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Protocol

Evaluation of a Behavioral Mobile Phone App Intervention for the Self-Management of Type 2 Diabetes: Randomized Controlled Trial Protocol

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Abstract

Background: Patients with type 2 diabetes mellitus (T2DM) struggle with the management of their condition due to difficulty relating lifestyle behaviors with glycemic control. While self-monitoring of blood glucose (SMBG) has proven to be effective for those treated with insulin, it has been shown to be less beneficial for those only treated with oral medications or lifestyle modification. We hypothesized that the effective self-management of non-insulin treated T2DM requires a behavioral intervention that empowers patients with the ability to self-monitor, understand the impact of lifestyle behaviors on glycemic control, and adjust their self-care based on contextualized SMBG data.

Objective: The primary objective of this randomized controlled trial (RCT) is to determine the impact of *bant2*, an evidence-based, patient-centered, behavioral mobile app intervention, on the self-management of T2DM. Our second postulation is that automated feedback delivered through the mobile app will be as effective, less resource intensive, and more scalable than interventions involving additional health care provider feedback.

Methods: This study is a 12-month, prospective, multicenter RCT in which 150 participants will be randomly assigned to one of two groups: the control group will receive current standard of care, and the intervention group will receive the mobile phone app system in addition to standard of care. The primary outcome measure is change in glycated hemoglobin A1c from baseline to 12 months.

Results: The first patient was enrolled on July 28, 2015, and we anticipate completing this study by September, 2018.

Conclusions: This RCT is one of the first to evaluate an evidence-based mobile app that focuses on facilitating lifestyle behavior change driven by contextualized and structured SMBG. The results of this trial will provide insights regarding the usage of mobile tools and consumer-grade devices for diabetes self-care, the economic model of using incentives to motivate behavior change, and the consumption of test strips when following a rigorously structured approach for SMBG.

Trial Registration: ClinicalTrials.gov NCT02370719; https://clinicaltrials.gov/ct2/show/NCT02370719 (Archived at http://www.webcitation.org/6jpyjfVRs)

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KEYWORDS

diabetes mellitus; type 2; telemedicine; evaluation; self-care; randomized controlled trial; mobile applications; motivation; blood glucose

Introduction

Background

The increasing global prevalence of diabetes is challenging traditional approaches towards diabetes management. It is not sustainable, nor cost effective, to assume that there will be an increase in health care delivery resources to address the growing prevalence of diabetes. Novel self-management tools, which aim to engage patients in daily diabetes care and optimize the role of health care professionals, may facilitate a more robust, scalable, and effective approach to the management of diabetes [1].

While self-management is a major component of chronic disease management, the majority of patients are not provided, or do not have access to, the tools and personalized education needed to engage in daily self-care practices [2] . Self-monitoring of blood glucose (SMBG) continues to be prescribed to patients as a self-management tool without the additional context, education, and frequent feedback required to interpret trends and adjust behaviors accordingly [3,4].

Furthermore, recent policy changes have reduced the reimbursements for test strips for patients who are not treated with insulin, further limiting access to SMBG as a self-monitoring tool [3]. These policy changes have been informed by evidence that evaluated SMBG as a standalone intervention, without the training required to understand the results of SMBG or frequent feedback from health care providers (HCPs). As such, patients that are not treated with insulin have limited support for test strip reimbursements, and also lack the education and tools needed to interpret and derive actionable knowledge from SMBG data.

Recent evidence has shown that when SMBG is performed in a structured manner, and is coupled with appropriate feedback and education, it may lead to positive health behavior change amongst patients with type 2 diabetes mellitus (T2DM) who are not treated with insulin [3]. As such, we hypothesized that the effective self-management of non-insulin treated T2DM requires a behavioral intervention that empowers patients with the ability to self-monitor, understand the impact of lifestyle behaviors on glycemic control, and adjust their self-care based on contextualized data.

The popularity of smartphones has presented an opportunity to deliver this type of intervention in the form of an evidence-based and user-centered diabetes self-management app [5-8]. The systematic design of the mobile health (mHealth) app *bant2* was informed by evidence and feedback from end-users, and is following a rigorous evaluation framework [1]. The evaluation framework is a blended model of the Knowledge to Action and Medical Research Council's framework for complex interventions, and ensures that the intervention and study design, as well as the evaluation, follow a robust methodological approach [9].

The primary objective of this randomized controlled trial (RCT) is to determine the impact of the evidence-based, patient-centered, mobile app for the self-management of T2DM. Although there are many diabetes-focused electronic health (eHealth) tools currently available, the majority require a third party HCP to facilitate decision making [5]. Our second postulation is that automated feedback delivered through the mobile app will be as effective, less resource intensive, and more scalable than interventions involving additional HCP feedback.

Methods

Trial Design

The *bant2* study is a 12-month, prospective, multicenter, unblinded, parallel RCT in which 150 participants are randomly assigned to one of two groups: the control group receives current standard of care, and the intervention group receives the mobile phone app system in addition to standard of care. During the study period, all participants (intervention and control) attend quarterly clinic visits (standard care) and receive usual care.

The primary recruitment strategy for this study is through self-referral at primary care and community practices throughout the Greater Toronto Area. This area includes sites that are situated in urban and suburban settings. The University Health Network Research Ethics Board (REB) approved the study (14-7978-AE). Local institutional REB approvals were also obtained from the following participating sites: St. Joseph's Health Care Centre (#2015-010), Trillium Health Partners (#698), and North York General (#15-0038). For sites without an institutational REB, namely the Taddle Creek Diabetes Education Program and LMC Diabetes and Endocrinology, approval was obtained from an Institutional Review Board (Pro00016415).

Randomization is being conducted at the patient level, using random block sizes of four and six to reduce the variance across the entire sample, with a 1:1 allocation ratio. Stratificaiton is also conducted by recruitment site. The allocation envelopes contain a piece of paper with either *control* or *intervention* written upon it, as well as a random patient identifier. The study coordinator allocates each participant by taking the envelope on the top of the stack, and enrolls the participant into the appropriate study arm, as indicated.

Intervention

The participants randomly assigned to the intervention group will receive an iPhone 5S loaded with the *bant2* app, as well as a Bluetooth-enabled (a standard protocol for short distance wireless communication) Wahoo weight scale (Wahoo Fitness, Atlanta, GA, USA), a Jawbone UP24 (Jawbone, San Francisco, CA, USA) wrist-worn activity monitor, and a Jazz blood glucose meter (Agamatrix, Salem, NH, USA) [9]. We will also provide BlugluLe, a Bluetooth adapter that connects to the glucose meter and enables the wireless transfer of readings from the meter to the iPhone. The *bant2* mobile app also enables users to capture meal photos using the built-in camera, and track medication adherence on a weekly basis. In addition to the wrist-worn activity monitor, steps could also be tracked through the mobile phone itself using the built in accelerometer.

The *bant2* app, shown in Figure 1, facilitates self-monitoring of lifestyle behaviors, and enables patients to correlate their lifestyle behaviors with their glycemic control through paired (pre- and post-prandial) blood glucose testing [10]. Upon data capture, the app will assess the other data points in context, identify positive and negative behaviours based on the analysis, and faciliate remedial decision making. The app also enables patients to set goals and receive reminders, participate in a closed-gated social community, and accumulate points for positive behaviors, which can be redeemed for tangible gift cards (eg, groceries, gym memberships) [9]. This app builds on a previous version of the *bant* app, which focused on engaging adolescents in the self-management of type 1 diabetes mellitus (T1DM). A 12-week pilot of *bant* app demonstrated positive behavior change amongst the adolescents with T1DM [11].

We have ensured that all of the appropriate safeguards are in place to protect personal health information. For example, the iPhone requires a passcode to access the app, and the app itself requires a username and password. In the event that the device is lost or stolen, we can remotely wipe the device using mobile data management software (Airwatch, Atlanta, GA). The *bant2* app is intended to provide guidance and facilitate diabetes self-management, and is not classified as a medical device. Given that the app poses minimal risk to the patient, Health Insurance Portability and Accountability Act requirements do not apply.

Figure 1. The bant2 mobile app enables users to monitor lifestyle behaviors and correlate them to their overall glycemic control.

(a) (b) (c)

Participants

The inclusion criteria for participants include: definitive diagnosis of T2DM, not treated with insulin, at least 18 years of age, a baseline glycated hemoglobin A1c (A1c) of 7.5% or higher, and ability to speak and read English.

Exclusion criteria include: inability to use a mobile phone (eg, due to vision problems) or to comply with home monitoring (eg, due to suffering from anxiety or depression), and duration of diabetes under one year. Participants who have had diabetes for less than one year are excluded because they typically demonstrate a higher adherence to self-care and have high levels of motivation [12].

Outcomes

The primary outcome measure is change in A1c from baseline to 12 months. Each recruitment site is provided with a DCA Vantage Analyzer (Siemens, Munich, Germany) point of care A1c device to reduce the variability in the A1c laboratory assays. As secondary end points, A1c measurements are also collected at 3-month intervals (3, 6, and 9 months). Clinical staff within the patient's circle of care are conducting the point of care A1c tests.

Secondary outcomes include blood pressure (mmHg), weight (pounds), total cholesterol (mmol/L), Low Density Lipoprotein cholesterol (mmol/L), and weight at baseline, 3, 6, 9, and 12 months. The number of participants who achieve optimal glycemic control (A1c <7%), as well as the type and frequency of medication changes, will also be measured. Furthermore, validated instruments described in Table 1 are being used to collect and measure burden of disease and diabetes-related self-efficacy and self-care, pre-, mid-, and post-study.

Table 1. Validated instruments administered pre-, mid-, and post-study.

Measure	Description
Diabetes Distress Scale (DDS)	The DDS is a 17-item instrument that assesses the emotional, physician-related, regimen-related, and interpersonal aspects of diabetes distress, and provides an indication of diabetes-related quality of life [13].
Diabetes Empowerment Scale - Short Form (DES-SF)	The DES-SF is a 28-item instrument used to measure psychosocial self-efficacy of diabetes self-management. This tool focuses on (1) managing diabetes, (2) assessing readiness to change, and (3) willingness to set goals and change behaviors [14,15].
Summary of Diabetes Self-Care Activities (SDSCA) measure	The SDSCA is a 11-item instrument that assesses individual levels of diabetes self-care, focusing on general diet, specific diet, exercise, medication adherence, blood-glucose testing, smoking, and foot care [16].
The Mobile Application Rating Scale (MARS) App - User Version	The MARS is a 26-item instrument used to evaluate the quality, functionality, and overall satisfaction of the mobile app itself [17].

Sample Size

The sample size estimation was based on detecting a minimum reduction of 0.5% in A1c values. Given our inclusion criteria of A1c >7.5%, we anticipate that A1c levels will be highly clustered around 8.5% (standard deviation 1.0). A minimum of 63 participants per group is necessary to detect a difference of 0.5% in A1c, at an 80% power with a one-sided 5% significance level in all anticipated cases. With a further 15% adjustment for potential dropouts, a final sample size of 150 subjects will be required for both groups, with 75 participants in each study arm. All calculations were performed using the R software package, *epibasix* [18].

Recruitment Procedure

Physician Recruitment

The lead physician (or research administration staff) of the recruitment site is first approached by email regarding their interest in the study, and a 20-30 minute presentation is offered as a way to disseminate the study details and gauge interest across the site. If the lead physician is interested in participating, they contact the clinicians within their site, disseminate information regarding the study, and identify the clinicians interested in participating in the study. Upon receiving REB approval, a staff member at the participating site generates a list of eligible participants and has the list vetted by the respective physicians for appropriateness.

Patient Recruitment

The participating sites send invitation letters to eligible and appropriate participants, explaning the study goals and protocol. The letter invites participants to contact the study coordinator directly, either by email or phone call, if they are interested in participating in the study. Upon initial contact, the study coordinator describes the study and answers any of the patient's study-related questions. If the respondent is interested in participating, the coordinator will schedule an appointment with the respective clinic, and email or mail the patient the consent form in advance for review.

Data Analyses

The principal analysis strategy will be the use of linear mixed models in the Statistical Analysis System (Cary, NC, USA) using the PROC MIXED procedure. This approach provides a simple method to incorporate baseline values and the correlation of each participant over time (using a random effect). This model is more powerful than the repeated measures *analysis of variance*, as it can easily examine differences between the RCT groups at all time points, and can accommodate potential confounders. Furthermore, although the A1c measurements will be made at 3-month intervals, our primary analysis will focus on A1c levels at the conclusion of the 12-month study. A contrast will be constructed to test this primary comparison among all possible pair-wise tests; no adjustments for multiple testing will be required. Subsequent adjustments will be made for potential confounding variables as necessary, such as baseline parameters that may vary between groups (eg, age, sex).

Secondary contrasts will be used to examine differences from baseline for all other time points; however, these will be of exploratory interest only. Moreover, we will use regression analysis to separate the contribution of the different intervention components (activity monitor, weight scale, SMBG, mobile app features), and determine their independent effects on the primary outcome at 12 months. This approach will identify which aspect of the mHealth intervention contributed to the change in A1c.

Results

This trial is currently open for recruitment. The anticipated completion date for the study is September, 2018.

Discussion

SMBG is an essential part of managing glycemic control. However, for T2DM patients that are not treated with insulin, the standard approach of simply recommending SMBG without the appropriate guidelines and training will not facilitate behavior change [4]. Polonsky outlines four main considerations for SMBG amongst this specific population: (1) SMBG should be structured and performed regularly around key events (eg, meals), (2) patients need to be provided with SMBG-related training, (3) clinicians must be able to view SMBG data and use it to inform clinical decisions, and (4) useful display of SMBG data to facilitate pattern identification [3]. To our knowledge, the *bant2* app is the first mobile app to facilitate structured SMBG, enable simple pattern and trend detection, and potentially facilitate communication between the patient and HCPs during clinic visits.

This RCT will evaluate the use of the *bant2* app as a self-management tool compared to standard care, over a period of 12 months. We anticipate that the use of the app will provide patients with a greater understanding of which aspects of lifestyle behaviors impact glycemic control, increase participation in self-care activities, and potentially improve diabetes outcomes. We also anticipate that along with higher levels of engagement, patients will initiate conversations with their HCPs, using the SMBG summary data displayed in the app as a reference during consultations. The sharing of such data may result in earlier treatment optimization and medication changes in the intervention group compared to the control group.

A considerable limitation of the study is that the iPhone provided to the intervention group is likely to be a secondary device, potentially hindering the complete immersion of the app into daily routines.

At the time of the intervention design, there were no Bluetooth-enabled blood glucose meters available in Canada. In order to facilitate the wireless transfer of blood glucose readings to the app, and reduce burden and errors associated with manual entry, we had to develop a customized Bluetooth adapter [9]. Future studies should explore how apps can be installed directly on an individual's personal devices, and explore ways to utilize off-the-shelf meters that consumers are already familiar with (and which meters are potentially reimbursable). These issues highlight the challenges of RCTs as an evaluation approach for mobile apps. Given the rapid evolution of technology (eg, Bluetooth-supported devices), the mHealth interventions evaluated in trials are often no longer relevant once the lengthy trials have concluded several years later [19].

Furthermore, as outlined by Polonsky [3], we were not able to provide additional education and skills training to providers. However, we anticipate that through the use of *bant2*, patients will develop an understanding of glycemic control and self-management skills, leading to improved lifestyle management.

The results of this study will further our understanding of how an evidence-based behavior modification mobile app can guide patients in the self-management of their diabetes. Specifically, we will be able to assess how various features of the *bant2* app influence self-management behaviors. For example, we will examine how consumer-grade devices (such as wearable devices) facilitate chronic disease management, and how incentive mechanisms potentially motivate behavior change. Most importantly, the study data will demonstrate how test strips are consumed when SMBG is performed in a systematic way, and the impact of immediate feedback on glycemic control and trends.

Conclusions

This RCT is one of the first studies to evaluate an evidence-based mobile app that focuses on facilitating lifestyle behavior change driven by contextualized and structured SMBG. The results of this trial will provide insights regarding the usage of mobile tools for diabetes self-care, the effectiveness of consumer-grade devices for chronic disease management, the economic model of using incentives to motivate behavior change, and the consumption of test strips when SMBG follows a rigorously structured approach. The findings from this study will inform the next generation of diabetes education, guidelines for SMBG, and potentially inform health policy pertaining to strip reimbursements for T2DM patients that are not treated with insulin.

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Authors' Contributions

SG developed the concept and led the design of the study, and JC, CY, GL, ES, and MR contributed to the design of the study. SG drafted the manuscript, and JC, CY, GL, ES, and MR edited and reviewed the manuscript. JC is the principal investigator of this study.

Conflicts of Interest

None declared.

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Abbreviations

A1c: glycated hemoglobin A1c
DDS: Diabetes Distress Scale
DES-SF: Diabetes Empowerment Scale - Short Form
HCP: health care provider

MARS: Mobile Application Rating Scale
mHealth: mobile health
RCT: randomized controlled trial
REB: Research Ethics Board
SDSCA: Summary of Diabetes Self-Care Activities
SMBG: self-monitoring of blood glucose
T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus

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Protocol

Baby Steps - An Online Program Promoting the Well-Being of New Mothers and Fathers: A Study Protocol

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Abstract

Background: Parental well-being can be seriously impacted during the challenging perinatal period. Most research and support services focus on perinatal psychopathology, leaving a need for programs that recognize and enhance the strengths and well-being of parents. Furthermore, fathers have received minimal attention and support relative to mothers, despite experiencing perinatal distress. New parents have limited time and energy to invest in program attendance, and web-based programs provide an ideal platform for delivering perinatal well-being programs. Such programs are globally accessible, available at any time, and can be accessed anywhere with an Internet connection.

Objective: This paper describes the protocol of a randomized controlled trial investigating the effects on first-time parents' perinatal well-being, comparing two versions of the online program Baby Steps.

Methods: The clinical trial will randomize 240 primiparous mother-father couples to either (1) Babycare, an online information-only program providing tips on selected childcare issues, or (2) Well-being, an online interactive program including all content from the Babycare program, plus parental well-being-focused content with tools for goal-setting and problem solving. Both programs will be supported by short message service (SMS) texts at two, four, seven, and ten weeks to encourage continued use of the program. Primary outcomes will be measures of perinatal distress and quality of life. Secondary outcomes will be couple relationship satisfaction, parent self-efficacy, and social support. Cost-effectiveness will also be measured for each Baby Steps program.

Results: Participant recruitment commenced March, 2015 and continued until October, 2015. Follow-up data collection has commenced and will be completed May, 2016 with results expected in July, 2016.

Conclusions: Perinatal distress has substantial impacts on parents and their infants, with potential to affect later childhood adjustment, relationships, and development. This study aims to test the impact of a highly accessible online program to support

parental coping, and maximize the well-being of both parents. By including fathers in the program, Baby Steps has the potential to engage and support this often neglected group who can make a substantial contribution to familial well-being.

