancer, and (3) living outside Catalonia, due to difficulties in follow-up.

Study Design

We performed a mixed cohort study (prospective and retrospective) [18] using a convenience sample of women diagnosed with breast cancer. We studied disease progression (recurrence, death from breast cancer, death from a cause other than breast cancer, or remaining disease-free), and exposure factors (lifestyle, nutritional changes, quality of life, social network, emotional well-being, and use of CAM, among others).

Recruitment

We recruited women diagnosed with and/or treated for cancer at different stages, with and without relapse between 2003 and 2013. Thus, the cohort consists of women diagnosed with breast cancer at different phases of disease progression, and with information from the time of diagnosis onward. Candidates for inclusion received a letter from the hospital inviting them to participate. This letter was accompanied by two further documents: (1) information about the study, explaining the objectives, the institutions and hospitals involved, and the women's rights if they decided to participate in the study; and (2) two informed consent forms signed by the lead investigator of the study, one of which was a copy for the participant to keep, and the other to be mailed back in a postmarked envelope.

Coinciding with the beginning of the recruitment phase, we sent information to the participants and to professionals involved in their treatment and follow-up, to sensitize and inform them about the study. The professional recipients included: hospital specialists, primary care physicians, nurses, case managers, psycho-oncologists, and professionals in the Women's Sexual and Reproductive Health Care Program (PASSIR, in Spanish). We also distributed flyers with information about the study to hospitals, primary care centers, and Concerned Women's Associations. Two months after sending the women this information for the first time, we resent it to those who had not yet responded.

Ethical Approval and Consent to Participate

This study was evaluated first by the Clinical Research Ethics Committee of Parc de Salut Mar, and then by the corresponding committees of each hospital. Following the initial contact by the hospital, all women received two informed consent forms signed by the lead investigator; they kept one for themselves, and were asked to sign and return the other, which was an essential requirement for participation in the study. The informed consent form explained the subjects' rights, including the right to withdraw from the study at any time. Completed surveys and the databases created using them were anonymized using a code to link all information exchanged between the hospital and the study coordinating center.

Information Sources

We obtained information from various sources, including: (1) telephone interview and ad-hoc questionnaire; (2) hospital clinical records; (3) data from the National Statistics Institute, which we used to obtain ecologic indicators that then allowed us to analyze the influence of structural determinants; and (4) hospitals, relatives, and the Civil Register, which was our main source of the mortality information. The advantage of the civil register is that is contains almost real-time mortality data, while the mortality register provides data with almost two years delay. However, a disadvantage of the civil register is that it only records deaths that occur in Barcelona city, but those of women from Barcelona who died outside the city are not in this source of information.

Field Work

We had three data collection points or phases: Initial Welcome Call, Study Survey, and *Review of Medical Records*.

Initial Welcome Call

After receiving the informed consent forms, we called each candidate by phone and administered the Welcome Survey, which was intended to accomplish three things: (1) welcome the participant to the study and thank her for her participation; (2) determine her social profile; and (3) explain how we would continue developing the study, proceed to the next phase, and continue the study survey itself. The study survey was self-administered, and participants had the option to complete it online or send it by post.

Study Survey

Using either conventional mail or email, we sent participants a link to complete the survey online. To help resolve doubts, we offered participants follow-up and telephone or mail support at all times. If individuals had not responded within a month after sending the survey, we sent them a reminder by email or post and resent the survey if necessary. This survey collected the following data: sociodemographic data, health data, data on breast cancer and treatment received, lifestyle (tobacco, alcohol, nutrition, physical activity), emotional well-being (including information about social networks, emotional support, quality of life, mental health), satisfaction with health services (health professionals, personal treatment, information received), and use of unconventional therapies. Table 1 shows the parts of the questionnaire in detail and the origin of the questions.

Review of Medical Records

After completing this process, we reviewed the participants' clinical records, including: information at the time of diagnosis, tumor nodes metastases (TNMs; international classification of tumor, nodes, and metastases); status, biological characteristics, and characteristics of the tumor; treatment received; relapse; how the woman felt during her last visit to the hospital; and date. The number of women who followed the process from beginning to end can be seen in Figure 1.