ClinicalTrial: Australian & New Zealand Clinical Trials Registry: ANZCTR12614001256662; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=367277 (Archived by WebCite at http://www.webcitation.org/6ibUsjFIL)

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KEYWORDS

Perinatal; Wellbeing; Fathers; Mothers; Online Intervention; Randomized Controlled Trial; Quality of Life; Mental Health

Introduction

The perinatal period is challenging for parents, and the changes and demands encountered during this life transition can seriously impair parents' well-being. The impact of these challenges is well-recognized in mothers with postpartum depression rates of approximately 20% in Australian women [1]. Most new mothers (50-80%) experience some distress [2]. A meta-analysis of fathers' postpartum mental health found comparable rates of depression (10%) [3], with Australian figures reporting the rate at approximately 5% [4,5]. Initiatives by *beyondblue* and the Federal Government have increased perinatal depression screening and intervention rates in Australia. However, screening and preventive programs for perinatal depression have not been universally available [6], and have been almost non-existent for fathers, despite the potential suitability of the Edinburgh Postnatal Depression Scale (EPDS) for fathers [7]. Lack of availability of these father-specific programs is a reflection of both supply (eg, a focus on mothers, service capacity, and staff adherence) and demand issues (eg, reluctance to disclose symptoms and receive treatment) [8]. An accessible perinatal well-being intervention designed for both mothers and fathers is the target of this trial.

Postpartum distress has significant and wide-ranging consequences. In mothers, postpartum distress affects attachment [9], child development [10], and academic achievement [11]. Some effects can be long-lasting, including increased risks of later childhood behavioral problems [12] and subsequent episodes of parental depression [13]. More recently the negative effects of paternal postpartum distress have been reported, including its association with emotional difficulties in children [14], the impact on marital relationships and family well-being [15], and the detrimental effect on the mother's relationship with her child [16].

In addition to significant costs to family well-being, perinatal distress has high economic costs. The annual health costs associated with perinatal depression and anxiety could be up to AUD $70 million in new mothers and AUD $16 million in new fathers, if their baby was delivered in 2012 [17]. The cost of psychological distress in otherwise healthy adults is substantial. For example, lost productivity cost Australian employers AUD $5.9 billion in 2009; productivity losses for each treatment seeker were AUD $19,810 for men and AUD $9183 for women [18]. The cost from one year's lost productivity for untreated maternal depression is AUD $142 million [17].

Many mothers prefer psychosocial treatments during the postpartum period, especially while breastfeeding [19]. Rapid acting, easily communicated treatments for depression in other contexts involve behavioral activation [20], physical activity [21], problem solving [22], parenting skills and self-efficacy [23-25], social support networks [24,26], and meditation mindfulness [27]. Treatment with a mental health professional is not easily accessible for non-urban populations, creating a barrier for treatment [28].

There is growing evidence, however, that interventions may not always require substantial clinician involvement to reduce distress. A single face-to-face psychoeducational session with a maternal and child health nurse was found to reduce depression and anxiety in women without psychiatric histories [23]. Another study found no difference in clinical outcomes between a psychoeducational booklet and group cognitive behavior therapy (CBT) in primary care [29]. In the second study, however, 60% of eligible women turned down group CBT, highlighting that traditional interventions may not match the needs of new parents. Adherence to treatment appeared especially low when symptoms were mild, women had competing commitments, or motivation was limited. Women also cited time, childcare, and transportation as further barriers to engagement.

Online interventions may overcome these uptake barriers, as the Internet is a highly accessible and cost-effective vehicle for the delivery of flexible and sustainable support. In 2012-2013, 83% of Australian households had Internet access [30], and 89% had a mobile phone with Internet access [31], indicating that electronic interventions are available to most Australians. Internet-based interventions have well-established efficacy for alleviating depression and anxiety, and for promoting well-being [32]. Clinical gains approximate those from face-to-face treatment, especially when dealing with low-severity problems [33]. In addition, stigma is avoided and location inequities are minimized.

The Internet has already proven feasible for screening postpartum depression in mothers [34]. Furthermore, randomized controlled trials (RCTs) for two online postpartum depression treatment programs found decreases in postpartum depression at 12 weeks [35] and 17 weeks [36] respectively, as compared to conventional treatment. Online treatment for postpartum depression shows promise, and may address the substantial economic, community, and family impact of perinatal distress. Development of programs that promote the maintenance and enhancement of perinatal mental well-being should be a priority.

The perinatal period is a time of transition [37], offering a window of opportunity when timely introduction of tools and information could positively influence later outcomes [38]. For

example, a study investigating the well-being of 5000 mothers found that positive maternal outcomes after birth are influenced by mental and physical well-being during the perinatal period [38]. Perinatal well-being is a complicated construct determined by an individual's perception and evaluation of their life during the perinatal period [37]. If expectant and new parents were offered tools to support and enhance well-being throughout this process, both maternal [39] and paternal [40] outcomes could be improved . However, few universal strategies for preventing perinatal distress and enhancing well-being have been evaluated in rigorous, large-scale studies [37].

Online programs targeting prevention of postpartum depression are in their infancy. A fully-automated program developed for pregnant women presented psychological strategies across 44 short sessions [41]. Information in this program was presented on a schedule, and this lack of flexibility may be a deterrent for some mothers. An RCT testing the effectiveness of this program is currently underway [42]. A second online prevention program has been evaluated in a pilot trial, but the study found no differences in effectiveness between the online program and the information-only control condition [43]. A limitation of this study was the minimal program use by participants, suggesting that email or text message reminders could be used to increase retention and use of the program. Furthermore, the intervention was linear in design, meaning that if earlier program material was not of significant interest to participants, program use would discontinue.

Although some programs addressing the prevention of postpartum depression in women have succeeded in engaging fathers [23,44,45], fathers' mental health and well-being has not been specifically targeted. Fathers are offered little support in the way of treatment or prevention of perinatal distress. Syntheses of studies investigating men's experiences ante- and postnatally found that fathers felt overlooked in antenatal classes [46], and excluded and unsupported by maternity services in general [47]. Despite this limitation, fathers reported a desire to be actively involved in this life experience, and to be supportive of their partners [48], indicating that an opportunity to involve invested fathers is being missed. Based on qualitative interviews with new fathers, Kowlessar et al recommend that men are actively engaged, informed, and offered support [48], and that the presentation of psychoeducation material and well-being tips may help fathers feel more involved and valued during this life stage [40]. More research is required, and high quality RCTs of interventions that promote psychological well-being in both mothers and fathers are needed [49].

To date, no study has trialed a web-based intervention targeting perinatal well-being in both mothers and fathers, nor has a related cost-effectiveness analysis been conducted. This proposed study addresses these gaps, and constitutes one of few trials that focus on well-being and universal prevention, rather than the treatment of established depression. Due to this novelty, our results are likely to have wide application. Electronic programs have the potential to alleviate maternal and paternal distress, and help recent parents enjoy the enriching and exciting experience of early parenthood by increasing access to effective support at minimal cost. By addressing parents' well-being and supporting childcare, participants may also assist in promoting positive parenting, offering potentially long-range benefits for this and future generations of Australian children.

Trial Aims

The aim of this trial is to conduct the first RCT of a web-based intervention, *Baby Steps*, that targets perinatal well-being in both mothers and fathers (trial registration number ANZCTR12614001256662). Specifically, the first aim is to compare the effectiveness on indices of well-being using two versions of the *Baby Steps* program for first-time parents: *Babycare* (an online information-only program providing information and tips on selected childcare issues) and *Well-being* (an interactive online program including all *Babycare* content, plus parental well-being-focused content with goal-setting and problem solving tools). The second aim is to assess the cost-effectiveness of the *Well-being* program compared to the *Babycare* program.

Hypotheses

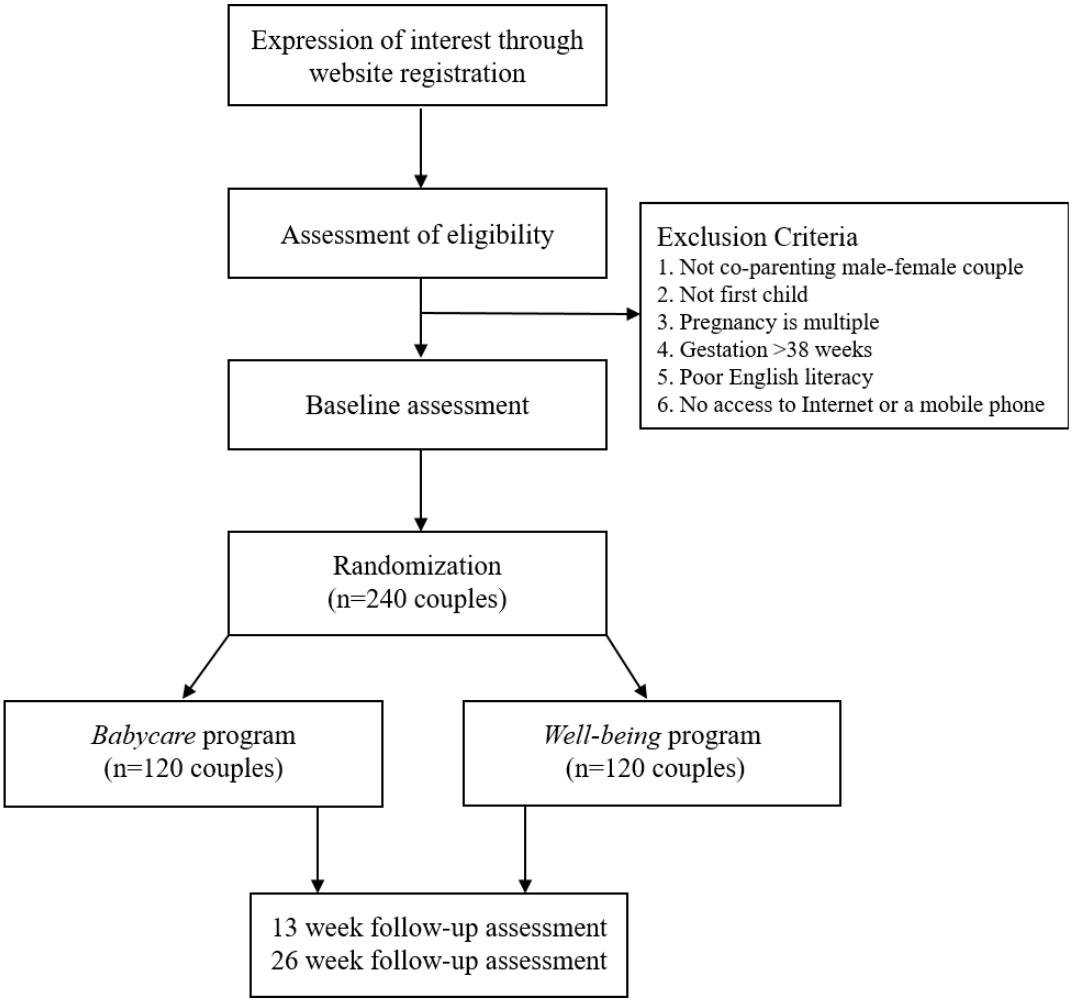
It is predicted that participants receiving the *Well-being* program will show lower levels of distress and a higher level of quality of life at 13 and 26 weeks post-baseline, compared to participants receiving the *Babycare* program. In addition, couple relationship satisfaction, parental self-efficacy, social support, and cost-effectiveness are predicted to be greater at 13 and 26 weeks post-baseline for participants receiving the *Well-being* program, compared to participants receiving the *Babycare* program.

Methods

Study Design

This study is an RCT designed to evaluate the effectiveness of an online intervention targeting perinatal well-being in first-time mothers and fathers. After baseline data are collected, participating couples will be randomly allocated to receive either the *Babycare* program or the *Well-being* program. Figure 1 provides a summary of participant flow through the trial.

Figure 1. Flowchart of the study design.



Study Sample and Procedure

Recruitment Procedures

A total sample of 240 primiparous mother-father couples will be recruited. Participants will primarily be recruited through private and public antenatal parent education classes at the Mater Mothers' Hospital, Brisbane, Australia. A member of the research team will visit the class immediately before the session commences to inform participants about the study and program. Couples will have the opportunity to ask questions and those interested in participating will be assisted with registration for the study. Participants will also be recruited through an exposition targeting expectant parents, and nationally through advertisements on social media and parenting forums, which will direct couples to the program website. Interested couples will be given the opportunity to ask further questions of the research team via email or telephone. During registration, all participants will be asked to select from a dropdown box regarding how they were first informed about the research trial.

Inclusion Criteria

Participants will be included in the trial if they are a co-parenting male-female couple aged 18 years or older, this is the first child for both parents, gestation is between 26 and 38 weeks at registration (couples registering before 26 weeks of gestation will be reminded by email to retake the screening survey when they reach the 26-week time point), and the pregnancy involves a single child. Participants must also be literate in English, have Internet and mobile phone access, and complete the baseline assessment. Both parents must be eligible for the couple to participate. Exclusion criteria are presented in Figure 1.

Screening and Baseline

Couples will register for the study by creating a website account for each user with email addresses and passwords. Registrants will then be individually emailed with a link to the screening survey, in which the trial information statement is provided. Participants will confirm that they have read and understood the statement, and that they consent to participate in the research before continuing. Participants will then complete the screening survey to confirm that they meet the study inclusion criteria. Eligible participants will be directed to the online baseline assessment survey, and both parents must complete the survey before the couple is randomly assigned to an intervention condition. Registrants who are not eligible for the study will still be able to access the *Babycare* program.

Reminder emails will be sent to registered participants on an automated schedule if they or their partner have not completed the screening survey three days post-registration, or the baseline survey three days post-screening. If the survey is still not complete 10 days post-registration, participants will be contacted by a research officer to assist with completion of the survey (if

the couple gives ongoing consent to participate). If both individuals have not completed the baseline assessment four weeks after eligibility is confirmed, couples will be withdrawn from the study and offered access to the *Babycare* program. After completion of the baseline assessment and randomization, couples will be telephoned by a researcher (blind to treatment allocation) to welcome them to the study, collect postal address details, and provide the research team's contact information.

Follow-Up Assessments

Follow-up assessments will be at 13 and 26 weeks post-baseline. For the purposes of these assessments, couples will be treated as individual participants and emailed an individualized online survey link. To maximize retention, participants will be reminded to complete the survey via scheduled emails. If the participant has not responded within two weeks of the due date, a researcher (blind to treatment allocation) will phone the participant, establish ongoing consent from the participant, and attempt to obtain the assessment over the phone. Participants will be offered an AUD $20 gift voucher (AUD $40 per couple) for completing each follow-up assessment.

Risk Management

Given the high frequency of perinatal distress, it is expected that some participants will experience distress during the study. Although the program focuses on well-being and does not specifically address depression, participants will be monitored for signs of elevated distress through their responses on the EPDS, and will be followed-up with according to the protocol outlined in Table 1. Researchers who make these calls will be trained in risk assessment procedures, will receive clinical supervision weekly to fortnightly, and will be blind to treatment allocation.

Table 1. Risk management protocol after administration of the Edinburgh Postnatal Depression Scale.

Risk level	Risk cut-offs	Action
Low	Women: 0-9 total score Men: 0-5 total score AND 0 on Item 10	No action required.
Medium	Women: 10-12 total score Men: 6-8 total score OR 1 on Item 10	1. Email participant to organize a time to speak on the phone. Call within one week. 2. Re-administer the EPDS and check score against cut-offs. If now low risk, briefly discuss change between previous EPDS and current EPDS, and discuss what to do if situation worsens. Email referral information. If now high risk, follow protocol for high risk. If still medium risk, follow protocol below. 3. Discuss support options (ie, partner, family, friends). 4. Give support and referral information over the phone and by email: - PANDA (Post and Antenatal Depression Association) 1300 726 306 http://www.panda.org.au/ - Lifeline 13 11 14 https://www.lifeline.org.au/Get-Help/ - Mensline 1300 78 99 78 http://www.mensline.org.au/ - Family doctor - Psychologist www.psychology.org.au/FindaPsychologist/Default.aspx?ID=5911
High	Women: >13 total score Men: >9 total score OR 2 or 3 on Item 10	1. Email participant to organize a time to speak on the phone. Call same day. 2. Discuss support options (ie, partner, family, friends). 3. Give support and referral information over the phone and by email: - PANDA (Post and Antenatal Depression Association) 1300 726 306 http://www.panda.org.au/ - Lifeline 13 11 14 https://www.lifeline.org.au/Get-Help/ - Mensline 1300 78 99 78 http://www.mensline.org.au/ - Family doctor - Psychologist www.psychology.org.au/FindaPsychologist/Default.aspx?ID=5911 4. Assist participant to make a plan to access support, including immediate support if needed. 5. Arrange to speak again in one week, at which time the EPDS will be re-administered, and check score against cut-offs. If still high risk, remain engaged with participant until they are engaged with appropriate professional.

Randomization

Allocations will be generated by the Goji program, a web-based research trials management system developed at Queensland University of Technology, Australia, by the same web developers who programmed the *Baby Steps* programs. When the researcher notifies Goji that a participating couple has completed their baseline assessment, Goji will allocate the participants to a research group, randomizing couples as a unit. Randomizations will be in permuted blocks, and stratified by scores on the EPDS: neither parent distressed (father <5; mother <7) versus either parent distressed (father >5; mother >7). These cut-off scores represent optimum screening levels for depressive

or anxiety disorders in fathers and mothers [7]. After randomization, a couple's access to the allocated program will be granted by a researcher not blind to treatment allocation, and participants will be notified by email that they are able to log into the online program through their registered account.

Dropout

Couples will be randomized as a unit but may elect to withdraw individually or as a couple. An individual will be able to continue participating in the trial if their partner withdraws, and this will not have any effect on their participation in the trial.

Sample Size

A total of 240 couples (120 couples per group) will be recruited. A sample size of 240 will give a power of .80 for detecting a significant *Time* x *Condition interaction* ($P<.05$) over three occasions of measurement, with a small effect size of f=0.082 [50,51].

Online Programs

Program Content, Tone, and Design

The content of the *Baby Steps* programs, *Babycare* and *Well-being*, was developed by a team comprised of clinical psychologists, midwives, and a neonatologist. *Baby Steps* is a modular, self-paced program designed to provide infant care and well-being information, and tools relevant for mothers and fathers during late pregnancy until their infant is approximately six months of age. Each module contains 4-8 categories that help to guide program users through the information contained within the module, or information presented through external websites and programs. Suggestions are offered for employing the information and tips individually, as parent and infant, as a couple, or as a family. A *Get Help* tab includes links to other parenting websites and programs, and links to face-to-face, telephone, or online health service providers.

Program information is written in an encouraging and non-judgmental tone, designed to create an empathic environment in which new parents can access information and tools. Inclusive language is used to aid engagement of both mothers and fathers in the program and gender role assumptions have deliberately been avoided when presenting the content. For example, information about returning to work after a brief leave is provided for both mothers and fathers, as are tips and suggestions for helping to feed an infant. Photos and images of both men and women interacting with their infants are used throughout the program.

Babycare Program – Control Condition

The *Babycare* program is comprised of four modules: (1) *Getting Prepared* – practical tools to help expectant parents prepare for the arrival of an infant, (2) *Feeding* – information about breastfeeding, formula feeding, and combined feeding, (3) *Improving Baby's Sleeping Habits* – information for understanding the patterns of infants' sleep and sleep cues, plus practical tools for creating a sleep routine, and (4) *Soothing* – information and practical techniques to calm a crying infant.

Short Message Service Reminders

Automated short message service (SMS) texts will be sent to *Babycare* participants two, four, seven, and ten weeks after program allocation to remind them to log into the program.

Well-Being Program – Experimental Condition

Babycare is an information-only program, while *Well-being* is an interactive program including the four *Babycare* program modules along with five additional modules promoting parental well-being, and utilizes interactive tools for the enhancement of well-being. The five additional modules are: (1) *Self-Care* – information and tips to assist new parents to look after their physical and mental health, (2) *Relationships* – tools for working through changes in the romantic relationship after an infant is born, (3) *Interacting with Baby* – information to assist new parents to understand, bond with, and play with their infant, (4) *Changing Roles* – tips to assist new parents to adjust to the new roles that parenthood brings, and (5) *Especially for Fathers* – well-being and infant care information targeted specifically to fathers.

After qualitative interviews with mothers and fathers who trialed the *Baby Steps* programs, the *Especially for Fathers* module was developed to provide additional father-targeted information. However, this module is also available to mothers who may wish to understand the role of fathers, and provides useful tips for his well-being.

My Plans

Within each module, *Well-being* participants can choose tips to send to the *My Plans* tool, which functions as a goal-setting, problem-solving, and behavioral activation tool. Participants are encouraged to develop plans to incorporate the chosen tips into their lives, including setting a specific date and time when the plan will be attempted, or a regular frequency at which they will complete the plan. Example suggestions for plans that may be attractive to mothers, fathers, or both parents are distributed throughout the modules. A participant using the *Self-Care* module could select the *Talk to someone about what's stressing you* tip, and choose to develop a plan to *Book an appointment with my General Practitioner* and to complete the plan on *November 10*th. Participants are able to review and update their plans throughout their use of the program, and can mark plans as completed.

Additional Tools

The *Well-being* program also includes a *Scrapbook* tool, in which participants can upload and view photos that remind them of pleasure and success. The participant's personalized *Dashboard* displays *Scrapbook* photos, upcoming plan due dates, rotating module tips, and light-hearted, infant-specific trivia questions.

Short Message Service Reminders

Participants allocated to the *Well-being* program will also receive automated SMS texts two, four, seven, and ten weeks after allocation, reminding them to log into the program, select useful tips, develop plans to enhance well-being, and regularly review the progress of their plans.

Intervention Integrity

Reporting of this study is guided by the Consolidated Standards of Reporting Trials statement [52] and international best practice. The randomization schedule is concealed within a secure database accessible only to the Goji development manager. Researchers collecting post-baseline assessments will be blinded to condition. Calls made to welcome participants to the study, or to conduct a risk assessment, will be made by a researcher blind to treatment allocation. Data analyses will be conducted based on the principle of intention-to-treat [53].

Study Measures

Measures will be restricted to minimize the burden on participants. Demographics collected will include details of income and occupational engagement. Economic information including healthcare data, work time/productivity data, and intervention establishment/delivery data will also be collected. Past and recent psychiatric history will also be assessed. Information concerning the outcome of the pregnancy will be collected 13 weeks post-baseline. The EPDS [54] will be used to assess perinatal distress and the four-item Social Support Survey [55] will measure satisfaction with social support. The Assessment of Quality of Life-8 Dimensions (AQol-8D) [56] will be used to assess quality of life, and relationship satisfaction will be measured by the Couples Satisfaction Index [57].

Three measures were designed specifically for this study. These measures were created to be brief, as to minimize time burden on participants, and designed to directly measure certain program components. Self-efficacy over the initial 13 weeks of child-rearing, and providing support to a partner (ie, *feeding your baby*, *putting your baby to sleep*, *settling your baby*, *providing support to your partner*), will be assessed on an 11-point scale. The scale increases in 10-point increments, and ranges from 0 (not at all confident) to 100 (extremely confident). Current satisfaction with participants' parenting role and skills, and with relationships and social support (ie, *relationship with their partner*, *support received from and given to their partner*, *practical and emotional support received from others*), will be rated on a similar 11-point scale from 0 (not at all satisfied) to 100 (extremely satisfied). The same rating scale will be used for program satisfaction at 13 weeks post-baseline (ie, *overall*, *relevance*, *usefulness*, *how easy it was to find what they wanted*). Timing of the assessments is presented in Table 2.

Table 2. Study measures and timing.

Measure	Domain	Baseline	13 week follow-up	26 week follow-up
Demographics	Demographics			
Work history and performance	Recent employment history and performance			
Birth items	Baby and birth details			
AQol-8D	Quality of life/well-being			
Edinburgh Postnatal Depression Scale	Perinatal distress			
Self-efficacy items	Parental self-efficacy			
Satisfaction items	Satisfaction			
Social Support Survey	Social support			
Couples Satisfaction Index	Relationship satisfaction			
Psychiatric history	Psychiatric history			
Recent medical history	Medical history, healthcare data			
Program satisfaction items	Program satisfaction			
Program use	Program engagement			

Both *Baby Steps* programs automatically collect program use data that are summarized into engagement variables (number of logins, module pages viewed, number of plans made, number of photos uploaded to the Scrapbook, and total time spent on the module pages).

Data Analyses

Version 22 of the IBM SPSS Statistics program will be used to perform all data analyses.

Descriptive Analyses

Baseline data from the two program groups will be compared to check for comparability of the groups. Chi-square tests will be used for categorical variables, ANOVA tests for normally distributed continuous variables, and Kruskal-Wallis tests for non-parametric data. Any differences detected will be controlled for during the subsequent analyses.

Primary and Secondary Analyses

All data analyses will be based on the intention-to-treat principle [53]. Continuous outcomes (eg, measures of perinatal distress, quality of life, couple relationship satisfaction) will be analyzed using general linear mixed models, and multilevel modelling will be used for nested data, to deal with any missing data.

Cost-Effectiveness Analysis

The evaluation will examine the perspectives of costs to health services and to society. Unit costs will be applied to resource-use data collected on health care (primary care and hospital data), work time/productivity, and intervention establishment/delivery.

The AQol-8D [56], a multi-attribute utility instrument, will be used and scored using the Australian algorithm [58]. Resultant utility weights will be multiplied by duration to estimate quality-adjusted life years. Incremental cost-utility ratios will be estimated as the primary outcome factor of the economic evaluation. An alongside-trial analysis will be undertaken. Sensitivity analyses will be used to identify key factors driving the results and bootstrapped standard errors will be used to estimate the 95% confidence interval for the incremental cost-effectiveness ratio.

Ethical Approval

This trial received ethical approval from the Human Research Ethics Committees of Queensland University of Technology (No. 1400000687) and the Mater Health Services (No. HREC/14/MHS/166). The trial will be implemented in compliance with this protocol and the Australian National Statement on Ethical Conduct in Human Research [59].

Results

Participant recruitment commenced March, 2015 and continued until October, 2015. Follow-up data collection has commenced and will be completed May, 2016 with results expected in July, 2016.

Discussion

Depression and distress have substantial impacts on new parents and their babies, with potential to affect later adjustment, relationships, and child development [11-16]. The economic impacts of such depression are also large [17,18]. The perinatal period is an opportunity to engage expectant parents in well-being-based programs, which is particularly important given that better well-being during this phase is associated with positive postpartum outcomes [38]. Although mothers are often the focus of support and interventions during the perinatal phase, fathers also experience perinatal distress, but have received little research attention or support from services, despite a desire to be involved during the perinatal period [45]. Internet interventions offer a flexible, accessible, cost-effective solution for enhancing perinatal well-being in mothers and fathers.

The current research addresses several issues. This project has developed an innovative program with a unique combination of modules, based on several related programs designed by the authors. *Baby Steps* screens for distress and depression, provides childcare resources and interactive tools, and addresses emotional and physical well-being of both fathers and mothers. Key foci are self-selected childcare issues and maintaining pleasurable physical and social activity. Personal tailoring, after-hours availability, rural accessibility, and low cost per user allow the platform to be easily disseminated to large numbers of people across Australia. This study conducts the first perinatal trial to differentiate component effects from a combined intervention of this type, examining distress, functioning, and childcare confidence, and is the first to compare cost-effectiveness of such interventions. As such, this project helps to facilitate the translation of research into policy and practice at state and national levels. *Baby Steps* is one of few trials that focuses on well-being and prevention rather than established depression (thereby having wide applicability), and is also one of the few trials to focus on the well-being of new fathers.

This project has the potential to influence standard services to support parents, thereby increasing their effectiveness, with minimal increases in cost. *Baby Steps* offers a strategy to engage and support fathers, improving their own outcomes as well as their support of mothers, and potentially preventing losses in work time and productivity associated with depression. In concert with other strategies to address the causes of depression and anxiety, this project assists in promoting the long-term emotional and physical health and well-being of Australian children and their families.

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Authors' Contributions

KH, DK, LD, JF, LH, JM, HR, PS, AW, KW and AWi secured funding. All authors contributed to the conceptualization and design of the study, and to the development and revision of the manuscript. All authors take public responsibility for this content.

Conflicts of Interest

None declared.

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Abbreviations

AQol-8D: Assessment of Quality of Life-8 Dimensions
CBT: cognitive behavior therapy
EPDS: Edinburgh Postnatal Depression Scale
RCT: randomized controlled trial
SMS: short message service

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Protocol

Systematic Early Intervention for Bereaved: Study Protocol of a Pilot Randomized Controlled Trial With Families Who Suddenly Lose a Partner and a Parent

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Abstract

Background: Grief has been associated with several long-term negative outcomes for both surviving parents and bereaved children, especially when it is preceded by unnatural and violent deaths. Nevertheless, it has been an underestimated public health problem with few, if any, empirically documented early preventive intervention programs. The best time to start them is also a major question that requires further evidence.

Objective: The overall aim of this study is to assess the feasibility of a future larger trial, informing sample size calculation, recruitment/randomization procedures, retention rates, data collection forms, and outcomes. This study will also explore: (1) the early effects of Systematic Early Intervention for Bereaved (SEIB) compared with the early effects of care as usual, and (2) the effects of the immediate SEIB version compared with the effects of the delayed SEIB version.

Methods: In a pilot randomized controlled trial (RCT) with a delayed intervention design, suddenly bereaved families will be assigned to: the immediate-SEIB intervention group, or the delayed-SEIB intervention group. Participants will fill in a set of self-report measures at baseline, and after 3, 6, and 9 months follow-up. Quantitative data on traumatic stress symptoms, complicated grief, psychological wellbeing, daily functioning, social support, parental capacity, parenting practices, and family functioning will be collected to inform power calculations and explore SEIB's preliminary effects. Data on the flow of participants throughout the trial will be analyzed in order to estimate recruitment and retention rates. Two brief questionnaires were developed to assess recruitment procedures, randomization, and data collection materials.

Results: Recruitment for this project started in August 2015, and follow-up data collection will be completed in June 2017.

Conclusions: This study prepares the ground work for the design and implementation of a main trial and may add preliminary knowledge to the significance of early supportive practices that have been commonly used regardless of their sparse evidence.

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KEYWORDS

traumatic death; complicated grief; mental health; family functioning; early intervention; randomized controlled trial

Introduction

Bereavement is a natural and common event, and most people are generally able to adapt to the resulting grief over time and regain function in their everyday life [1]. However, approximately 10% to 22% of bereaved people experience deleterious forms of mental distress that result in mental health deterioration [2]. The loss of a significantly loved person

through death can be a complex and disturbing life event that is linked to greater psychological problems, physical illness, and mortality. Individual grief reactions can vary from minor and shorter responses to more severe and prolonged manifestations [3]. More importantly, unnatural and violent deaths significantly cause more severe after effects than natural deaths [4].

Complicated grief encloses the more severe and prolonged symptoms that hamper social and occupational functioning [3,5]. It has been found to be related to higher rates of mental disorders, sleep problems, suicidality, cardiovascular and cancer diseases, and lack of social support [6-10]. Preoccupied thoughts of the deceased, intense searching and yearning for the deceased, avoiding memories of the deceased, death denying, and crying are among the core symptomatology of complicated grief [11]. In addition, other comorbid symptoms that meet the criteria for depression and/or posttraumatic stress disorder (PTSD) have been documented [12].

Acknowledging the individual and contextual risk factors for the potentially chronic complicated grief outcomes increase awareness on the subset of bereaved people who are in major need of assistance [13]. In several studies, the death of a parent is emphasized as one of the most demanding and traumatic events that can be experienced in childhood and youth [14,15]. It has been found to enhance the risk for a wide range of mental and behavioral problems, even when controlling for previous risk factors [16]. Parentally bereaved children have shown clinically significant indicators of psychological distress (eg, depression, anxiety, somatic complaints, withdrawal), traumatic grief (eg, yearning for the deceased, diminished acceptance of the death), lower academic functioning and self-esteem/self-efficacy, higher external locus of control, and social problems [17-19]. Furthermore, parentally bereaved children who suddenly and unexpectedly lose a parent (eg, following a suicide, an accident, or a natural death) were at greater risk of developing depression and PTSD symptoms [20]. A sudden and unexpected loss is seen as an existential crisis that threatens self-beliefs about safety [21] and self-ability to accept, confront, and adapt to what has occurred [22].

The manifold negative effects of parental death in childhood seem to be linked to increased rates of disorder in both bereaved parents and their children [20,23]. The surviving parents have to raise their children under extremely difficult conditions. On the one hand, they must deal with the loss of their partner and their own psychological problems, while facing the pressure of being a single parent [24]. On the other hand, parentally bereaved children can pose additional challenges for parents, expressing their adjustment problems through more disruptive behaviors [25].

In view of these detrimental influences of bereavement-related psychological distress on both the individual and the family system, it is crucial to break this cascade of negative cycles. It highlights the need of developing effective interventions aimed to promote resilience for both bereaved parents and their children, especially in the early stages that follow death [26,27] where the disabling consequences have been more strongly noticed [3]. Several clinicians and researchers in the loss and trauma field have emphasized the usefulness of early crisis intervention [26-28]. They argue that early intervention favors the attenuation of the initial dysfunctional appraisals and enables a better case management, and maximizes the chances of a more adaptive developmental pathway [27]. Norwegian studies on the users' perspectives show that traumatic bereaved participants ask for: (1) immediate assistance, (2) outreach help, (3) help for their children, (4) information about the event and potential reactions, (5) possibility to meet with others who experienced similar situations, and (6) help over time [22,29]. Nevertheless, meta-analytic findings failed to show a significant effect of preventive approaches, pinpointing diverse methodological limitations among the studies [30]. To our knowledge, none of these studies assesses interventions taking place immediately after the loss. The start of these preventive programs ranges from 2 to 6 months post loss [31,32]. Thus, it is essential to develop well-designed randomized controlled studies [33] attempting to increase understanding about the best time to provide early intervention.

In line with this, the Systematic Early Intervention for Bereaved (SEIB) was developed. It is the first Norwegian program that proposes professional family assistance starting in the first days after a sudden and traumatic loss. Within a family perspective, SEIB seeks to facilitate natural mourning, resolve grief complications, promote parental capacity, and help the bereaved partner and their children to develop or enhance satisfying relations/activities, and to regain control over their life. The basis of this approach is from the field of early crisis intervention [26-28]. The existing literature [3,25], the wishes for help as expressed by the bereaved themselves [22,29], and our extensive clinical practice, are at the heart of this approach.

The present study aims to expand knowledge in early intervention on family -related psychological distress following a sudden and unexpected death of a partner/parent. It consists of a pilot study to assess the feasibility of a future main trial, as well as SEIB's preliminary impact with suddenly bereaved families. Accordingly, the specific aims are to:

1. Assess recruitment materials and procedures.

2. Assess the usefulness of randomization and data collection materials.

3. Obtain reliable estimates regarding recruitment and retention.

4. Provide information on power calculations and possible outcomes (both parents and children).

5. Explore the 3-month SEIB effects' on traumatic stress symptoms, complicated grief symptoms, psychological wellbeing, daily functioning, social support, parental capacity, parenting practices, and family functioning, compared with the 3-month effects of care as usual.

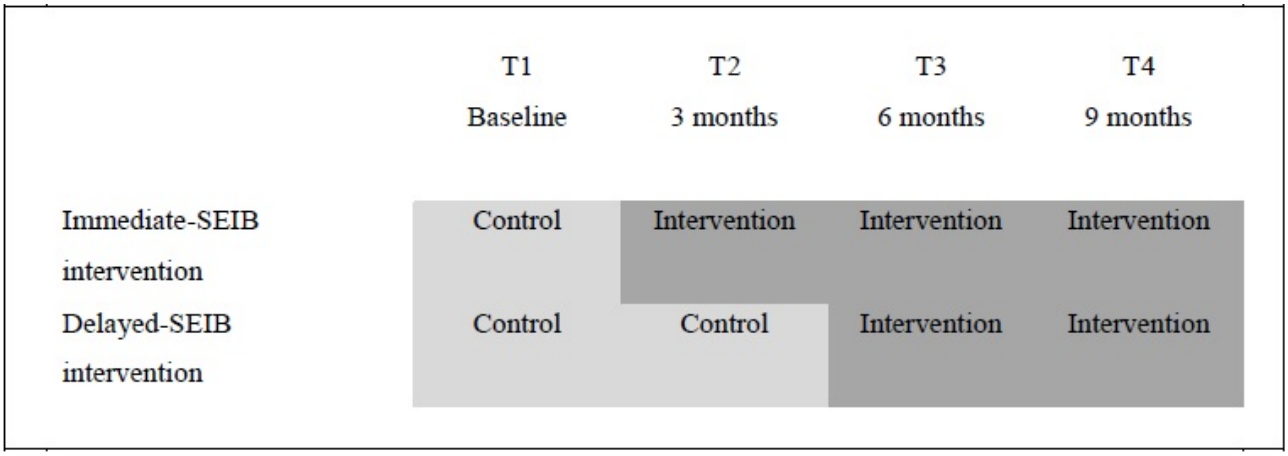
6. Explore the 3- and 6-month effects of the immediate-SEIB version on traumatic stress symptoms, complicated grief symptoms, psychological wellbeing, daily functioning, social support, parental capacity, parenting practices, and family functioning, compared with the 6- and 9-month effects of the delayed-SEIB version.

Methods

Trial Design

As outlined in Figure 1, this study is a one-center, pilot, randomized controlled trial (RCT) with a delayed intervention design in which suddenly bereaved families will be randomly assigned to: the immediate-SEIB intervention group (receiving SEIB in the aftermath of the loss) or the delayed-SEIB intervention group (control condition; receiving SEIB 3 months post loss). Both groups can make use of care as usual from their communities.

Figure 1. Design of the study protocol.



Participants and Eligibility Criteria

The sample will include bereaved families with children younger than 18 -years old, who suddenly and unexpectedly lose a partner and a parent. Bereaved partners and their children, aged from 12 - to 18 -years old, will be the informants of the study. To ensure a homogeneous sample, all family members must speak Norwegian. Eligible families are those who satisfy both of the criteria listed in Textbox 1.