Study Variables

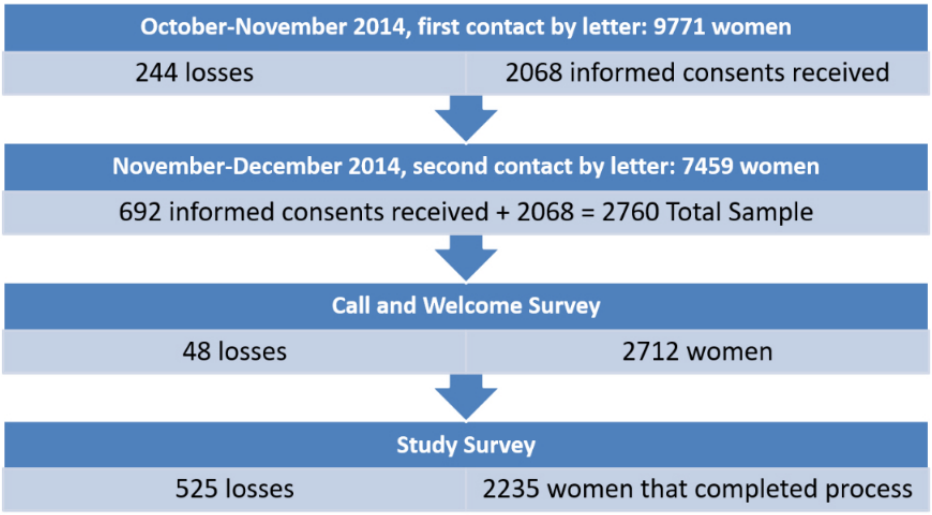
Dependent Variables

The main dependent variable is tumor progression or survival (relapse or metastasis, death, disease-free time). For objectives 1 and 2, the dependent variables are those related to: (1) lifestyle, including dietary habits, body mass index (BMI), smoking habits, and alcohol consumption (before and after diagnosis); (2) emotional well-being (quality of life, social networks, emotional support, and mental health), and use of CAM (type of CAM and frequency of use). Objective 3 is related to the clinical aspects of the tumor, and the dependent variables were: TNM at the time of diagnosis, stage, type of tumor (histology, hormonal receptors, Her2 expression), and type of treatment (mastectomy or not, reconstruction or not). For objectives 4 and 5, the dependent variable is tumor progression.

Table 1. Structure of the welcome survey and source of the questions.

Block and specific topic	Source
Health data	
General health	ESB-2011 (Barcelona Health Survey)
Fatigue	Brief Fatigue Inventory
Breast cancer data	
Diagnosis and treatment	Ad hoc
Lifestyle	
Tabacco	ESB-2011 (adaptation) and ad-hoc
Alcohol	EDADES-2011 (housing survey about alcohol and drug use in Spain)
Nutrition	Ad hoc
Physical activity	ESB-2011 (Barcelona Health Survey) and International Physical Antivity Questionnaire - Brief
Emotional well-being	
Quality of life	Two of the questionnaires from the European Organisation for Research and Treatment (EORTC) Quality of Life Questionnaire: QLQ-C30 (quality of life questionnaire in persons with cancer), QLQ-BR23 (specific for women with breast cancer)
Mental health	Hospital Anxiety and Depression Scale, ad hoc
Social support	Berkman-Syme Social Network Index, Modified Social Support Survey, ad hoc
Health care services	
Satisfaction	Ad hoc, Australian survey from Raupach and Hiller [19], some questions from Princess Margaret Hospital Patient Satisfaction Questionnary with Medical Doctor [20], article by Grunfeld et al [21].
Use of services	ESCA-2011 (Catalonia Health Survey)
Unconventional therapies	
General therapies	Complementary and Alternative Medicine adaptation, ad hoc
Cannabis	Ad hoc
Sociodemographic	
Social	ESB-2011 (Barcelona Health Survey), ESCA-2011 (Catalonia Health Survey), 2010/11 Survey of Health Ageing and Retirement in Europe - Wave 4
Personal	Ad hoc

Figure 1. Overview of the study process.



Independent Variables

We will study the variables for objectives 1 and 2 as dependent variables, and will also evaluate whether they are related to disease progression as independent variables (dietary habits, BMI, tobacco, alcohol consumption, quality of life, social networks, emotional support, unconventional therapy use). Similarly, the dependent variables in objective 3 (TNM, stage, type of tumor, and treatment) will also be used later as independent variables. Other variables include social class, based on the woman's job or that of the main person she lives with (according to the Spanish adaptation of the National Job Classification, CNO-2011 of the British Register General Classification), and level of education. We will also use contextual variables to perform multilevel analyses based on available family income, which is an index composed of: (1) academic qualification of the population measured as the proportion of higher degrees, (2) employment situation as the ratio of unemployed to working-age people, (3) ratio of cars to residents, (4) the power rating of new cars acquired by residents, and (5) second-hand residential market prices. Other contextual indicators can be selected according to the study variable for the various objectives (eg, distribution of green spaces, services, public transportation).