Textbox 1. Inclusion criteria.

- Criterion for unexpectedness: the loss shall occur following an accident, a suicide, a murder, or a disease, as well as situations where people are missing (presumed dead).
- Criterion for suddenness: the loss shall occur shortly, or within the same day as the event/disease happened or started. This period can be extended up to 5 days for people who do not regain consciousness after the incident (eg, illness/accident/suicide, etc). The families cannot enter this study later than 3 weeks after the death.

Potential participants with severe medical conditions for both bereaved partner and their children, such as serious physical impairment, intellectual deficit, severe child developmental problems, borderline personality disorder, history of psychosis (eg, schizophrenia, bipolar disorder), current substance use disorder (in the past 6 months), severe suicidal risk, or dementia will be excluded. Families receiving concurrent psychotherapeutic intervention for problems concerning loss and/or trauma will also be excluded.

Recruitment and Randomization

A continuous recruitment will occur through referrals from crisis teams of the entire county of Hordaland in Norway. Health care units of the general hospitals in Hordaland, as for instance emergency and intensive care units, will also recruit for this study to secure the inclusion of those who lose a family member to acute disease.

Bereaved partners will be informed about the study the first time they are in contact with the health care personnel immediately after the death, and potential participants will be given a study information brochure. They will then receive a phone call to schedule an appointment for a first meeting at their homes (or at our center if they prefer so). At the end of this first meeting, the families will receive a sealed opaque envelope containing information regarding their random group allocation. Randomization will be previously performed by an external and independent research assistant who will use blocks of 6 families (3 allocated to each arm of the trial) [34]. For each block of 6, containing 3 intervention condition cards and 3 control condition cards, the researcher will randomly draw a card assigning it to one family according to its order of entrance in the study. This will help to randomly vary the order of interventions within each block. Due to the nature of the intervention, it will not be possible to blind participants to group assignment. However, the researchers who visit and phone the families have no previous knowledge concerning allocation until the end of the first meeting. In addition, they will not be involved in the intervention phase.

Intervention

SEIB is a multidimensional clinical- and theory-based program designed to strengthen the resources of parentally bereaved children and their parents while adjusting to the major changes of a sudden and unexpected death of a parent/partner [26,27]. As suggested by others [28,30,35], SEIB attends to the unique needs of each bereaved family member, mapping the new ground that the families are entering and stimulating the benefits

of the social network support. It has been acknowledged that bereavement is a process that differs among individuals; hence, intervention programs should be tailored to each individual's needs [30].

Through a minimum of 5 sessions (or more if deemed necessary), SEIB's focus is placed on: (1) stabilizing the situation and decreasing arousal (eg, by emotion regulation) [26,27], (2) facilitating individual coping skills and healthy grief reactions [26-28], (3) promoting positive parenting (warmth, open communication, effective discipline) [25,26], (4) encouraging the adaptive expression of emotions among family members [25,26], (5) empowering parent-child relationship and family interactions [25], (6) stimulating occupational and social functioning [26], and (7) activating/monitoring social support provision [27,28].

Session 1

Session 1 is to take place within the first 3 days after the loss, whenever possible (no later than 3 weeks post loss). The initial aim of this session is to reduce bodily activation by calming and stabilizing family members, and stimulating their perception of being cared for. In addition, this session focuses on parental psychoeducational information about their children needs', stimulating open and direct communication, and ensuring that facts are shared within the family. In order to contextualize the facts, to establish coherence/structure, and secure equal access to facts within the family, every family member is invited to narrate their loss experience (facts, not feelings) with a special emphasis on the importance of hearing the children's perspective. Furthermore, this session provides concrete advice on sleep, work/school, use of medication, participation in rituals, and how to maximize support from their social network (for both children and adults). At the end of this session, the parents receive a booklet as a guide for them to talk with their children about death [36].

Session 2

Session 2 takes place within 2 to 4 weeks post loss. The initial aim of this session is sharing of factual information concerning the circumstances of the death and the death notification, as well as new available information (ie, from police, health personnel, or others), ensuring that everyone in the family (including children) have access to the information they need. As in the first session, this session continues to secure open and direct communication within the family. In addition, psychoeducational information concerning basic and common grief reactions is combined with concrete advice for dealing with school/work re -entry. Grief and traumatic reminders, guilty feelings, and intrusive material are also addressed, and self-help methods introduced. The use of self-help methods is based on feedback from the family members on what they find particularly difficult. Usual relevant self-help methods refer to techniques that help to gain control over intrusive memories, reduce bodily arousal or tension, and improve sleep hygiene [37]. Finally, this session discusses how family members interact with each other, and how they can effectively support and take care of each other. New distribution of roles among family members and how to make good use of their social support networks are addressed.

Session 3

Session 3 takes place within 5 to 7 weeks post loss. The initial aim of this session is to address and process trauma aspects of the loss. Family members go through what they knew and thought about what happened, as well as their sensory experiences and body reactions at the time (especially the most difficult ones). If trauma-related problems persist, such as intrusive memories or thoughts, trauma focused methods such as Eye Movement Desensitization and Reprocessing (EMDR) [38] and Thought Field Therapy (TFT) [39] can be applied. The family members are advised to imagine having a conversation or write to the deceased and say goodbye (eg, writing a letter to the loved one, mentioning what they did not have time to say/do; ask for forgiveness if there are any regrets) [40]. A discussion around the balance between maintaining a constructive bond with the dead and keeping the lost one too close is also addressed. In addition, an emphasis is placed on living with grief over time, principally for the next coming months (eg, resume normal activities, interact with the environment, organize/tidying the dead person's belongings, set goals for the family, use self-help techniques with videos found on the Internet). Finally, parents receive information for learning more about children's reactions [41].

Session 4

Session 4 takes place within 3 to 6 months post loss. This session starts with a discussion on what has happened since the last meeting in order to: identify what is presently regarded as most important for the family and/or the individual family members; and reinforce the acquisition of new skills and the changes that were made as a family. A special emphasis is placed on living with grief over time and recovering daily functioning, particularly in the social and work/school spheres of life (eg, family interaction, be part of and sustain a helpful social network, etc). Additionally, if the dead continues to be kept very close (ie, nothing has been changed, as if the person died the day before), some changes are encouraged such as organizing/tiding up belongings, decreasing the number of grave visits and the amount of time spent in talking or thinking about the dead, and so on. The use of the "postponed worry-technique" [42] is introduced. Specific work regarding any sleep problems is included, as well as EMDR and TFT for trauma-related problems that persist over time. Finally, this session continues to stimulate family communication and discusses how they support each other.

Session 5

Session 5 takes place around or following the first anniversary of the death (12-13 months after death). This session starts with a discussion on how it is to have gone through a whole year without the lost person, and how was it to pass the anniversary in order to: identify what is presently regarded as most important for the family and/or the individual family members; reinforce the acquisition of new skills and the changes that were made as a family; and prepare for the life ahead. A special emphasis is placed on living with grief over time and recovering daily functioning, particularly in the social and work spheres of life. Finally, it is discussed how family members can give themselves permission to grieve less.

The rationale for both immediate-SEIB and delayed-SEIB versions relies on the need to minimize the initial misconceptions and maladaptive appraisals that may emerge in the aftermath of a traumatic event and that may exacerbate the onset of posttraumatic symptoms and complicated grief [27]. As a result, both immediate-SEIB and delayed-SEIB seek to enhance more appropriate coping responses that are expected to have an increasing effect over time. Also, early intervention may foster an open family climate that help the family to share facts and make decisions (eg, participating in rituals, school/work reentrance), favorable for them in a long-term perspective [27]. Traumatized parents tend to shield their children from facts, thus it seems important to stimulate proper levels of family communication, emotional expressiveness, and cohesion within the first weeks after a crisis event. This may decrease the individual and family arousal, increase family resilience, and stimulate a safer environment for trauma recovery [26]. These arguments constitute the base for our immediate-SEIB intervention and are in line with our clinical and research experience, showing bereaved people ask for immediate assistance [22,29]. The immediate-SEIB first follow-up period (session 4) is consistent with the International Classification of Diseases, suggesting that complicated grief meets its diagnostic criteria when the symptoms persist beyond 6 months after the death [43]. The immediate-SEIB second follow-up period (session 5) is consistent with the Diagnostic and Statistical Manual of Mental Disorders, requiring a minimum of 12 months [44].

The delayed-SEIB proposal is informed by the literature, given most preventive studies tend to start intervention within 2 to 6 months post loss [31,32]. For the delayed-SEIB intervention group, the first 3 sessions contain less advice on the acute handling of the situation (including children in rituals, return to work and school, securing social support) and less focus on reducing bodily activation by calming family members. They prioritize the traumatic aspects surrounding the death, and psychoeducation is adjusted to the reactions usually seen at this time-point (~3 months following the loss), when the unreality has abated and the social network is often less active in their support.

Four psychologists will be responsible for SEIB delivery. They have extensive clinical experience with grief, bereavement, and trauma, and are familiar with the theoretical and empirical background that lies beneath the development of SEIB. A SEIB manual was developed and reviewed together with the psychologists. The intervention protocol is described in session-by-session detail in order to maintain treatment fidelity. The psychologists will meet with the project leader and the manual developer (first and final author) during program implementation to secure supervision and adherence to the SEIB protocol. Session-by-session, short, semistructured logs in which the psychologists and family members note their own impressions about the intervention process will also be used and discussed in the supervision contacts.

Outcome Measures

SEIB consists of a complex intervention [45], designed to tailor both individual and family needs, that is expected to entail several interacting components and outcomes. Considering the relevance of SEIB's intervention components in the almost immediate aftermath of a potential traumatic loss, we anticipate the primary outcome of SEIB refers to traumatic stress symptoms of both parents/children. The secondary outcomes of SEIB may refer to the individual level of complicated grief, psychological wellbeing, daily functioning, and social support in parents and children, while tertiary outcomes possibly refer to the parenting/family level and include parental capacity, parenting practices, and family functioning.

Given SEIB's initial focus on the potential misconceptions/maladaptive appraisals that usually follow a sudden death, and the early provision of trauma-reducing self-help methods, it is foreseen that SEIB may reduce traumatic stress symptoms of both parents/children. The reduction of this symptomatology may favor psychological wellbeing and optimize daily functioning, which in turn may strengthen the individual sense of self-efficacy and the ability to use the support from others within the social network, minimizing the chances for complicated grief. For the surviving parent, these conditions may set the stage for a more resourceful, stable, and organized parent more considerate of the child's needs. Enhanced emotional availability in parents, combined with SEIB's family perspective, may ultimately improve family functioning. Textboxes 2 and Textboxes 3outline the parent and child self-report measures that will be used.

Textbox 2. The parent self-report measures.

- Impact of Event Scale-Revised (IES-R) [46] – assesses the subjective distress following a traumatic event. It is composed of 22 items rated on a 5 -point scale ranging from 'not at all' (0) to 'extremely' (4).
- Inventory of Complicated Grief (ICG-19) [47] – assesses the severity of complicated grief symptoms. It is composed of 19 items rated on a 5 -point scale ranging from 'never' (0) to 'always' (4).
- General Health Questionnaire (GHQ-12) [48] – assesses general psychological wellbeing. It is composed of 12 items rated on a 4 -point scale. Items indicating health range from 'more than usual' (0) to 'much less than usual' (3), and items indicating illness range from 'not at all' (0) to 'much more than usual' (3).
- Work and Social Adjustment Scale (WSAS) [49] – assesses functional impairment at work, home, and social life. It is composed of 5 items rated on a 9 -point scale ranging from 'not at all' (0) to 'very severely' (8).
- Crisis Support Scale (CSS) [50] – assesses perceived and received support after the occurrence of a crisis event. It is composed of 7 items rated on a 7 -point scale ranging from 'never' (1) to 'always' (7).
- Parenting Coping Scale (PCS) [51] – assesses general parental ability to cope with the role of parenting. It is a brief single -item composed of 5 statements, forming a 5 -point scale rated from 'coping very poorly' (1) to 'coping very well' (5).
- Alabama Parenting Questionnaire (APQ) [52] – assesses several dimensions of parenting. A total of 14 items referring to parental involvement (7 items) and parental discipline (7 items) will be used and rated on a 5-point scale ranging from 'never'(1) to 'always' (5).
- Family Assessment Device (FAD) [53] – assesses family climate and functioning. The General Functioning Scale is one of its subscales and the one that will be used. It focuses on family (un)healthy functioning and it is composed of 12 items rated on a 4-point scale ranging from 'strongly disagree' (1) to 'strongly agree' (4).

Textbox 3. : The child self-report measures

- Children's Impact of Event Scale (CRIES-8) [54] – assesses the subjective distress following a traumatic event. It is composed of 8 items rated on a 4-point scale ranging from 'not at all' (0) to 'often' (5).
- Inventory of Prolonged Grief for Adolescents (IPG-A) [55] – assesses symptoms of prolonged grief disorder. It is composed of 30 items rated on a 3-point scale ranging from 'almost never' (1) to 'always' (3).
- Strengths and Difficulties Questionnaire (SDQ) [56] – assesses psychological adjustment in children and adolescents. It is composed of 25 items rated in a 3-point scale ranging from 'not true' (0) to 'certainly true' (2), and an impact supplement focusing on functional impairment.
- Alabama Parenting Questionnaire (APQ) [52] – encloses a parent and child version. The equivalent items of the parent version will be used in the child version.
- Family Assessment Device (FAD) [53] – can be filled in from 12 -years -old onward. The same items will be used for both parent and child.

Measures were selected based on relevance, satisfying psychometric properties, brevity, and availability in the Norwegian language.

To assess both children's and parents' perspectives on the help and support they received following the death, we developed a self -report measure to relate their perception of SEIB and/or care as usual throughout their participation (Help Questionnaire).

As shown in Textbox 4, the families will be assessed at 4 time-points: baseline (T1), and after 3- (T2), 6- (T3), and 9-months (T4) follow-up. T1 will just comprise the use of two questionnaires: GHQ-12/SDQ and IES-R/CRIES-8. Given the closeness in time of T1 to the death, we expect the families to be acutely distressed at this time. Apart from T1, all the above-mentioned parent and child questionnaires will be included at the other time-points for assessment. These questionnaires will provide useful information on future power calculations and possible SEIB outcomes.

Textbox 4. Assessment time-points and measures for all participants.

T1: Baseline

Sociodemographics

- Parent: IES-R; GHQ-12
- Child: CRIES-8; SDQ

T2: 3 months

Help Questionnaire

- Parent: IES-R; ICG-19; GHQ-12; WSAS; CSS; PCS; APQ; FAD
- Child: CRIES-8; IPG-A; SDQ; APQ; FAD

T3: 6 months

Same as T2

T4: 9 months

Same as T2

We will inspect data on the flow of participants throughout the trial in order to estimate recruitment and final retention rates. Partial retention rates for those entering the trial who do not complete questionnaires at 9-months follow-up will also be calculated. Besides, the psychologists will inform the research team about the number of attended sessions and reasons for dropping out treatment.

To assess recruitment materials and procedures we developed a brief questionnaire that will be sent to the recruiting agencies at the end of the recruitment phase. The usefulness of randomization and data collection materials (eg, sealed opaque envelopes, informed consent forms, questionnaires) will be evaluated by the researcher who will fill in a 'brief family log' after visiting the family.

Sample Size and Statistical Analyzes

In light of the small state of knowledge about early intervention in the aftermath of a potential traumatic death of a partner/parent, this study is not aimed to test SEIB effectiveness. Power analysis is not used to determine the final sample size, because it is not recommended for pilot studies that do not rely on inferential statistical tests [57]. Following a general rule of thumb that suggests the inclusion of 30 participants or more to determine a parameter (eg, mean/standard deviation) of an outcome variable [58], we will recruit a total of 60 families (30 families in each group). Rather than focusing on hypothesis testing, this pilot study builds on the practical limitations of recruitment and topics of incertitude, such as the need to gather initial estimations for sample size calculation [57,59,60].

Statistical analyzes will be computed using IBM SPSS Statistics and multiple imputation methods will be used to impute values of missing data [61]. Descriptive data will be computed to characterize the sample. On the basis that pilot study analyzes should be mostly descriptive and should provide confidence interval estimation [60,62], descriptive statistics (including mean, percent, standard deviation, and range), and confidence intervals will be used to describe all outcome variables at T1, T2, T3, and T4 providing important information regarding recruitment and randomization procedures, data collection forms, retention rates, future power calculations, and SEIB most appropriate outcomes.

Given the acknowledged low power of pilot studies [57], an emphasis will be placed on evaluating indices of clinical significance. Independent of the normal distribution and sample size, the effect size estimation has been considered a strong predictor of clinically meaningful change in studies with small sample sizes [63]. Accordingly, Cohen's *d* effect size of the differences in outcomes between groups and Cohen's *d* effect size of change from baseline to follow-up will be performed and judged as follows: small ($d \geq 0.2$), moderate ($d \geq 0.5$), large ($d \geq 0.8$), or very large ($d \geq 1.3$) [64]. The preliminary early effects of SEIB will be addressed by comparing descriptive data and effect sizes at T2 of both immediate-SEIB group and delayed-SEIB group (receiving care as usual at T2). The preliminary effects of both immediate and delayed SEIB versions will be addressed by comparing descriptive data and effect sizes of the immediate-SEIB group at T2 and T3 to the delayed-SEIB group at T3 and T4.

Ethical Considerations

The Regional Committee of Research and Ethics in Western Norway (no. 599832) approved the design and procedures of this study. The ethical principles for research in the social sciences and the humanities will follow the Helsinki Declaration guidelines' [65]. From the start, participants' needs will prevail over research interests. The agreement to participate in the study and an explicit written informed consent will precede data collection. Participants will be informed about all the relevant aspects of the study (eg, aims, methods, allocation, etc). They will also be reassured that their participation is voluntary and that they can withdraw at any time without detriment. The participant's privacy and confidentiality will be assured throughout all research phases. Both researchers and psychologists will monitor potential adverse effects or special circumstances that will require participants' removal from SEIB. Additionally, all participants can make use of care as usual, which seems particularly significant to those in the control condition who are waiting for the delayed SEIB program.

The participant's informed consent will be obtained shortly after the death. However, several researchers have underlined the difference between being distressed, and not being capable of making decisions around enrollment in a bereavement research study [66,67]. In fact, bereaved people are often involved in complex decision-makings concerning the funeral planning, their financial situation, and so on. Besides, they do not report their research participation as undue strain [68]. Acknowledging a temporary distress, they emphasize their research participation as positive, without showing regrets, and highlight the benefits of participation when they are being respectfully, sensitively and properly cared for [68]. Nevertheless, given the closeness of T1 to the death, where the families may be acute distressed/disturbed, it is necessary to limit the potential strain that can be added to the families. Presenting many questions to the family members at this early time following the loss may lead to problems or even discourage their retention in the study. In addition, their diminished cognitive resources may negatively affect their ability to properly fill in many questionnaires at this time. Therefore, T1 will just comprise the use of the above -mentioned 2 questionnaires.

Project Organization

This is a one-center study conducted in Norway for a timeframe of 3 years. It was initiated in November 2014 and will be completed by November 2017. An expert advisory board with representatives from (inter)national universities and institutions with special competencies in the grief/trauma field will provide on the study during the research process. This is of primary importance as there are few international (and none Norwegian) studies informing early follow -up practices following loss and trauma.

Results

The present pilot study is ongoing and started enrolment of families in August 2015. Data collection is expected to be completed in June 2017.

Discussion

Implications of the Study

This pilot study will evaluate the plausibility and practicability of a future main trial. Furthermore, it will explore the preliminary short -term effects of an early multidimensional program designed to promote families' grieving process and adjustment after a sudden death of a partner/parent, and to decrease the risk for complicated grief in both bereaved children and their surviving parents. The rationale for this study is embedded in the existing literature [26-28], our clinical experience, and the wishes for immediate assistance, outreach help, and help for their children expressed by the bereaved themselves [22,29].

Strengths and Limitations

To our knowledge, this is the first study proposing an early preventive program that starts up in the first days following loss with the potential to adapt the intervention to the needs of bereaved families over time. It is also one of the first trials employing the delayed intervention design in the grief field in order to explore the effect of time on outcome variables. Therefore, this study will provide preliminary knowledge about the value of very early intervention following bereavement, which crucially calls for empirical support and clarification. In addition, the delayed intervention design overcomes some important ethical, methodological, and logistical constraints, because it assures intervention for all participants [69]. On the one hand, it seems to suit the needs of the families, who may show a strong wish for immediate assistance [22,29]. On the other hand, it can minimize possible dropout effects as our former experience in conducting research makes us believe that these families are likely to show a high expectation of receiving intervention from us. Accordingly, the delayed intervention design minimizes possible disappointment effects of those who are not allocated to their treatment choice, preventing the risk of refusing randomization [70]. As a result, we consider that the use of the delayed intervention design will maximize recruitment and retention. Consequently, considering that the lack of evidence of preventive interventions for bereaved has been linked to higher levels of complexity in implementing these studies [30], we think this delayed intervention design takes into account the interests of our bereaved families, promoting the study's integrity, its effective implementation, and full potential.

Nonetheless, this pilot study may entail a number of possible limitations. First, recruitment constraints may lead to a small and/or possibly selective sample. The Norwegian population is small and our recruitment potential is not large, given that we need to wait for the potential traumatic event to happen. Besides, the intervention takes place at our center, which means we can only recruit in the surrounding county. Further, the bereaved families are contacted at the first time they meet health care personnel following the death, which may be particular demanding for some families, undermining their willingness to participate in the study.

Second, both early-SEIB and delayed-SEIB intervention groups can make use of care as usual, which may lead to carry -over effects [71]. This refers to the first support and help these families can receive from the crisis team, general practitioner, hospital, church, and/or school in the community. In communities outside the urban area, and in recruiting hospital wards, care as usual will vary greatly. However, families receiving other concurrent psychotherapeutic intervention will be excluded from the study and the Help Questionnaire may help to monitor some of these potential carry -over effects.

Third, a longer follow -up assessment should have been considered, as it would allow us to report on possible long -term effects, and to explore the sustainability of change over time [72]. Financial unfeasibility is the main reason that hinders the likelihood of looking at possible SEIB's long -term effects. Grant providers should recognize bereaved people as a particularly vulnerable, sensitive, and 'hard -to -reach' group that requires additional resources, both financial and from the research team.

Fourth, family participation may entail a small burden because it involves the fulfillment of a set of questionnaires at 4 time-points. The expected distress in relation to filling in questionnaires is anticipated to be highest at T1, because it takes place in the near aftermath of the death where families may be stunned or shocked. We try to minimize this burden by using 2 questionnaires at T1 (with an estimate short time to complete them: 15 to maximum 30 minutes), and having a researcher present with the families to provide help and assistance with the task. Besides, previous research have showed that the burden of filling in questionnaires was outweighed by the meaningfulness of participation, as it tends to increase families' understanding of their grief reactions [68]. The intervention will take 1 to 2 hours per session and will require that the families express what help they think they need. Considering the needs of suddenly bereaved families, SEIB will hopefully operate as a protective factor, promoting individual and family's adjustment. This is likely to stimulate a safer and less stressful mourning environment, which may even help to prevent further maladaptive trajectories. Therefore, we consider that the benefits for the individual and the family exceed the minimal constraints that this study may entail.

Conclusion

In sum, rather than evaluating SEIB efficacy or effectiveness, the current pilot study assesses the feasibility of a fully-powered trial. This study encompasses 3 major strengths that are the development of SEIB, the sample of bereaved families at considerable risk for complicated grief, and the use of the RCT with a delayed intervention design. It will possibly expand knowledge on the usefulness of a proactive, holistic, and supportive approach that may be of major importance for public mental health services, governments, and crisis teams.

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Conflicts of Interest

None declared.

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Abbreviations

APQ: Alabama parenting questionnaire
CRIES-8: children's impact of event scale
CSS: crisis support scale
EMDR: eye movement desensitization and reprocessing
FAD: family assessment device
GHQ-12: general health questionnaire
ICG-19: inventory of complicated grief
IES-R: impact of event scale-revised
IPG-A: inventory of prolonged grief for adolescents
PCS: parenting coping scale
PTSD: posttraumatic stress disorder
SDQ: strengths and difficulties questionnaire
SEIB: systematic early intervention for bereaved
T1: baseline
T2: after 3-months follow-up
T3: after 6-months follow-up
T4: after 9-months follow-up
TFT: thought field therapy
WSAS: work and social adjustment scale

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Protocol

Incorporating Novel Mobile Health Technologies Into Management of Knee Osteoarthritis in Patients Treated With Intra-Articular Hyaluronic Acid: Rationale and Protocol of a Randomized Controlled Trial

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Abstract

Background: Osteoarthritis (OA) of the knee is one of the leading causes of disability in the United States. One relatively new strategy that could be helpful in the management of OA is the use of mHealth technologies, as they can be used to increase physical activity and promote exercise, which are key components of knee OA management.

Objective: Currently, no published data on the use of a mHealth approach to comprehensively monitor physical activity in patients with OA are available, and similarly, no data on whether mHealth technologies can impact outcomes are available. Our objective is to evaluate the effectiveness of mHealth technology as part of a tailored, comprehensive management strategy for patients with knee OA.

Methods: The study will assess the impact of a smartphone app that integrates data from a wearable activity monitor (thereby both encouraging changes in mobility as well as tracking them) combined with education about the benefits of walking on patient mobility. The results from the intervention group will be compared with data from a control group of individuals who are given the same Arthritis Foundation literature regarding the benefits of walking and wearable activity monitors but who do not have access to the data from those monitors. Activity monitors will capture step count estimates and will compare those with patients' step goals, calories burned, and distance walked. Patients using the novel smartphone app will be able to enter information on their daily pain, mood, and sleep quality. The relationships among activity and pain, activity and mood, and sleep will be assessed, as will patient satisfaction with and adherence to the mobile app.

Results: We present information on an upcoming trial that will prospectively assess the ability of a mobile app to improve mobility for knee OA patients who are treated with intra-articular hyaluronic acid.

Conclusions: We anticipate the results of this study will support the concept that mHealth technologies provide continuous, real-time feedback to patients with OA on their overall level of activity for a more proactive, personalized approach to treatment that may help modify behavior and assist with self-management through treatment support in the form of motivational messages and reminders.

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KEYWORDS

mHealth; osteoarthritis; pain; physical therapy

Introduction

Osteoarthritis Management and Mobility

Osteoarthritis (OA), a prevalent condition afflicting nearly 27 million US adults, is one of the leading causes of disability in the United States [1,2]. Pain and the other symptoms associated with OA of the knee have a profound negative impact on patients' quality of life, affecting both physical activity and psychological well-being [3-5]. Limitations in walking, stairclimbing, and kneeling are common and greatly interfere with activities of daily living and recreation, which may have negative effects on patients' social interactions, sleep, and mental functioning [4].

The primary goals of most treatments for OA are to reduce pain and improve the function of the affected joints [6,7]. Optimal management of OA requires a combination of both pharmacologic and nonpharmacologic methods to achieve these goals [6-8]. Pharmacologic methods include oral or topical analgesics or intra-articular therapies, such as viscosupplementation, that focus on reducing pain, whereas nonpharmacologic methods include weight loss, physical activity, and exercise [6-9]. Although, there is no standard program of education or exercise and no clear benefit of one exercise program compared with another [7], 1 study found that a regular walking program can be associated with reduced pain and improved quality of life [10], while another study has demonstrated that walking can significantly reduce the risk of functional limitations in patients with knee OA [11]. This suggests that walking, which is an intrinsic activity of daily living, by itself can have a substantial impact on reducing symptoms of OA and maintaining function. Multiple societal guidelines also recognize patient education and self-management strategies as important components of knee OA management [6-8]. When implemented in conjunction with weight loss and exercise activity, these programs can increase adherence to prescribed management paradigms and may increase the overall effectiveness of treatment [12].

Unfortunately, the majority of patients do not routinely incorporate exercise or physical activity into their lives, despite their well-known benefits [13]. Patients with knee OA have been found to be particularly sedentary and being less sedentary has been associated with better physical function in these patients [14]. Increasing mobility and decreasing sedentary behavior may also lead to improved blood pressure, reduced cardiovascular risk [15], and improved quality of life [16]. One relatively new strategy that may be used to enhance OA management and increase physical activity is the use of mHealth technologies (ie, the use of mobile apps for health care). These technologies can provide continuous feedback to patients on their overall level of activity; they can also assist with self-management by providing treatment support in the form of motivational messages and reminders. To date, however, no published data are available on the use of mHealth technologies in the management of knee OA. Research is thus needed on the potential effectiveness of mHealth technologies as part of a tailored, comprehensive management strategy.

mHealth Technologies and Limitations: Brief Background

This brief section is intended for the clinical audience who may be less familiar with mHealth technologies. The development of mHealth devices, apps, social media, and Web-based services is leading to a paradigm shift in health care, and these technologies can serve a multitude of functions, such as facilitating customized communication to or between health care providers and consumers, collecting data, and delivering care. They can also provide individual level support for both health care providers (eg, education) and consumers (eg, appointment or medication reminders or test result notifications) [17]. Wearable devices, such as bracelets, watches [18,19], skin patches/strips [20,21], and even "smart" apparel, which contain biosensors [22-24], can now be used to monitor, track, and transmit health metrics continuously and in real time. Personalized information can be provided to guide health and wellness that may facilitate interactive, individualized treatment and give feedback to motivate patients to adopt a new behavior or excel in an existing activity. Increasingly, smartphones themselves are providing feedback by using the embedded sensors that have become standard fare to capture data. It is not unusual to combine these data sources with information from external sources, such as Google Maps, Google Traffic, National Oceanic and Atmospheric Administration, and even Facebook to deliver actionable information to the patient. mHealth also empowers patients with user-friendly information, which allows them to have more say and take more responsibility for their treatment.

mHealth has the potential to provide numerous benefits for patients, physicians, and other key individuals involved in health care delivery [25]. One of the most common apps is a reminder for patients to take their medications (via either phone calls or SMS text messaging (short message service, SMS)), but mobile phones can also be used to deliver insurance information, as well as increase the efficiency of emergency services and responses. The Web-based pharmacy, Walgreens, offers one of the most successful mHealth mobile apps, which provides reminders to take medications, facilitates requests for medication refills, and is now used by millions in the United States while providing Walgreens loyalty points for doing so. mHealth services can also promote healthy behavior and provide real-time patient monitoring and communication. All of the above could improve the overall efficiency of health care by reducing costs.

Unfortunately, the overall quality of the data gathered by these technologies is low. A systematic review and meta-analysis of controlled trials of the effectiveness of mobile technology interventions conducted in 2013 concluded that none were high-quality trials [17]. The majority of the trials examined in this review tested interventions directed at health care providers, not patients, with mixed results, and none reported any objective clinical outcome. Many of the studies focused on the impact of using SMS text messaging either to provide information, such as test notifications and reminders for appointments, or to affect patient behavior, such as treatment adherence or smoking cessation [26-31], yet failed to provide sufficient evidence of the benefit of these apps.

The nature of the data captured by these devices is different from classical clinical data, as it is patient-generated and not directly observed by clinical researchers. Currently, no standards or guidelines have been developed to interpret data from wearables or how to transform it into data that are quantifiable and clinically meaningful. The data tend to be available as streams rather than traditional clinical episodic data points, and researchers are unsure about how to relate trending data to other data points. Data from these types of devices and apps also need to be put into the proper context. For example, a device may indicate that a patient's mobility is increased, but increased mobility does not necessarily mean that a patient is feeling better and may not even be the best indicator of improvement.

Devices have varying capabilities, do not measure activities in the same way, apps are often device-specific, and the need for software/hardware updates is common, making comparison a technical challenge. Different devices have various combinations of accelerometers, gyroscopes, and electronic compasses. Some have built-in global positioning system technology or access location data from paired smartphones. Sampling rates, processor power, and motion data analytic software capabilities vary widely. Many are associated with false-positive and false-negative results. Activities such as horseback riding can register as substantial activity or movement, whereas riding a stationary bike may register only as minimal activity (or none at all). Most current devices are unable to capture water-based activities. To capture data correctly, patients must be compliant and wear or use the device as directed, but it is impossible to confirm that the individual is actually wearing or using the device.

Finally, there are financial barriers with regard to implementation of mHealth technologies. Although 91% of the adults in the United States own a mobile phone, with 61% of these individuals owning a smartphone [32], a portion of the population still cannot afford such a device. The current fee-for-service health care model also hinders uptake of mHealth technologies, with little financial incentive for practitioners to implement preventive care; and value-based care is not foreseen to overtake fee-for-service care until 2020. An exception to this paradigm is the upstart insurer Oscar Health, which received a $32.5 million investment from Google in 2015 and provides its insured customers with activity monitors and financial incentives to use them. Oscar Health operates in New York and New Jersey and will expand into California and Texas in 2016. Many self-insured employers are also making activity monitoring and feedback a central component of their corporate wellness programs.

Overview of mHealth in Support of Osteoarthritis Management

Innovative mHealth technologies specifically designed for patients with chronic conditions such as OA may be particularly useful. They can be used to help change behavior or improve (and possibly simplify) disease management (eg, by increasing adherence to prescribed medication) and can provide definitive objective information (eg, "I walked 5000 steps yesterday" or "I walked 15% more this week over last week") rather than subjective feedback (eg, "I was as active as I normally am"), which would be beneficial, as many of the tools used for assessments in OA, such as visual analog scales, are subjective. Patients from different backgrounds (geographic locations as well as ethnic backgrounds) have different, subjective perceptions of pain. Developing objective assessment measures for OA would thus be an advance in terms of assessing patients' physical status as well as the effectiveness of new treatments. Furthermore, the symptoms of OA are often variable depending on patients' activity level, changes in weather, and various other factors. Patients may not have pain at rest but can have severe pain during activities such as climbing stairs. As such, validated, documented questionnaires, such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC 3.1), which is used to assess pain, stiffness, and physical function over a specific time frame (ie, the last 48 hours) in clinical trials [33], can completely miss the effect of treatment. For instance, a patient in a clinical trial of treatment for knee OA may present for a regularly scheduled study visit at week 12, noting that pain over the last 4 weeks has been low, whereas pain over the last 3 days (when the patient has been gardening and shopping and/or there has been a dramatic weather change) has been high. The opposite scenario could also occur: a patient may feel unwell for several weeks and then decide to rest, so the target knee on the day of assessment may feel good. mHealth technologies may allow establishment of baseline activity or pain levels (eg, in patients where movement is impaired by pain) so that any change in real time over the course of the study may be more objectively assessed and treatment adjustments can be made. Finally, reported pain can be indexed to actual activity to see the personalized correlation between reported pain and activity.

mHealth technologies have the potential to provide more continuous, real-time monitoring of patient health, which would be helpful for patients with chronic conditions, such as OA, as it may provide a more proactive, personalized approach to treatment. For example, patients with diabetes would greatly benefit from continuous monitoring of blood glucose to facilitate changes in treatment, as would cardiac patients with arrhythmias if changes in heart rate could be captured with a mobile device. In fact, the Dexcom Mobile Continuous Glucose Monitoring system [34] includes an activity sensor that reports activity to the patient as part of its therapy management system, and the iRhythm ZIO XT [21] patch can provide continuous monitoring of cardiac arrhythmias [35] and is preferred by patients over traditional Holter monitors [36]. Patients with OA could similarly benefit from continuous monitoring of activity and pain. There are already beds and pillows with sensors that capture body movement and position during sleep for assessment of sleep apnea, floors with sensors that capture changes in gait (for fall prevention), and digital cameras and programs that analyze skin color for assessment of liver, kidney, or cardiac diseases. Although many of these devices are prototypes, they will likely lead to improved, more reliable, and more sophisticated technologies. Patients may be particularly open to the use of mHealth technologies in the management of their OA for many of the reasons above. In one recent study of attitudes toward wearable technology, patients with knee OA expressed the perception that wearable technology could positively benefit their sense of control over their condition,

improve awareness of progress and communication with their clinician, and empower their self-management [37].

Development of Evidence to Assess Effectiveness of mHealth

Evidence is accumulating regarding the effectiveness of mHealth interventions. Two systematic reviews have described a robust evidence base for the use of SMS text message reminders to improve attendance at health care appointments [26,38]. Another systematic review found that mobile app–based interventions promote weight loss [39]. Increased physical activity following use of Internet- and mobile app–based interventions has been observed in several studies such as those promoting a healthy lifestyle [40], workplace-based increased walking [41], engagement in regular physical activity in cancer survivors [42], maintenance of physical activity after cardiac rehabilitation [43], and post-rehabilitation exercise persistence in patients with chronic obstructive pulmonary disease [44]. Conversely, however, a systematic review of studies that used the Internet to deliver the primary component of treatment has shown only modest effects on health-related behavior [45], and a recent systematic review of the effectiveness of online social network health behavior interventions found modest benefits at best (most were small in magnitude and nonsignificant) [46].

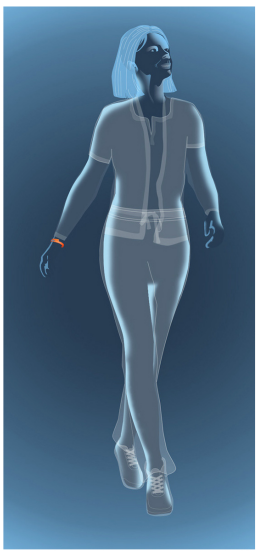
At this time, no published data are available on the use of a mHealth approach to comprehensively monitor physical activity in patients with OA, and no data have been published on whether mHealth technologies can impact outcomes. Studies have shown that regular phone contact can improve the clinical status of patients with knee OA [6,47]. For example, a randomized controlled trial in 439 patients with OA demonstrated that monthly phone contact aimed at promoting self-care for patients with knee OA could be associated with improvements in joint pain and physical function [47]. This suggests that smartphone apps may be helpful in improving outcomes in patients with knee OA. A new clinical trial (presented herein) will prospectively investigate this hypothesis by assessing the ability of a mobile app to improve the mobility of patients with knee OA who are treated with hylan G-F 20, an elastoviscous high molecular weight fluid containing hylan A and B polymers that is approved for the treatment of pain in moderate to severe OA of the knee [48].