Analysis

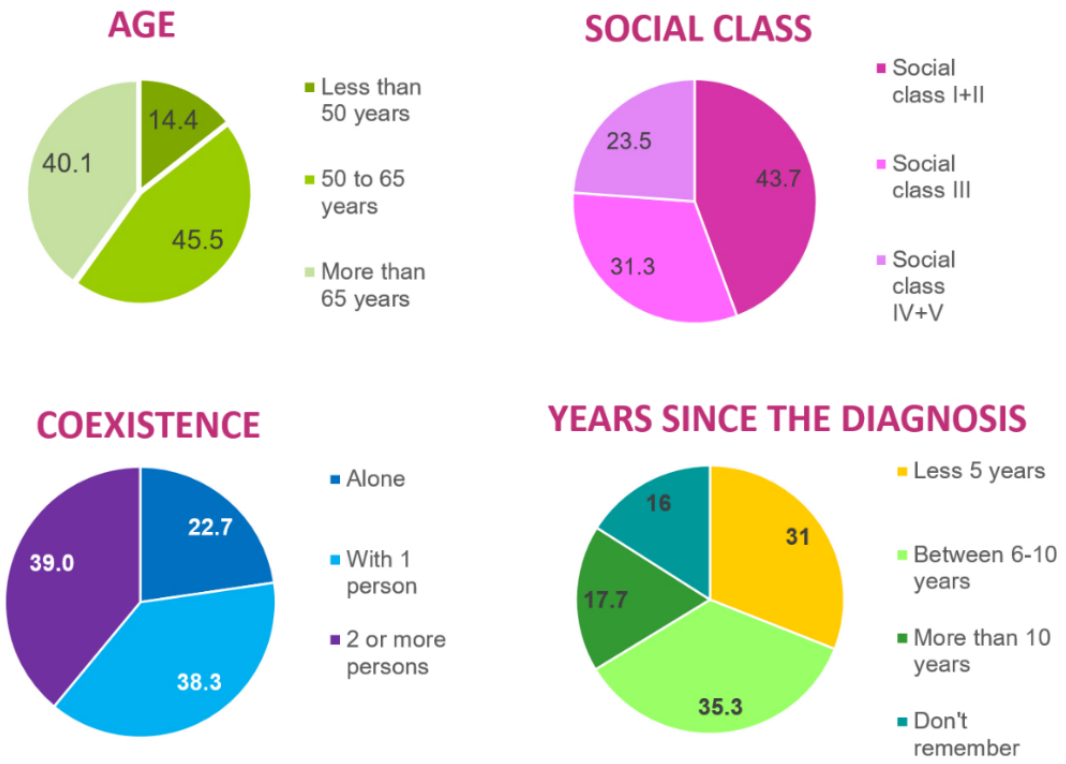
First, we will perform a descriptive analysis of each study variable. To test for differences in lifestyle before and after breast cancer diagnosis, we will use the appropriate paired data hypothesis tests for each data distribution, which we will stratify by socioeconomic status and cultural origin. We will perform a bivariate analysis to measure the degree of relationship between different study components within emotional well-being and unconventional therapy use according to socioeconomic level, age group, and years since diagnosis. We will compare means or percentages using student's t-tests or analyses of variances for continuous variables, and Chi-square tests for categorical variables. We will then carry out a multilevel analysis, adjusting regression models to observe the possible relationships between the dependent variable and lifestyles, emotional well-being, use of unconventional therapy, and social class.

We will use Cox regression to perform survival analyses of the number of relapses or metastasis and death, and with the following dependent variables: lifestyle components, emotional well-being, unconventional therapy, and socioeconomic status. We will calculate the hazard ratio and 95% CI for breast cancer, controlling for covariates using the Cox model and controlling for various risks. Women who did not present any of the events of interest at the time of the analysis will be considered right-censored. We will carry out this analysis using information from successive surveys or as mortality information becomes available. In these models, we will also perform a multilevel analysis which, in addition to analyzing individual variables, takes into account a second level consisting of the relationship of the event of interest with the contextual variables mentioned above. All analyses will be performed using STATA v11 and SPSS v18.

Profile of Women Recruited to the DAMA Cohort

We determined the final cohort based on the answers to the welcome survey, which was completed by 2712 of the women who were sent an informed consent form 98.26% (2712/2760). Forty-eight women did not respond for various reasons, but primarily because we could not locate them (Figure 1). As shown in Figure 2, 14.1% (391/2712) respondents were under 50 years of age, 45.50% (1234/2712) were between 50 and 65 years of age, and 40.08% (1087/2712) were over 65 years of age. By social class, 43.69% (1185/2172) belonged to the highest social classes (I and II), 31.27% (848/2712) to the middle class (III), and 23.49% (637/2712) to the working classes (IV and V). Forty-two respondents had missing data. In terms of cohabitation, 22.71% (616/2712) lived alone, 38.31% (1039/2712) lived with one person, and 38.97% (1057/2712) lived with two or more people.

Figure 2. Profile of the women of the DAMA Cohort by age, social class, number of people cohabiting, and number of years since diagnosis.



Regarding employment status, 34.96% (948/2712) of respondents were currently working, 20.46% (555/2712) were not currently working (either on leave or for a similar reason), and the remainder were either retired 33.52% (909/2712), or had a temporary or permanent disability 8.85% (240/2712) Sixty respondents had missing data. In terms of caregiving, 14.20% (294/2070) of cohabiting women lived with someone with a disability; of these, 24.83% (73/294) took care of the disabled person themselves, 7.82% (23/294) had help from their partners, and 5.78% (17/294) had hired help. We observed various domestic work situations, the most common being the woman assuming the work herself 37.39% (1014/2712), followed by cases where the woman had hired help 28.98% (786/2712). Regarding the evolution of breast cancer, 10.99% (298/2712) of the women reported having had a local or metastatic relapse (Table 2).

Given the option of responding to the questionnaire on paper or online, 29.98% (813/2712) of respondents chose the online version. Upon receiving the completed questionnaires, we sent the women a brochure with a complete menu of healthy food options, designed specifically for the women of the DAMA Cohort by a prestigious, internationally-known chef. A total of 2235 women completed this study and the entire process lasted 15 months.

Table 2. Description of the sample of women that comprise the DAMA Cohort. Some data are missing due to nonresponse.

Parameter	Number	Percentage (%)
Educational level, N=2712		
Primary or less	821	30.27
Secondary	813	29.98
University	879	32.41
Other situations	199	7.34
Working status, N=2712		
Currently working	948	34.95
Not currently working	555	20.46
Disability	240	8.84
Retired	904	33.33
Living with a disabled person, N=2070		
Yes	294	14.20
Who cares for this disabled person? N=294		
The subject alone	73	24.83
Shared with the partner	23	7.82
Shared with a hired helper	17	5.78
Who performs domestic tasks? N=294		
The subject alone	1014	37.36
Shared with the partner	418	15.41
Shared with a hired helper	786	28.98
Relapse, N=2712		
Yes	298	10.98
No	2392	88.20

Discussion

This is the first study performed in our context that is focused on analyzing different aspects that concern women diagnosed with breast cancer, but still remain unknown among health care professionals. The lack of knowledge, in combination with higher levels of patient interest over time, may have allowed us to successfully create the DAMA cohort with high levels of participation. Considering the total study population of 10,612 women, the theoretical sample size was 1928, which was markedly overcome by the actual number of participants enrolled in the DAMA cohort.

Limitations and Strengths

This study presents a number of limitations but also has strengths and important contributions. The fact that this is a self-administered survey with two ways to respond (online and on paper) introduces an initial bias since the choice depends on the type of woman answering the questionnaire. Furthermore, the online survey makes many questions obligatory in order to proceed, such that the paper survey has a higher probability of blank or poorly answered responses.

There is an implied and inevitable memory bias due to the fact that participants are asked about events that occurred a long time ago (in some cases more than 10 years earlier) and often before their breast cancer diagnosis. The same bias is also triggered by the fact that, as one of the participants mentioned, some women were reminded of issues they wanted to forget, in contrast to other women who had experienced them recently. This problem implies that the bias will operate in opposing directions.

Despite being the most important hospitals in Barcelona, which care for the largest number of women (approximately 85% of the total number of cases of breast cancer), the fact that we created this cohort using only patients that were in public hospitals implies that we probably do not have a representative sample of all women with breast cancer. In addition, more than 10,000 women were invited to participate, but those who accepted voluntarily participated. Therefore, a volunteer bias also exists.

It would be desirable to compare the participants of the study with the nonparticipants. However, the information available comes from hospital records, due to the lack of an official Cancer Registry, which do not allow this comparison. We still know that, in terms of age, the women who make up the DAMA Cohort are representative of the total number of women with breast cancer in Catalonia. Nonetheless, this is the first time that a study with these characteristics has been carried out in

our setting, and that explores factors beyond the hospital environment (that are also very important) that often leave women with a feeling of helplessness. This issue implies that women's personal resources and their social and structural environment are important for their opportunities and capacity to find day-to-day solutions to face the new personal challenges that arise in their new circumstances of dealing with the disease.

Perhaps for this reason, participation in the study was higher than expected, which is one of its strengths. The Welcome Survey was also key in raising women's awareness of being part of the cohort, as a way to establish direct and personalized contact with them.

The fact that this study deals with such diverse issues will allow us to solve hypotheses and answer questions while raising new ones. Over time we will be able to establish causal relationships, but for now this study already allows us to make some estimations because it includes women who have had the disease for different lengths of time, and at various stages of progression.

The information obtained will allow us to identify the main shortcomings, needs, and difficulties that women face after treatments for breast cancer. The study will also identify which population groups are more vulnerable than others; from this information we will be able to establish priorities upon which to intervene. This information will lay the foundation for designing and evaluating interventions that, if effective, can be integrated into health services and be equitably offered to all women with breast cancer.

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Authors' Contributions

RPR wrote the manuscript. All other authors drafted the manuscript, reviewed it, and made corrections and suggestions for improvement.