MARCHE Study Rationale

The MARCHE trial was conceptualized to help patients with knee OA connect management of their mobility and monitoring of their functional abilities with self-management strategies. The study is designed to assess the impact of a smartphone app (which encourages changes in mobility) that integrates data from a wearable activity monitor (which will capture changes in mobility) with education about the benefits of walking (Figure 1). The data will be compared with those from a control group of individuals who are given Arthritis Foundation literature regarding the benefits of walking and who do not have access to the data from their wearable activity monitors. The activity monitors will capture estimates of step counts, comparing them with patients' step goals, calories burned, and distance walked, whereas the novel smartphone app will allow patients to enter information on their daily pain, mood, and sleep quality. Assessment of the relationships among activity and pain, activity and mood, and sleep will be performed, as will assessment of patient satisfaction with and adherence to the mobile app. Data will be indexed to time of day and date.

The activity monitor and mobile app will allow continuous monitoring of patient activity levels and will be a more objective parameter compared with established and validated scores, such as WOMAC and visual analog scales. Patients with OA may indicate that they would like to be more active and are aware of the benefits of exercise, but that they are limited by pain. Being able to actively, objectively, and continuously monitor activity levels could provide key insights in personalizing patients' treatment regimens.

Figure 1. Conceptualization of the MARCHE clinical trial. Study participant (a) receives a motivational message from the OA GO smartphone application and then (b) begins to walk.



Textbox 1. Patient inclusion criteria.

- Must have osteoarthritis of the knee, which the investigator decided to treat with hylan G-F 20 according to the approved label in the United States.
- Must be able to read, understand, and sign an informed consent form, understand requirements for follow-up visits, and provide information at the scheduled evaluation.
- Must be able to read and understand English.

Textbox 2. Patient exclusion criteria.

- Age <30 or >80 years.
- Being pregnant or currently breast-feeding (women of childbearing potential not protected by highly effective contraception also excluded).
- Unfamiliarity with smartphones.
- Baseline pain in target-for-treatment knee while walking on a flat surface >9 on 11-point numeric rating scale.
- Bilateral disease (but may be included if only one knee is treated and contralateral knee pain must be <4 while walking on a flat surface on 11-point numeric rating scale).
- Body mass index >35.
- Short life expectancy (<12 months).
- Current use of Jawbone, Fitbit, or any other wearable activity monitor or an analogous device.
- Ongoing litigation or workers' compensation claim related to knee pain.
- Surgery on any lower extremity joint.
- Significant medical condition or other factor that investigator would feel would interfere with study evaluation or participation.
- Chronic narcotic use.
- Daily step average <500 or >8000.

Methods

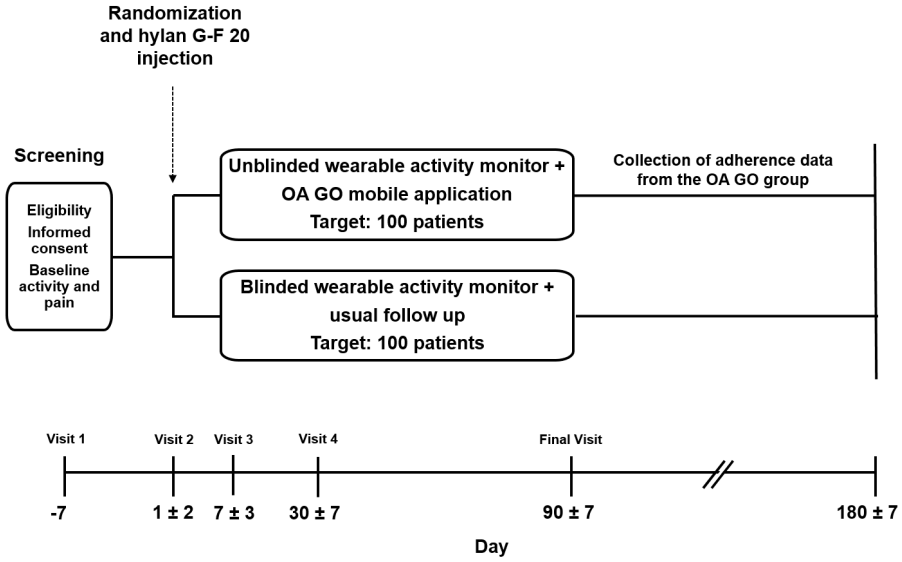
Patient Eligibility Criteria and Study Design

Patient inclusion and exclusion criteria are listed in Textboxe 1 and Textboxe 2. The inclusion criteria were designed to identify patients who were candidates for treatment with hylan G-F 20 and would be capable of using the wearable activity monitor and a smartphone.

The MARCHE study is a randomized (1:1), open-label, multicenter, parallel-group study in patients with OA of the knee treated with hylan G-F 20. The trial will be conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice, and each investigator will obtain institutional review board or ethics committee approval. The primary objective of the study is to demonstrate the impact of a mobile app (OA GO) plus a wearable activity monitor in increasing the mobility of patients with knee OA who were treated with hylan G-F 20. Secondary objectives include evaluating the impact of the OA GO app combined with the wearable activity monitor on a 6-minute walk test, assessing patient and physician satisfaction with the OA GO app and the wearable activity monitor, determining the percent change from baseline in steps per day, and determining between-group changes from baseline in the Patient Activation Measure-13 (PAM-13), which assesses patient activation regarding health self-management. Relationships among mobility, pain, mood, and sleep will also be established.

Figure 2 shows the study protocol. Patients who are selected by the investigator for treatment with hylan G-F 20 for OA of the knee will be screened for eligibility, and their baseline pain will be assessed. Patients will also be required to provide written informed consent. If eligible, patients will be given a wearable activity monitor (Jawbone UP24) that will record their daily steps and other variables over the next 7 days (to establish their baseline activity level). Jawbone UP24 is a commercially available wearable activity monitor designed to be worn on the wrist. After at least 7 days, patients will return for assessment of baseline activity, mood (using Visual Analog Mood Scales (VAMS) [49]), and a baseline 6-minute walk test. Eligible patients will receive a single intra-articular injection of hylan G-F 20 in the knee and will be randomized to receive either the mobile OA GO app (unblinded and able to view data from their wearable activity monitor on an ongoing basis) or standard-of-care instructions (blinded with no access to activity recorded by the wearable monitor); randomization will be stratified by site. Additional study visits are performed at days 7 and 30, with the final visit at day 90, when the last evaluation of the primary endpoint will be performed, along with assessments of pain, 6-minute walk test, mood (VAMS), PAM-13, and patient/physician satisfaction. At the end of the trial, all data from the mobile OA GO app will be downloaded and patient adherence will be checked.

Figure 2. Design of the MARCHE clinical trial.



Study Treatment Groups

The study consists of 2 treatment groups, both of which will include the wearable activity monitor. Participants in group A will receive the OA GO mobile app, and their wearable activity monitors will be unblinded. They will be able to view the data from their monitors on an ongoing basis. The OA GO mobile app, which will be downloaded to an iPhone (provided by the study sponsor), contains motivational messages and requests that the patients enter their pain and mood on a daily basis. Training on the use of the mobile app will be provided by the study site. The OA GO app will obtain information from the wearable activity monitor and combine the data with data entered by the patient (such as daily pain and mood). In group B (the control arm of the study), the wearable activity monitors will be blinded; that is, patients in group B (who are blinded to their wearable activity monitor) will not have any access to data recorded by the wearable activity monitor. Data will be downloaded by the study team at last visit. Patients in both treatment groups will receive regular follow-up per the standard-of-care information regarding the benefits of walking from the Arthritis Foundation [13].

Results

Study Outcomes

The primary study endpoint is the difference in the change in mobility (assessed by steps per day) between groups at the end of 90 days. Baseline steps per day will be the average of the steps recorded on the wearable activity monitor over 7 days during screening, and the final-visit steps per day will be the average of the steps recorded on the wearable activity monitor over the last 7 days for which steps are recorded. Secondary efficacy endpoints include physical function, assessed by the change from baseline in the 6-minute walk test (distance and pain (pain assessed on an 11-point numeric rating scale, ranging from 0-10)), and percent change from baseline in steps per day. The 6-minute walk test is a validated measure sensitive to assessing changes in the physical performance of older adults [50,51], and has been found to be a reliable measure of functional performance in patients following total hip and total knee arthroplasty [52,53].

Patient-reported outcomes include patient and physician satisfaction with treatment (measured by 6 items for each, on a 7-point Likert scale, and a final item assessing likelihood of using the device in the future (patient) and recommending the device (physician)), PAM-13 scores (responses on a Guttman-like scale ranging from 1-4 (strongly disagree to strongly agree), resulting in possible scores from 13-52 and converted to activation scores ranging from 0-100, the highest degree of activation), and patient-entered values for daily pain and mood for those in the mobile OA GO group. The PAM-13 [54,55] is a reliable and valid measure of patient activation, with higher scores associated with increased self-management behaviors, increased self-efficacy, and activation making it useful for evaluating interventions in a clinical setting.

Tertiary endpoints include target knee pain with walking and at rest, as measured by the 11-point numeric rating scale at final visit; mood at final visit (as measured by the VAMS (capturing 8 domains of mood with raw scores transformed into T-scores with a mean of 50 and standard deviation of 10)); pain and mood as entered into the OA GO app by patients in the mobile OA GO group; sleep quality as measured by the wearable activity monitor; and change from baseline in weight. The VAMS is a brief measure of internal mood state validated in both normal and neurologically impaired individuals [56,57]. Analysis of the relationships between activity and pain, activity and mood, and sleep will also be performed. Lastly, adherence to the use of the mobile OA GO app plus the wearable activity monitor over 90 days after completion of the trial (in patients who received the mobile app) will be determined. Adverse events, including device-related complaints, will also be assessed.

Data Analysis

The target sample size in this study is 200 participants, which assumes an attrition rate of 15%. Based on a two-sided significance level of 5%, the study will have 80% power to detect an average increase of 25% in the change from baseline

in steps per day for those in the unblinded wearable activity monitor group using the OA GO mobile app, compared with those in the blinded wearable activity monitor group who did not have the mobile app.

Efficacy outcomes will be analyzed in the modified intent-to-treat population (all randomized patients with baseline and on-treatment values for the primary endpoint from day 30 onward). Analysis of covariance with baseline mean steps per day as covariate and treatment and pooled site as class variables will be used to compare between-group outcomes. Satisfaction surveys at last visit will be summarized. Safety outcomes will be analyzed for all patients provided a wearable activity monitor.

Discussion

Summary and Limitations

Adoption of mHealth technologies into the management of knee OA and other chronic diseases that rely on self-management has the potential to improve patient outcomes; however, data to support this potential are needed. The approach of using these new technologies will also need to be validated. As a first step, the MARCHE study evaluates the impact of a mobile app, combined with a wearable activity monitor, on mobility in patients with knee OA treated with hylan G-F 20. The first patient was enrolled in August 2014, and study enrollment has since been completed.

One limitation of the study is that the investigators are not blinded to the intervention, which could bias the delivery of other aspects of care to the patient. In addition, the step count is only an estimate of the patients' mobility and is specific to the Jawbone device, so it may not be representative of all devices. The study was focused on activity monitoring and could have included an evaluation of WOMAC scores to assess patient subjective evaluation of changes in condition and function. Finally, the 6-minute walk test could be considered less representative of real-life mobility compared with 6 minutes of walking taken at different time intervals. Future studies could use "continuous walk tests" over a 24-hour period, an example of which would include both a 6-minute walk test and a 25-foot walk test that could be continuously run with algorithms in place to discard, for example, periods of rest, sleep, and driving.

The field of mHealth will continue to evolve. In particular, wearable devices may eventually become implantable devices, which are increasingly being used for health purposes.In 2004, the US Food and Drug Administration approved radio frequency identification tags for human implants, although some safety concerns are associated with these tags. They are small, which means they can move under the skin and become difficult to remove. Internally powered tags could also cause electromagnetic interference with medical devices such as defibrillators. Implantable sensors are currently in development for monitoring glucose and free-floating proteins as biomarkers.

Conclusions

Ultimately, as technology continues to advance, medicine will do so in kind. The MARCHE study may provide the first real-world evidence of the benefits of health technology in the treatment of knee OA and may provide patients with greater control in the management of their disease.

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Conflicts of Interest

Donald Jones reports receiving consulting fees from Sanofi, Scripps Translational Science Institute, Trial Fusion, Scripps Digital Medicine, Qualcomm, Wireless Life Sciences Alliance, Milken Institute Advisory Committee on Biomedical Innovation, and World Economic Forum Global Agenda Council on Digital Health, and is on the board of Mio Global, which makes a product similar to the Jawbone device that was used in the MARCHE clinical trial. Nebojsa Skrepnik has nothing to disclose. Bruno Leroy is an employee of Sanofi. Richard M. Toselli was an employee of Sanofi at the time the work was conducted and is currently an employee of Cochlear Ltd., Sydney, Australia.

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Abbreviations

OA: osteoarthritis
PAM-13: patient activation measure-13
SMS: short message service
VAMS: visual analog mood scales
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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Original Paper

A Multifaceted Nurse- and Web-Based Intervention for Improving Adherence to Treatment in Patients With Cardiovascular Disease: Rationale and Design of the MIRROR Trial

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Abstract

Background: Poor adherence to medication is one of the limitations in the treatment of cardiovascular diseases, thereby increasing the risk of premature death, hospital admissions, and related costs. There is a need for simple and easy-to-implement interventions that are based on patients' perspectives, beliefs, and perceptions of their illness and medication.

Objective: The objective is to test the effectivity of this intervention to improve medication adherence in patients with established cardiovascular disease, that is, in secondary prevention.

Methods: In this study the effect of a personalized visualization of cardiovascular risk levels through a website aiming at supporting self management in combination with a group consultation and communication intervention by a nurse on adherence to treatment in 600 patients with manifest cardiovascular diseases will be assessed. The health belief model was chosen as main theoretical model for the intervention.

Results: Primary outcome is adherence to treatment calculated by refill data. Secondary outcomes include the Beliefs about Medication Questionnaire and the Modified Morisky Scale. Patients are followed for one year. Results are expected by 2015.

Conclusions: This study assesses adherence to treatment in a high-risk cardiovascular population by applying an intervention that addresses patients' capacity and practical barriers as well as patients' beliefs and perceptions of their illness and medication.

ClinicalTrial: ClinicalTrials.gov NCT01449695; https://clinicaltrials.gov/ct2/show/NCT01449695 (Archived by WebCite at http://www.webcitation.org/6kCzkIKH3)

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KEYWORDS

medication adherence; cardiovascular; eHealth; nursing

Introduction

Background and Rationale

According to the World Health Organization, almost 50% of all chronic patients do not adhere to their prescribed drug regimen [1]. This is also true for cardiovascular diseases (CVD); only 60% of all cardiovascular patients adhere to their cardiovascular medications (eg, statins, antihypertensives, antithrombotic agents) [2]. This prevalence is similar across all individual CVD medications and occurred in patient who take these medications for primary and secondary prevention of CVD [2]. These figures are startling given that poor adherence results in an increased risk of death in cardiovascular patients [3-5].

Current methods for improving adherence are mostly complex and have limited effectiveness; simple interventions that are easy to implement in daily practice are preferred [6]. Evidence suggests that interventions should be based on the patients' perspective [7], target patients' capacity and practical barriers, and address their beliefs and perceptions regarding illness and medication [8,9]. In CVD, life-long adherence is important, and interventions should improve patients' intentions to take medication as well as solve emergent practical barriers.

These principles were used in the development of the current trial. Specifically, the intervention is based on the health belief model (HBM) [10,11], tailored for the specific purpose of this trial. HBM provides a useful framework for designing behavior change strategies [12]. It is based on the understanding that a person will take health - related action (eg, being adherent to cardiovascular medication) given four main factors. The first two factors are perceived susceptibility and perceived severity: understanding of the high personal risk and seriousness of a condition (eg, because of the cardiovascular event in the past I am at greater risk for another cardiovascular event). The third factor is perceived benefit, or a belief that a negative health condition can be avoided (eg, being adherent to the cardiovascular medication can help to prevent another cardiovascular event). The last factor is perceived barriers. Cue to action and self - efficacy and the belief in the ability to successfully undertake the recommended health action (eg, I know how to take my medication on a daily basis) [12,13].

Trial Design and Aim of the Study

The study will use a single - center, prospective, randomized controlled clinical trial design and examine the effectiveness of a new intervention that incorporates HBM and behavior change strategies to improve adherent behavior in cardiovascular patients. The intervention consists of a patient-based screening method, a specific nurse-based intervention (structural informative consulting and motivational counseling), and personalized visualization of cardiovascular risk levels via a website. The objective is to test the effectiveness of this intervention to improve medication adherence in patients with established CVD (ie, in secondary prevention).

Methods

Study Setting

Participants will be drawn from a hospital - wide screening program. This screening program is situated at the cardiovascular outpatient clinics in an academic medical center in Nijmegen, the Netherlands. All new patients diagnosed in the last 6 months with acute coronary syndrome, peripheral arterial disease, an aneurysm of the aorta, or stroke/transient ischemic attack (TIA) and referred to the departments of vascular surgery, neurology, or cardiology are automatically included in this program.

Eligibility Criteria

From this population, participants aged 18 years and older will be selected based on the following inclusion criteria: presence of CVD (acute coronary syndrome, peripheral arterial disease, an aneurysm of the aorta, or stroke/TIA), diagnosed in the last 6 months by a medical specialist, willingness to remain in follow - up for a period of one year, and provision of signed informed consent. Exclusion criteria are pregnancy (reported by the patient), severe comorbidity (eg, a mental health diagnosis considered by a physician to be a contraindication), problems with the Dutch language (reported by the nurse), or logistic problems such as lack of computer access.

Intervention

For the intervention, participants will be split in three groups. Participants in group I (control group) receive only usual care. Group II participants receive usual care plus access to a personalized website. For the group III participants, in addition to usual care and access to the personalized website, the intervention program will also include a single group consultation of 60 minutes led by a nurse and a pharmacist followed by two individual consultations of 30 minutes with a nurse.

We want to test if treatment II (only the Web portal) can give the same results as treatment III (the Web portal and the single group consultation followed by two individual consultations). The need for low-cost effective interventions in our health care system led to the motivation for this 3-arm protocol.

Usual Care (Groups I, II, and III)

All new CVD patients receive the hospital - wide screening program according to the Dutch guidelines [14] (based on the European guidelines [15]). The screening assesses cardiovascular risk factors in all patients with CVD. It screens for lifestyle risk factors, blood lipid levels, blood pressure, waist circumference, body mass index, blood glucose levels, and a family history of CVDs. Lifestyle is evaluated through a questionnaire which is a compilation of existing validated questionnaires regarding demographic data, smoking, alcohol use, physical activity, and eating habits. For each of these lifestyle issues, the patient's motivation to change is evaluated [16]. Adherence is measured by the Modified Morisky Scale (MMS) [17] and the Beliefs about Medication Questionnaire (BMQ) [18]. Medication use will be monitored. If necessary and if the patients agree they attend consultations with a nurse

based on motivational interviewing to help them lose weight, stop using alcohol, or stop smoking.