Conflicts of Interest

None declared.

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Abbreviations

BMI: body mass index
CAM: complementary and alternative medicine
DAMA: Dones Amb Càncer de Mama
FEDER: Fondos European Regional Development Fund
TNM: tumor nodes metastases

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Protocol

Participant-Centric Initiatives and Medical Research: Scoping Review Protocol

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Abstract

Background: Significant advances in digital technologies have meant that health care data can be collected, stored, transferred, and analyzed for research purposes more easily than ever before. Participant-centric initiatives (PCI) are defined as "tools, programs, and projects that empower participants to engage in the research process" using digital technologies and have the potential to provide a number of benefits to both participants and researchers, including the promotion of public trust in medical research, improved quality of research, increased recruitment and retention, and improved health care delivery.

Objective: The main objective of this scoping review is to describe the extent and range of PCIs across the United Kingdom, United States, and Japan that are designed to facilitate medical research.

Methods: The methodological framework described by Levac et al will be applied to this scoping review. We will search electronic databases (MEDLINE, EMBASE, PsychINFO, Cumulative Index to Nursing, and Allied Health Literature and CiNii), grey literature sources, Internet search engines (Google and Bing), and hand search key journals and reference lists of relevant articles. All digital tools and programs will be eligible for inclusion if there is a description of key features and functions that fall within the parameters of a PCI. Only those that play a role in medical research will be included.

Results: Preliminary searches conducted in MEDLINE and EMBASE retrieved 1820 and 2322 results, respectively. The scoping review will be completed by January 2018.

Conclusions: The scoping review will be the first to map the extent and range of PCIs currently available across the United Kingdom, United States, and Japan, and will be the first review to contribute to a better understanding of what PCIs patients may benefit from. Researchers and practitioners will be able to use information in this review as a guide for patients and also as a guide for the development of future tools and programs. The results will be disseminated through a peer-reviewed publication and conference presentations.

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KEYWORDS

patient engagement; patient public involvement; digital technology; patient participation; research participant; dynamic consent; data sharing; patient empowerment

Introduction

Over the last few decades there have been significant advances in digital technologies for health care provision and medical research. These offer new and innovative ways to recruit participants and conduct research, including the use of biobanks, data repositories, and social media, as well as the potential for secondary analyses of routinely collected data, such as administrative data and medical records [1,2]. This technological progress also means data can be stored, transferred, and analyzed more easily than ever before.

While there is vast potential for this to improve health care, there is a growing concern for participants' privacy, in particular how their data is being used and who has access to it. A traditional model of participant consent applies to the majority of research that is conducted; therefore, it is possible that once broad consent has been obtained, unbeknown to participants, their data may be shared with a variety of actors [3]. These technical advances and improved capabilities have coincided with the recognition of the importance of involving the public more closely in medical research, especially with regard to their views on privacy and consent.

The traditionally paternalistic attitude to medical research is also changing, with a shift towards a participant-centered model where the individual takes a more "active" role in the research process. It is believed that this approach is more ethical, can improve the quality of the research conducted, and may enhance the agency and control individuals have over their health and relevant data [4]. While the evidence to support this is currently limited, there remains a growing consensus about the importance of adopting this approach [5].

Participant-centric initiatives (PCIs) are platforms and programs that have been developed in order to facilitate the "active" role participants can take in medical research. PCIs are defined as "tools, programs, and projects that empower participants to engage in the research process" using digital technologies [6]. The characteristics can vary greatly between PCIs, however, the core features remain the same: the participant is placed at the center of decision-making and the user interface enables them to engage with the research process. Detailed explanations of PCIs and their features have been published elsewhere [6,7]. Briefly, PCIs fall into the following broad categories: (1) matchmaking, (2) direct-to-consumer (DTC), (3) dynamic negotiation, and (4) citizen science.

The matchmaking category refers to digital tools and platforms that enable individuals to connect and communicate with researchers and identify studies in which they might be eligible to participate, based on their personal information and preferences. Matchmaking tools put the individual in control of when, how, and what types of studies they are invited to participate in.

The DTC category refers to the commercial organizations that offer individuals a service in addition to opportunities to communicate with researchers and ways of being involved in research. Services can include social media networks where individuals can interact with others who have the same condition. Evidence suggests that peer-to-peer support has a variety of benefits for patients, particularly for those who are suffering from rare or stigmatizing conditions [8,9]. Other services may include genetic testing or tools to search for opportunities to participate in clinical trials.

Tools that were developed to give individuals greater control of how their data is used and shared for research purposes fall into the dynamic negotiation category. This offers participants an alternative to the traditional broad consent model that usually accompanies participation in medical research, enabling them to tailor their preferences and expectations [3].

Citizen science is a form of research driven by participants where they are heavily involved in some or all of the design, data collection, analysis, and dissemination of the study findings. A number of platforms have been designed to encourage this type of community-based approach to research that engages and involves participants at various points throughout the process. This type of research means that citizens can direct the research agenda to their own interests, develop their knowledge and skill sets, and bring a range of perspectives and expertise to a project [10].

PCIs have the potential to provide a number of benefits to both participants and researchers, including the promotion of public trust in medical research, improved quality of research, increased recruitment and retention, and improved health care delivery [7]. Because of this, we believe it is important to understand what PCIs are currently available to researchers and potential participants, and how they differ in terms of their key features and functions.

The main objective of this review is to describe the variety and prevalence of PCIs across 3 countries: United Kingdom, United States, and Japan.

We chose these countries because they differ with regard to the health care systems in place, the levels of engagement and involvement patients typically have in decisions regarding medical care and research participation, and public attitudes towards participation in medical research [11-14].

The United Kingdom and United States are leaders at the forefront of the patient-centric approach to health care. National organizations, such as INVOLVE and *Patient-Centered Outcomes Research Institute* (PCORI), which were set up over the past decade, provide support and guidance to stakeholders regarding the involvement and engagement of patients in medical research [15], and enable more informed health care decision-making through that research [16].

In comparison, in Japan, a paternalistic model of health care largely remains and research indicates that there is widespread satisfaction in this model [17]. A qualitative study conducted in Japan (2004) indicated that members of the public often make decisions about participating in research studies based on whether they trust the doctor they are speaking to or not, and described feelings of obligation when asked to participate by a doctor they like and trust. Participants also expressed a lack of interest in medical research; they felt it was something disassociated from them [14].

A survey conducted in 2009 by the National Institute of Science and Technology Policy (NISTEP) of the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) in Japan suggested that members of the general population are less interested in issues regarding science compared with individuals in the United Kingdom and United States [18]. However, a study we conducted in Japan that explored attitudes of patients to the potential use of digital technology for engaging with health care and medical research revealed that patients are interested in the use of digital platforms for this purpose [19]. So there is growing support in Japan for a more patient-centered approach to health care and medical research [17,20], but it is still very much in its infancy.

These differences in infrastructure and culture make for interesting comparisons in the types of PCIs that are currently available in the United Kingdom, United States, and Japan.

Methods

A scoping review was considered the most appropriate design to address the aims of this study for a number of reasons. Firstly, the aims of this review are very broad and unlike a systematic review or meta-analysis, we are not trying to answer a specific question, but rather "examine the extent, range, and nature of a research activity" [21]. Secondly, a scoping review is rigorous and requires implementing a comprehensive and systematic approach to searching for relevant literature. The scoping review methodological framework described by Levac et al [22] will be applied to this scoping review. The framework is based on the seminal work of Arksey and O'Malley [21] and comprises the following stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) consultation.

Stage 1: Identifying the Research Question

This study has built on the work by Kaye et al [7], which discussed the key features, benefits, and challenges of implementing PCIs. We describe examples of PCIs currently available for research purposes. Understanding the range and features of PCIs available was deemed important as it could inform researchers', clinicians', and also potential research participants' decisions about research. The research question was developed by a multidisciplinary research team which included academic researchers from a range of fields including law, bioethics, and public health, and was refined as the research team became more familiar with the literature.

Key Definitions

We use the term "medical research" throughout to refer to a broad range of research that can be applied to medical treatments, services, and settings. In addition, we refer to the "extent and range" of PCIs throughout this protocol. By "extent" we are referring to the prevalence of PCIs within each country and "range" refers to the type of PCI (using the categories described above) and the key features of each PCI included in the study.

Research Question

Our research question is: What is the extent and range of participant-centric initiatives available for medical research across the United Kingdom, United States, and Japan?

Objectives

The objectives of the study are to (1) identify existing PCIs currently used for medical research purposes across the United Kingdom, United States, and Japan; (2) compare the number and types of PCIs available within the United Kingdom, United States, and Japan; (3) estimate the number of participants using such platforms, tools, and programs across each country; (4) where possible, identify the model of consent used; (5) identify and describe the key features of PCIs available within each country; and (6) identify gaps in PCI provision within the United Kingdom, United States, and Japan.

Stage 2: Identifying Relevant Studies

To guide the search strategy a set of parameters was developed by the research team, which included inclusion and exclusion criteria (Textbox 1), which scientific databases to search, where to search for grey literature, search terms to use, search limitations applied, and which experts to consult with regard to review findings. To verify which countries a particular PCI is available in, we will take the following multistage approach: (1) identify the country of origin or use reported either in the journal article describing the PCI or directly on the website, platform, or tool; (2) if it is not possible to identify this from the journal article or PCI website, platform, or tool, we will contact the organization that developed the PCI or the authors of the journal article; (3) if we do not receive a response detailing the country of origin/use, we will try to identify the Web address of any Internet-based PCI (ie, '.co.uk' or '.jp') and any country-specific requirements for participants to access PCIs (ie, National Health Service [NHS] number in the United Kingdom or social security number in the United States). In the event that we identify PCIs that are based in one country but available for use in another, we will report the PCI as available in both countries. For example, some PCIs are based in the United States, but open to a global audience, such as Patients Like Me. This would be reported twice, as a PCI that is available within both the United Kingdom and United States. Because the aims of this review are broad, we felt it was beyond the remit of this review to include all citizen science platforms, programs, or tools. The term "citizen science" is used to describe a wide variety of activities [10] and we have decided to take a pragmatic approach and focus our search on matchmaking, dynamic negotiation, and DTC PCIs only.