According to European guidelines [15], all patients with established CVDs (this means all participants of this trial) should have antiplatelet therapy (eg, aspirin or clopidrogel) and a lipid lowering drug (eg, simvastatin or atorvastatin). The use of antihypertensive drugs is dependent on the systolic blood pressure. Except for the specific additions for the study, all participating and nonparticipating patients receive the same regular preventive cardiovascular care including monitoring of medication use. All patients receive regular vascular care from their medical specialist.

Website (Groups II and III)

The website contains an individualized Web portal called Interactive File Vascular Care (Interactive Dossier Vaatzorg, or iVAZ). This is developed to support patient-based self-evaluation and management [19,20]. Patients can log on and see their own cholesterol levels, blood pressure, and lifestyle (smoking habit, exercise, and eating habits) in a risk monitor. Patients can ask questions by email to their nurses, and they can enter changes in their medication. iVAZ provides risk communication, the feedback of clinical outcome will be provided individually, and patients are invited to be active in managing their illness and medication.

Group and Individual Consultations (Group III)

For group III, the intervention program will also include a single group consultation of 60 minutes led by a nurse and a pharmacist followed by two individual consultations of 30 minutes with a nurse.

During the group consultations patients receive information about their disease, cardiovascular medication (statins and antihypertensive and antithrombotic agents), and the importance of treatment adherence. Patients will receive an information booklet with all information presented during the plenary session. At the end of this consultation patients are asked to keep a diary of their medication intake during a 2-week period and to set a personal goal for the upcoming individual consultation with a nurse. The group consultation is regarded as an efficient way to increase knowledge and understanding of the risks. It also provides a gathering with other patients (peers).

During individual consultations, the intervention is further tailored based on the goal previously set, patient's concerns, and necessities using the results of the screening questionnaire (see Data Collection). The following topics will be discussed during the individual consultation: patient's motivation and confidence (barriers, concerns, and positive self-motivational statements about their adherence behavior), options for increasing adherence to treatment, and a global summary of the counseling session.

Both the group and the individual consultations take place at the outpatient clinic. The involved nurses have had training in motivational interviewing [21] and were especially trained for this intervention by a psychologist.

For each of the constructs, we used the recommended behavior change strategies [12,13]. We tailored the intervention further by using the taxonomy of Abraham and Michie [22,23] and the coding manual by de Bruin [24] to categorize the behavior change techniques to be included in the intervention. For each of the components of HBM, the determinants, techniques, and application strategy were developed and are detailed in Figure 1-4.

Figure 1. Techniques and applications influence perceived susceptibility in the current trial. The main determinant behind perceived susceptibility is a lack of knowledge regarding prescribed medications and the influence on risk reduction.

Technique	Practical applications/Strategy
Increase understanding	Group consult: Providing general information about atherosclerosis
Provide general information	Providing written material with information about cardiovascular medication and how it should be taken
Risk communication	Providing general information about cholesterol and blood pressure and their influence on cardiovascular risk.
Persuasive communication	Providing general information about cardiovascular medication and how it works.
Group sessions with peers	Discussion within a group of cardiovascular patients about being adherent and non-adherent to medication

Figure 2. Techniques and applications influence perceived severity in the current trial. The main determinant behind perceived severity is patients' beliefs, perception and management of their illness (awareness, outcome expectations).

Technique	Practical applications/Strategy
Risk communication Feedback of clinical outcome	Personalized website: Visualization of the personal cardiovascular risk through a risk monitor
Revaluation of outcomes, self-evaluation	Individual consult: Evaluating a medication taking diary
Goal setting	Group consultation and individual consult: Ask patients to describe a goal according to their medication adherence and evaluate this on their next appointment with their nurse

Figure 3. Techniques and applications influence perceived benefits in the current trial. The main determinant behind perceived benefits is patients' beliefs, perceptions, and management of their illness (awareness).

Technique	Practical applications/Strategy
Persuasive communication	Individual consult: Consults are given based on motivational interviewing and goal setting
Revaluation of outcomes, self-evaluation	Evaluating target levels
Reinforcement on behavioural progress	Personalized website: Providing a risk monitor that will be green if outcome targets are achieved

Figure 4. Techniques and applications influence perceived barriers, cue to action, and self-efficacy in the current trial. The main determinant behind perceived barriers is skills and self-efficacy.

Technique	Practical applications/Strategy
Self-report of behaviour	Let the patient keep a diary of his medication taking two weeks for each individual consultation
Verbal persuasion	Individual consult: Talk with the patients about the barriers and effect and side effects of the medication
Plan coping responses	If necessary, the nurse and patient make a plan together how to overcome the barriers.
Set graded tasks, goal setting	The patient and nurse formulate a goal at the end of each consultation reflecting the barriers they evaluated

Results

Primary Outcome

The primary outcome of our study is adherence to the CVD medication (classified by the Anatomic Therapeutic Chemical classification system) measured with a dedicated calculation of refill data of the used plated aggregation inhibitors and lipid modifying agents obtained from patient's pharmacy.

Refill records of computerized pharmacy systems will be collected from 3 years prior to a patient's cardiovascular event through up to 3 years after the study follow‐up period. Prescription records include the names of all of the dispensed drugs, prescribed daily dose, quantity dispensed at each pharmacy fill, and the dates of the prescription fills. Adherence will be calculated for the CVD medications as the theoretical duration divided by the period between the start date and the date of the last prescription filled. The theoretical duration will be calculated by dividing the number of units dispensed by the prescribed daily dose [25].

Patients with an adherence level of at least 80% will be classified as adherent, and patients with an adherence level less than 80% will be classified as nonadherent. Secondary prevention studies showed that patients with an adherence of less than 80% have an increased risk of death [26].

Refill adherence rates have been used extensively for the assessment of drug acquisition and dispensing. Compared with electronic monitoring, refill data provide researchers with a relatively simple method for investigating exposure to medication in large populations [27-29]. Moreover, this method is suitable for investigating long‐term persistence to treatment and gaps in medication supply [30].

Secondary Outcomes

All secondary outcome measurements will be obtained just before inclusion (in the usual care screenings program) and one year after inclusion. The secondary outcome measurements include clinical responses to drug therapy (eg, cholesterol level), self-report questionnaires, and changes in systolic blood pressure.

Clinical responses to drug therapy will be recorded. A recorded low-density lipoprotein cholesterol level above 20% of preestimated low-density lipoprotein cholesterol reduction during follow-up will be considered as possible indication of poor adherence. If the patient also uses antihypertension drugs, the blood pressure on baseline will be compared to blood pressure after one year and will need to be within target blood pressure for cardiovascular risk management (systolic <135 mm Hg). These office blood pressure measurements are performed according to the recommendations of the European Society of Hypertension [15] with a validated automated device; data will be based on a mean of four office measurements.

Second, two validated self-report questionnaires will be used. The MMS will be used to measure adherence [17]. Each of the 8 items measures a specific medication‐taking behavior. MMS scores can range from 0 to 8 and can be classified into three levels of adherence: low adherence (score of less than 6), medium adherence (score of 6 to less than 8) and high adherence (score of 8) [31]. The BMQ will be used to provide information about the beliefs, perceived necessity, and concerns patients have regarding their illness and prescribed medication [18]. Respondents indicate their degree of agreement with each individual statement about medicines on a 5‐point Likert scale. It is then possible to differentiate between patients on the basis of their beliefs about the necessity of their medication and their concerns about taking it. Patients can be classified into four different categories: accepting (high necessity and low concerns), ambivalent (high necessity and high concerns), skeptical (high concerns and low necessity), and indifferent (low concerns and low necessity) [32,33].

Participant Timeline

Baseline scores will be collected for all groups. Follow-up scores will vary depending on group and will be collected at 6 and 12 weeks (all groups) and 16 and 28 weeks (intervention groups II and III) (see Figure 5 for flow chart).

Sample Size

This study is mainly powered on the primary outcome, the detection of a significant difference between the three degrees of care (usual, additional website, additional counseling) on medication adherence as determined by refill records of computerized pharmacy systems. Based on previous research in our population and data from the literature [26], we estimate that the adherence at the start of the study will be 65% in each group with a standard deviation (SD) of 30%. We hypothesize that the intervention given in group II and the intervention given in group III will result in an increase of 10% in adherence to treatment, resulting in mean adherence rates of 75% and 85% in groups II and III, respectively. To detect these differences in medication adherence the estimated group size with a power of 80% and an alpha of .05 (2‐sided) would be 200 in each group, resulting in 600 participants in total.

Recruitment

All cardiovascular patients who receive the regular cardiovascular preventive care will be asked to participate by a nurse when they arrive at the outpatient clinic for their screening consult. Patients will receive a letter explaining the study, documenting their ability to withdraw at any time without explanation, and confirming that their medical care will in no way be influenced by their decision regarding participation. At a minimum of 24 hours later, written consent will be sought by a research assistant prior to the patient entering the study.

We chose to include all cardiovascular patients in our study rather than only nonadhering patients as done in many other studies [6,9,34]. The reason is that we plan to do a 3-year follow-up and want to be able to see how adherence develops over time for initial adherers and nonadherers alike.

Assignment of Interventions

Patients who meet the criteria and consent to participate will then be randomized by the nurse stratified by department (eg, neurology, vascular surgery, and cardiology) in a 1:1:1 ratio into one of the three groups using computer randomization.

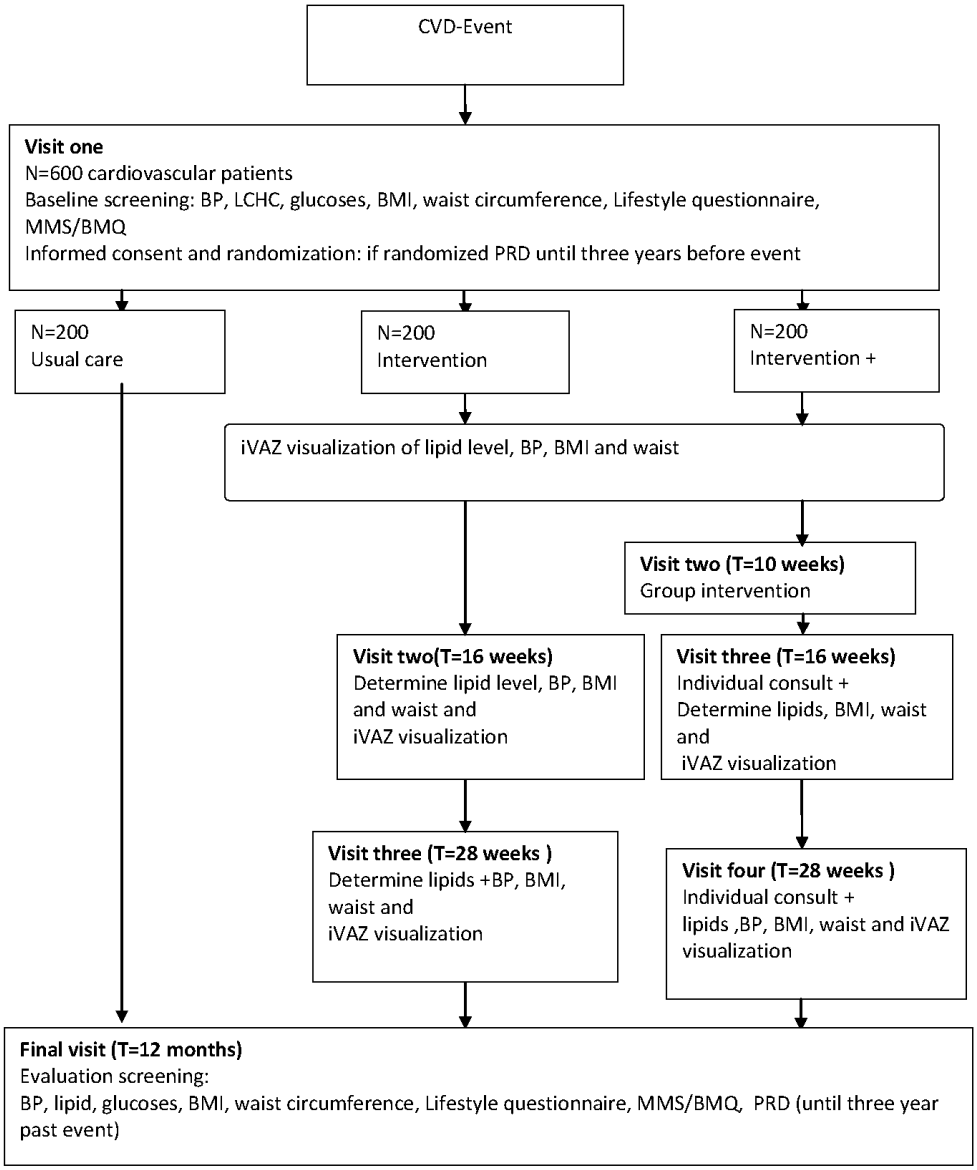
Blinding

The principal investigator and the researcher will be blind to randomization. However, due to the need for active participation, the patient, nurse, and pharmacist delivering the individual consultations will not be blind to assignment of individuals in group III.

Data Collection and Management

The primary data collected will be provided by the initial screening. Obtained data from the screening are blood lipid levels, blood pressure, waist circumference, body mass index, blood glucose levels, and medication use. Lifestyle is evaluated through a questionnaire which is a compilation of existing validated questionnaires regarding demographic data, smoking, alcohol use, physical activity, and eating habits. For each of these lifestyle issues, patient's motivation to change is evaluated [16]. Adherence is measured by the MMS [17] and beliefs about medication by the BMQ [18].

Figure 5. Patient flow chart.



To monitor whether the website intervention is used, log - in information per patient, expressed as the number of log - ins and times and dates of log-in, will be recorded.

To measure the nurses' performance skills required in the individual consultations, the behavior change counseling index will be used [35]. This validated checklist aims to measure the nurses' competence in behavior change counseling and adaptation of motivational interviewing in healthcare settings. The group consultations are videorecorded and evaluated in order to validate the quality of the motivational interviewing techniques applied.

Data will be entered by the nurses who perform the screening and the intervention consults in iVAZ. iVAZ is a secured website which can only be entered by the participants by using their social security codes and by selected nurses using security codes. In addition, all patient pharmacists will receive a letter of information about the trial, consent of the ethical committee, and the informed consents of the participants. They will be

asked to send the data on refill records of their computerized pharmacy systems through a secured email address. All the data will be anonymized according to the privacy protocols from the ethical committee and imported by the researcher into SPSS (IBM Corp).

Statistical Methods

The data will be analyzed based on the intention - to - treat principle and evaluated using SPSS, with descriptive statistics (mean, median, SD, and interquartile range) being determined for all variables. The data will be presented in quantitative format (eg, biometrics, laboratory results, blood pressure, lifestyle scores, adherence score on the basis of refill data, and the MMS) and in descriptions of observed effects (eg, change in BMQ, determinants for adherence, evaluation of the use of iVAZ, and appreciation of nurse intervention).

To evaluate the difference between the groups, an analysis of variance test will be performed on the outcome measures for the three patient groups. The independent variable will be the three intervention groups. The dependent variable is medication adherence measured with the dedicated calculation of refill data. Specifically, we will compare the difference between the first and last time-point between groups for the primary and secondary outcomes measures. For the intervention groups II and III, we will also compare the outcomes of the clinical data at 16 and 28 weeks. To correct for multiple comparison, a Duncan's multiple range test will be performed. Furthermore, we will perform a receiver operating characteristic (ROC) curve analysis to compare the outcome of the screening instruments (MMS and BMQ) with the pharmacy refill dates. In the ROC curve plot, specificity of the questionnaire is on the x-axis and sensitivity of the question is on the y-axis.

Plausible relations between parameters of cardiovascular risk factors, motivation to change, socioeconomic class, and parameters of adherence (calculated refill score and BMQ and MMS scores) will be tested in a univariate manner. Individual parameters will be tested for normality using the Kolomogorov-Smirnov test in order to select adequate univariate tests. Multiple logistic regression analysis will be performed to assess the relative importance of selected parameters for the likelihood of low adherence, as defined by the refill data algorithm. In all analyses, potential confounders will be included if they independently changed the beta coefficient for dedicated calculation of refill data by at least 5% or when consensus about inclusion existed within the team of researchers supported by clinical evidence from literature.

Missing data is unfortunately very common in eHealth research. We follow the recommendation for eHealth research to use the multiple imputation technique in SPSS when analyzing our dataset with missing observations [36].

Ethics and Dissemination

The study protocol has been approved by the local ethical committee before inclusion of patients into the study. The study has been registered (trial registration ID number NCT01449695, approved May 2011). Subjects may leave the study protocol at any time for any reason without any consequences for regular cardiovascular care. The investigator or patient specialists may also decide to withdraw a subject from the study for urgent medical reasons.

Discussion

Nonadherence to medication prescriptions in cardiovascular patients reduces the positive effects of medical treatment in chronic care. However, improvement of medication adherence in these patients is a serious challenge. Patient beliefs, perceptions, and management of medication, their illness (intentional nonadherence), and skills to integrate medication taking in their daily life (unintentional nonadherence) need to be addressed to make an intervention successful.

There is no one - size - fits - all solution for nonadherence [9,34] nor does previous research provide evidence to choose a single intervention [37]. By reviewing the literature it becomes evident that determinants for nonadherent behavior are complex, and underlying theory for a successful intervention is frequently lacking [34,38,39]. In a review of 193 health behavior change articles, only 36% of the authors mentioned a theory and only 22% of them applied the theory [40].

We based our method on HBM, adopted the approach of Horne [41], and defined the main determinants of nonadherent behavior in intentional and nonintentional determinants. Because we address both types of determinants, we expected to develop an intervention that will be more successful than most existing interventions, which only take into account one of these sets of determinants.

Specifically, by choosing a group consultation, information is provided in an efficient manner and the patient is given an opportunity to discuss the need for adherence (intentional nonadherence) as well as getting practical information (unintentional adherence) with peers. Further tailoring the intervention in individual contacts provides the opportunity for the nurse to identify the need to change objectives of unintentional or intentional nonadherence (or a mix of both). These individual consultations are patient - centered, with emphasis on patient perspectives and shared decision making [42]. The individual website and visualization of personal cardiovascular risk furthermore addresses one of the difficulties in cardiovascular adherence: awareness of the influence of taking medication on personal cardiovascular risk [40]. Lastly, the combination of Web-based intervention with face-to-face contact is expected to give better results than either alone [43]. Based on this integration of factors, we hope that the resulting data of this trial will contribute important knowledge about adherence in this population.

Conflicts of Interest

None declared.