Search Strategy

Three systematic reviews assessing different aspects of patient and public involvement (PPI) within health care decisions [23-25] were used to develop the original search strategy for this scoping review. Preliminary searches were conducted in MEDLINE and EMBASE to further develop the search terms, Medical Subject Headings (MeSH), and limitations used. A specialist subject librarian was also consulted and provided guidance on search strategy.

Textbox 1. Inclusion and exclusion criteria.

Inclusion

- Article or website describing PCI
- Published in English language or Japanese
- Adult population (18 or more years)
- Focus on medical/health care research purposes
- Complies with PCI definition described by Anderson et al [6]
  - Digital device or tool/computer program/digital platform
  - Enables potential participant to take initiative within either of the following research processes:
    - To connect and communicate with researchers
    - To control what data is used and shared for research purposes
  - Available to participants residing in the United Kingdom, United States, or Japan

Exclusion

- Platforms that enable patients to connect and communicate with other patients only
- Platforms that use data for research, but participants are not engaged or empowered by the process
- Citizen science

Search terms included a mixture of keywords and MeSH terms using combinations of the terms listed in Textbox 2. Proximity search functions were used to link related terms and narrow the search. Similar searches will also be conducted in Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Psych-Info. Equivalent terms in Japanese will be used to search CiNii.

Due to the topic of this scoping review, it is likely that many PCIs will exist that are not written about in scientific literature. Therefore, we will conduct a thorough search of grey literature to identify non-indexed relevant literature. The grey literature search will focus on conference abstracts and PPI organization websites. We will therefore search Open Grey (grey literature database), Google, and Bing using the same terms listed in Textbox 2.

We will also hand search key journals (Digital Health, The Journal of mHealth, International Journal of Digital Health care, and Journal of Japan Society for Health care Management), and the reference lists of relevant articles for citations that were not identified from the original database search.

Finally, we will contact experts within the field of PCIs and invite them to participate as part of an expert panel. The panel will be made up of bioethicists, clinicians, PPI experts, and digital health specialists who reside in the United Kingdom, United States, and Japan. The panel will be consulted to provide feedback on our findings and to ensure that we have identified all relevant literature.

All searches will be conducted by members of the research team and reference management software will be used to store all relevant literature.

Stage 3: Study Selection

The study selection process will be conducted in 2 stages. In the first stage, one researcher in the United Kingdom will conduct the search for English language literature and another researcher will conduct the search for Japanese literature. Titles and abstracts or website content will be reviewed based on the defined inclusion and exclusion criteria. At this initial stage the goal is to be more inclusive and articles or websites will only be excluded if it is clear that they fall outside of the eligibility criteria. If the reviewer is uncertain at this stage, the article or website will be included. In the second stage, full text articles will be obtained and 2 reviewers will independently review the articles and websites that have been collected in the first stage. The articles and websites will be grouped into 3 categories: included, excluded, and uncertain. The reviewers will then compare categories to ensure inter-rater reliability and validity. If there are any discrepancies that cannot be resolved, a meeting will be held with a third reviewer to discuss the articles and websites until a consensus is reached. If a consensus cannot be reached, the decision of the majority will be taken.

Stage 4: Charting the Data

This stage involves extracting the relevant data from included articles and websites that will help to address the original aims of the scoping review. A data extraction form will be developed based on key characteristics by the research team and members of an expert panel will be consulted to ensure that all relevant details will be obtained.

Two researchers will then pilot the data extraction form on the first 25 articles or websites to be included. The research team will meet to discuss findings of the pilot to decide whether amendments need to be made.

Textbox 2. Search terms.

- Participant
  - participant
  - public
  - citizen
  - stakeholder
  - communit*
- Engagement
  - engage*
  - involve*
  - PPI
  - citizen science
  - participatory
  - empower
  - consult
  - partner
  - collaborate
  - collaboratory
  - crowdsourc*
- Medical research
  - trial
  - RCT
  - research
  - studies
  - study
  - qualitative
  - quantitative
  - evaluation
  - observational
  - cohort
  - case control
  - research design
- Technology
  - technology
  - digital
  - platform
  - online
  - Internet
  - computer
  - website
  - software
  - program

Textbox 3. Preliminary steps in the data extraction process.

- Researcher performing data extraction and date conducted
- Identifying characteristics of article or website (ie, author, year, title, website name, organization)
- Country of origin/use (United Kingdom, United States, or Japan)
- Description of PCI (aim, type of platform, and method of engagement)
- Approximate number of users
- Participant requirements for use such as subscription or access fee, clinician referral, participant personal identifier (ie, NHS number, social security number, post/zip code, etc)
- Type of organization (private/public or for profit/not for profit)

  Target population (general population or specific patient groups, global, or country specific)
- Nature of research conducted
  - Participant invited to take part in primary research studies
  - Secondary use of data already available (ie, routinely collected hospital data from medical records or data generated from discussion between participants)
- Who will conduct the research/access data
  - Commercial organizations
  - Public sector/non-profit researchers
  - Universities/other educational institutes
  - Other
- Type of interaction
  - Matchmaking
  - Dynamic negotiation
  - Direct-to-consumer
- Stakeholder interaction
  - Participant to participant
  - Participant to researcher
  - Participant to clinician/health care professional
- Model of consent
  - Broad consent: a participant signs up and agrees their data can be used for any research relevant
  - Explicit consent: a participant's consent is requested before each use with a study
  - Dynamic consent: a participant can specify particular future uses of their data that they will allow and uses that they will not allow
- Any additional key features
  - Ability to withdraw
  - Control over level of contact (study invitations/follow up procedures)
  - Other

This is an iterative process and a number of versions will be developed and reviewed before the full data extraction process can be conducted. Data extraction will be completed by 2 researchers and a random sample of articles will be chosen for review by a third researcher to ensure validity. Preliminary steps are shown in Textbox 3.

Stage 5: Collating, Summarizing and Reporting the Results

The breadth of this scoping review means it is likely that a large amount of data will be generated. In order to adequately address the aims of this scoping review, which are to map the extent and range of PCIs available across the United Kingdom, United States, and Japan, the results will be presented in the following ways: (1) we will use the Preferred Reporting Items for

Systematic Reviews and Meta-Analysis (PRISMA) flow chart template reporting the search process [26]; (2) results tables presenting the key characteristics of included PCIs that will be stratified by country and potentially also by patient groups; and (3) a narrative analysis which will include a description of key findings, a critical analysis of included PCIs, and summary of gaps within PCI provision across the 3 countries of interest.

The findings will be presented in accordance with the PRISMA reporting guidelines where appropriate. We will also consult our expert panel members after a first draft of results has been developed to explore whether our search strategy has identified all key PCIs that are related to our research objectives.

Stage 6: Consultation With Expert Panel

The consultation stage of the scoping review will provide opportunities for input from a variety of stakeholders to ensure that the knowledge produced from the project is relevant and accessible. We will employ an expert panel of stakeholders who we will consult with during stages 4 and 5 to ensure we are gathering data that is considered important, that our search strategy has identified all relevant PCIs, and that our findings are clear and understandable. The expert panel will be comprised of researchers within the area of PPI, patient engagement and health care digital technologies, clinicians, and members of patient organizations (lay patient/public representatives). In addition to this, the final stage of this review will ensure that the knowledge generated as part of this study will be disseminated to all relevant stakeholders. A lay summary of the findings will be produced and reviewed by our patient/public representatives. The final version will be sent to members of the wider stakeholder community along with a full text article of the review.

Results

Preliminary searches were conducted in November 2016. Initially, searches were retrieving too many results, rendering it impractical. Advice from a specialist librarian was sought and the search strategy was refined by combining search terms that described the study population and characteristics of PCI (ie, participant/ patient/ public AND engagement/ involvement/ recruitment, etc). The subsequent searches were conducted in MEDLINE and EMBASE and retrieved 1820 and 2322 results, respectively.

The remaining stages of the proposed scoping review will be complete in January 2018.

Discussion

The aim of this scoping review is to map the extent and range of PCIs currently available across the United Kingdom, United States, and Japan. This will be the first scoping review conducted within this area and will contribute to a better understanding of what PCIs patients may benefit from. The rapid advances in digital technologies over the last decade have contributed to a shift in how a lot of medical research is approached, including the ability to link large administrative datasets, which has led to an increase in the analysis of routinely collected data for medical research purposes [27,28]. However, with these benefits also comes an increase in privacy concerns for the participants within these research studies. PCIs have the potential to facilitate research recruitment, increase retention rates, and build public trust with researchers by transferring more control to participants and providing a more transparent view of the research process. Therefore, by identifying gaps within the current market, we hope that new and innovative platforms will be developed to engage, empower, and involve potential participants within the research process.

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Conflicts of Interest

None declared.

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Abbreviations

DTC: direct-to-consumer
PCI: participant-centric initiatives
PPI: patient and public involvement
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

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