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Abbreviations

BMQ: Beliefs about Medication Questionnaire
CVD: cardiovascular disease
HBM: health belief model
iVAZ: Interactive Dossier Vaatzorg
MMS: Modified Morisky Scale
SD: standard deviation

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Protocol

Effects of Charitable Versus Monetary Incentives on the Acceptance of and Adherence to a Pedometer-Based Health Intervention: Study Protocol and Baseline Characteristics of a Cluster-Randomized Controlled Trial

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Abstract

Background: Research has so far benefited from the use of pedometers in physical activity interventions. However, when public health institutions (eg, insurance companies) implement pedometer-based interventions in practice, people may refrain from participating due to privacy concerns. This might greatly limit the applicability of such interventions. Financial incentives have been successfully used to influence both health behavior and privacy concerns, and may thus have a beneficial effect on the acceptance of pedometer-based interventions.

Objective: This paper presents the design and baseline characteristics of a cluster-randomized controlled trial that seeks to examine the effect of financial incentives on the acceptance of and adherence to a pedometer-based physical activity intervention offered by a health insurance company.

Methods: More than 18,000 customers of a large Swiss health insurance company were allocated to a financial incentive, a charitable incentive, or a control group and invited to participate in a health prevention program. Participants used a pedometer to track their daily physical activity over the course of 6 months. A Web-based questionnaire was administered at the beginning and at the end of the intervention and additional data was provided by the insurance company. The primary outcome of the study will be the participation rate, secondary outcomes will be adherence to the prevention program, physical activity, and health status of the participants among others.

Results: Baseline characteristics indicate that residence of participants, baseline physical activity, and subjective health should be used as covariates in the statistical analysis of the secondary outcomes of the study.

Conclusions: This is the first study in western cultures testing the effectiveness of financial incentives with regard to a pedometer-based health intervention offered by a large health insurer to their customers. Given that the incentives prove to be effective, this study provides the basis for powerful health prevention programs of public health institutions that are easy to implement and can reach large numbers of people in need.

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KEYWORDS

physical activity; self-tracking; adherence; acceptance; pedometer; incentives; digital health intervention; cluster-randomized controlled trial

Introduction

In 2012, noncommunicable diseases (NCD) such as cardiovascular diseases, cancers, respiratory diseases, and diabetes were responsible for 68% of deaths worldwide [1]. Physical activity is known to reduce the risk of various NCDs, including cardiovascular disease, obesity, cancer, diabetes [2,3], as well as of mental illness such as depression [4]. However, it seems increasingly difficult to establish a daily activity routine considering the modern sedentary lifestyle and additional personal (eg, motivation), social (eg, lack of social support), and environmental (eg, time or weather) barriers [5,6]. Indeed, when people's daily activity is assessed empirically the majority of participants fail to reach activity goals associated with a health promoting lifestyle [7].

The emerging trend of self-tracking [8] and the public interest in self-tracking tools [9-11], offer great potential for providers of disease prevention programs to overcome the barriers to adopting active lifestyles. The health-related benefits of self-tracking tools can be explained by their support of self-regulating processes. For example, a pedometer provides real-time information regarding the number of steps walked per day. By doing so, the pedometer enables its user to monitor and evaluate his or her daily activity, and thus directly supports the user's self-regulating subfunctions [12]. According to the latter, self-regulation mediates external influences and provides the basis for purposeful action and self-directed change [12]. For example, if one is informed about insufficient physical activity by a pedometer, he or she may decide to go for a walk despite bad weather or to plan the rest of the day in order to reach self-set or given physical activity goals. Consequently, a pedometer may help its user to overcome the abovementioned barriers. A systematic review [13] and a meta-analysis [14] demonstrated the benefits of using pedometers to promote physical activity. Likewise, a metaregression of physical activity interventions found strategies supporting self-regulation to be more effective than other behavioral change strategies [15].

With health care costs being on the rise in Switzerland and other countries [16], health insurance companies are increasingly interested in the potential of pedometer-based physical activity interventions. However, privacy concerns may arise in a health insurance context as pedometers commonly measure very sensitive personal and health-related data besides step counts, such as heart rates, calories, location, and sleep. Privacy concerns seem to almost naturally accompany digitalization in various fields, because the benefits of digitalization often rely on the detection of patterns and correlations in different sources of personal information [17]. Research has addressed privacy concerns in different contexts for example in mobile apps [18,19], location-based services (eg, Google Maps) [20,21], driving behavior [22] or e-commerce transactions [23]. Lack of willingness to disclose personal data has also been identified as one of the main barriers for the digitalization of health care [24]. Privacy concerns have been shown to predict attitudes and behavioral intentions toward health information technology and electronic health care services [25-27]. In a recent study of 333 users of health care wearable devices [27], perceived privacy risks significantly predicted the adoption intention of wearable technology. On the other hand, a large public poll (N=995) illustrates that although 81% of health insurance customers indicated privacy concerns, a substantial proportion (32%) would still be willing to share personal health-related data with their insurance company [11]. These numbers may reflect a phenomenon researchers have titled the privacy paradox [28], namely that people do provide personal data despite expressing concerns regarding their privacy. Research has provided evidence for the privacy paradox for different kinds of information as well as different contexts, such as e-commerce [29] and Web-based shopping [30], finance services [28], and social networks [31]. Norberg and colleagues [28] demonstrated, for example, that in different market-research scenarios involving banks and pharmaceutical companies, participants disclosed significantly more pieces of personal information than they initially intended to disclose. Summarizing the outlined reasoning, it is unclear whether people are willing to participate in a pedometer-based physical activity intervention offered by a health insurance company. A pedometer-based intervention may give rise to privacy concerns, however research indicates that people sometimes do disclose personal information despite being concerned about privacy.

Two different streams of research suggest favorable effects of incentives (eg, financial rewards) when addressing the problem outlined above. First, financial incentives have proven to be beneficial in the context of health behavior interventions. Financial incentive schemes have been effectively used to tackle obesity [32], for smoking cessation [33-35], to increase physical activity [35-37], to promote vaccination [34], and to change many more health-related behaviors [38]. Within physical activity interventions, financial incentives have been shown to increase both performance of participants [36] as well as adherence to exercise sessions [39]. Effects of financial incentives on physical activity have also been assessed for pedometer-based interventions [40-43]. Of those studies, all but one [43] revealed positive effects of financial incentives either on step goal achievement [40,41] or weight loss [42]. However, the effect of financial incentives on performance may only reflect a short-term effect [39] or dissipate as soon as the incentive is withdrawn [44].

Recent research [45] has also considered the effect of charitable incentives as a variation of mere monetary incentives in a pedometer-based physical activity intervention. In contrast to mere monetary incentives, charitable incentives offer the opportunity to donate a specific amount of the received money to a charitable organization. Charitable incentives may thus lead to a sense of moral satisfaction [46] and have so far been typically applied in a marketing context to motivate purchase behavior [47]. However, they have yet to be evaluated in the domain of health behavior and physical activity. In order to

contribute to research in this area, we decided to consider financial and charitable incentives in the present study.

Second, rooting in the view of privacy as a commodity [48], most approaches explaining privacy disclosure behavior involve the concept of a privacy calculus (ie, weighting the costs and benefits of sharing personal information [23,24,49]). Specifically, sharing personal health data can be perceived as unfair, if no compensating benefit is provided [49]. Consequently, researchers have tried to augment the benefits of information disclosure by providing financial incentives among others in exchange for personal information [20,48,50-52]. For example, participants in a quasiexperimental setup were more willing to disclose personal information on a website for stock trading when they were offered financial gains [50]. Additionally, two-thirds of participants of a large public survey (N=1100) stated that they expect financial compensation in exchange for providing personal health-related data [53]. Thus, financial incentives can be used to increase the perceived benefits of sharing health-related information.

In conclusion, we assume the benefits of financial incentives to be 2-fold within a physical activity intervention offered by a health insurance company: first, a financial incentive may act as a benefit in the privacy calculus of potential intervention participants, compensating for possible privacy concerns. This effect should be reflected in higher participation rates for experimental groups (EG) in which a financial incentive is provided. Second, in line with previous research, financial incentives may have motivational effects and affect the treatment adherence of participants. Therefore, this study protocol describes the design and methodology in order to examine the effects of the two different incentives on the acceptance of and adherence to a pedometer-based health intervention (PHI). Demographics and baseline characteristics of study participants are presented in the results section. Subsequently, strengths and limitations of the study design are discussed.

Methods

Experimental Groups

Over the course of the PHI, participants had to achieve a fixed level of physical activity each month that was tracked using a commercial pedometer device or app that automatically counts the number of steps when walking. In order for the PHI to be effective, 150 minutes of moderate physical activity are recommended [54-56], which on average translates to a goal of 10,000 steps per day [7,57,58]. Upon achieving that goal, participants received a monthly incentive depending on the EG they were assigned to. Textbox 1 shows descriptions of the groups.

Textbox 1. Experimental group descriptions.

Financial incentive (EG1)

• In this condition, participants were entitled to a $10 reward each month they reached an average of 10,000 steps per day or more. Participants achieving more than 7500 steps per day were granted $5 in order to prevent frustration [7]. The minimum recommendation for daily physical activity is approximately 7500 steps per day [57,58].

Charitable incentive (EG2)

• Here, participants received the same rewards as in the financial incentive condition. However, participants had to decide whether a certain proportion of the money should be donated to a charitable organization chosen from a predefined list (proportions varied from 0% to 100% in steps of 5% with 50% being the default).

Control group (CG/EG1)

• Participants of the control group received no incentives over the first 3 months of the PHI. Due to the practical setting of our study, ethical consent and fair treatment of all participants is of highest relevance. Participants in the control group were therefore entitled to a $20 reward each month they averaged over 10,000 steps per day and a $10 reward each month they averaged over 7500 steps per day over the fourth to sixth month of the intervention. To avoid anticipatory effects on the participation rate, participants in the control group were not informed of the opportunity to receive financial rewards during the second half of the PHI.

Thus, all participants had the chance to earn a maximum of $60 that is paid at the end of the PHI.

Participant Acquisition and Sample

Customers of a large Swiss health insurance company that met the following requirements were eligible for participation: they had to be at least 18 years old, be registered in a complementary insurance program, accept the participation conditions and privacy terms, and declared to be free of any medical condition that prohibits physical activity. Absence of medical conditions was required in order to avoid potential negative effects on subject's health due to increased daily activity. In case of uncertainty regarding the health-related eligibility for participation the consultation of a physician was required. Privacy terms essentially stated that only the number of steps will be forwarded to the insurance company for bonus calculation and that data will be analyzed by researchers of the University St. Gallen and ETH Zurich for scientific purposes.

To avoid spill-over effects between the different incentive strategies [45], potential participants were assigned to the different groups based on their canton of residence and invitations were send out after the assignment was complete. As at the beginning of the program, the control group (CG) appeared to be the least attractive condition we wanted to contact a different number of potential participants for the 3 groups according to a proportion of 2 (EG1):2 (EG2):1 (CG/EG1). In order to do so and to further account for differences in activity preferences between urban and rural areas in Switzerland [59], cantons were grouped in blocks of 5 according to number of customers and population density. Each block contained 2 pairs

of cantons that were matched for geographical proximity. The matched pairs were then randomly assigned to one of the EGs and the remaining canton was assigned to the control group. To facilitate clustering, cantons with very few customers were combined and treated as one unit. We used the approach of Gao and colleagues [60] for nonaggregate cluster-randomized controlled trials with binary outcomes to estimate the number of participants to be contacted in order to detect an expected difference in participation rate. Being conservative in comparison to public polls [53] and studies [11], we expected a difference of 5% in participation rates (8% participation was expected for both intervention groups vs 3% for the control group). As participants in our study were clustered, a potential design effect had to be considered [60]. An assumed intracluster-correlation of .01 (according to [61]) and the average cluster size of mean (M) = 925 (standard deviation [SD] = 1356) yielded a design effect of 10.24. Thus, in order for the difference in participation rates to be significant at least 15,725 customers needed to be contacted (6475 for each experimental group and 2775 for the control group). We met this requirement by directly contacting 18,638 customers via email before the beginning of the PHI.

Procedure

After providing consent, all participants were instructed on how to use the pedometer or the app, respectively, and how to share the number of tracked steps via the Web-based platform of the health insurance company. The Web-based platform supported devices of the brands Garmin, Jawbone, and Fitbit, all commonly known manufacturers of wearables and fitness technology. Alternatively, participants could use the Fitbit app that is available for selected mobile phones. A systematic review has confirmed the validity of commercial pedometers [62], and recent studies provide evidence for the accuracy of smartphone apps for tracking physical activity data [63]. Owning an eligible tracking device (pedometer or smartphone app) was thus required for participation. Participants not owning an eligible pedometer were entitled to a 20% discount on a compatible device. All participants could use the Web-based platform any time to gain insight into their physical activity data as well as their degree of achievement with regard to their goal of 10,000 steps per day. In the charitable condition, participants could also log in to choose a particular charitable organization from a predefined list and set the proportion of money they want to donate. Participants were asked to set this proportion once at the beginning and once before the end of the PHI.

During the course of the intervention, participants received short informational texts in order to maintain motivation for daily physical activity (eg, “If you are going by bus consider getting off two stops prior to your destination to reach your goal of 10,000 steps per day”). Those texts were based on information material and recommendations for health effective daily activity provided by the Federal Bureau of Sports as well as on recommendations for increasing step count in everyday life [7] and on the Compendium of Physical Activities 3 [64]. Additionally, participants received a status mail on a monthly basis that informs them once again about their target achievement and the respective amount of money saved or donated during the past month. This mail also contained further season-based tips on how to increase the daily step count (eg, recommending free geocaching apps or websites for summer days or popular snowshoeing trails during winter). The content of the monthly status mails was developed in cooperation with the insurance company.

At any time, participants were able to opt out of the PHI and request the deletion of all submitted data without giving reasons. In order to prevent high dropout rates that have been observed in past pedometer-based interventions [13], no bonus will be granted for past achievements if the participant decides to opt out of the PHI.

Data Collection and Variables

Data for analysis is partly collected by submission of information by the participants via the Web-based platform of the insurance company and partly by administering a Web-based questionnaire at 2 different points in time (T_1 and T_2) over the course of the intervention. After participants registered their pedometer or smartphone at the Web-based platform of the insurance company, the number of steps were synchronized automatically with the Web-based platform each day at midnight. However, participants could choose to deactivate automatic synchronization and enter their step count manually on the Web-based platform. Days where no step data is available (eg, because the pedometer was not worn or not charged) will be treated as missing data. The first measurement (T_1) is set at the beginning of the PHI for all groups, whereas the second measurement (T_2) is set at the end of the intervention for the experimental groups and after the first half of the intervention for the control group before they received financial incentives. Additional data, such as age, gender, or participants’ health service billings, were provided by the insurance company. To guarantee appropriate response rates, participants received additional $5 for each time they completed the questionnaire resulting in an additional bonus of $10. See Figure 1 for an overview of the study design.

The following variables were measured for analysis: the participation rate represents the primary outcome and is measured by calculating the participation rate in total and for the different groups, respectively. Participation rate is defined as the proportion of active participants that is participants that shared their data with the Web-based platform of the insurance company at least once. Secondary outcomes are continued use of the pedometer, performance of the participants, and health condition. The number of days at which participants share their step count with their health insurance company is used as an indicator of the continued use of the pedometer. The number of steps and the amount of money saved or donated indicate the performance of the participants. Apart from the number of steps, physical activity was also assessed by questionnaire measures namely hours of moderate to vigorous physical activity and hours of walking per week at T_1 and T_2 (based on the International Physical Activity Questionnaire [65,66]), walking on the way to work, physical activity at work, and during spare time at T_1 and T_2. The proportion of money saved versus donated (at T_1 and T_2) is further used to evaluate the charitable incentive condition. We use health perception at T_1 and T_2

("How would you rate your overall health status?") [67-69] and improvement of health perception due to the intervention at T_2 (eg, "In general, my health improved due to the prevention program") [67-69] as subjective measures and service billing with the health insurance company (ie, amount of money repaid by the insurance company per participant) after completion of the prevention program and 1 year later as objective measures in order to assess effects on participants' health condition. Unless otherwise indicated, a 7-point Likert scale, from strongly disagree (1) to strongly agree (7), will be used for items requiring a response scale.

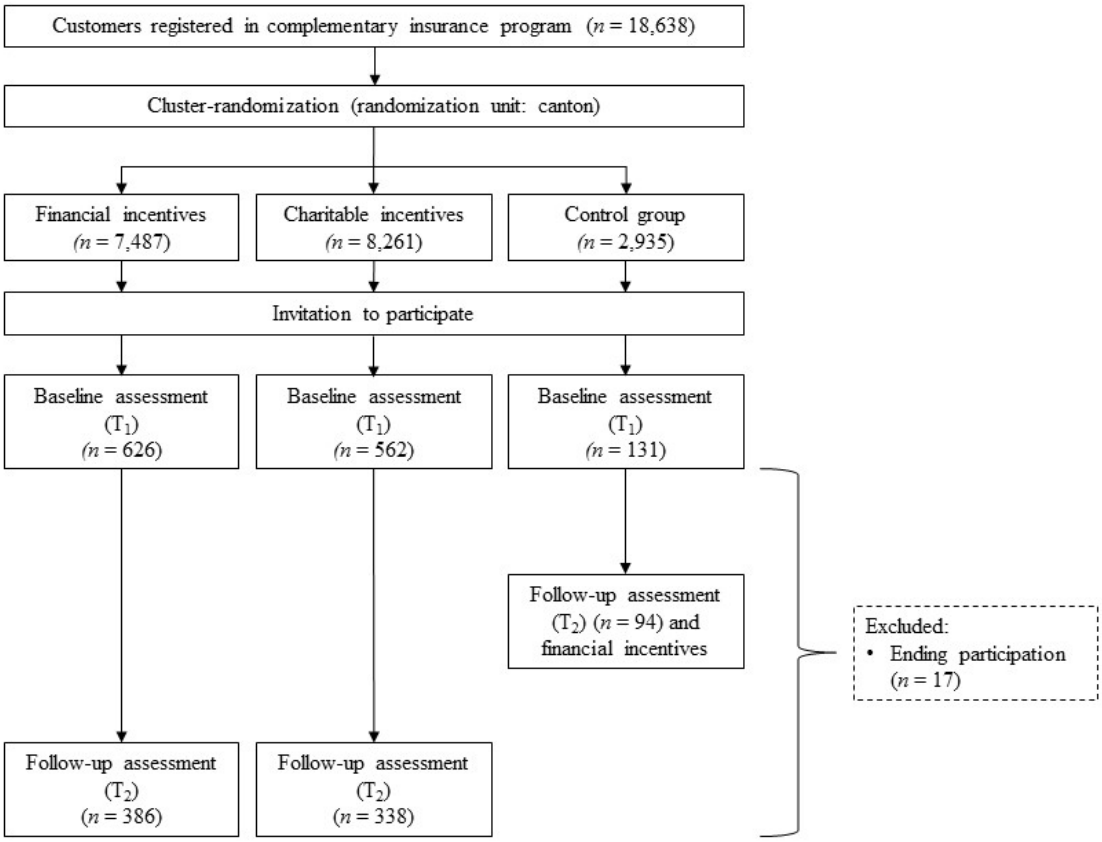
To exclude possible confounding influences, we will measure the following control variables: sociodemographic variables (age, gender, education, income, and nationality [67,70,71]) measured at T_1, technology readiness [72] measured at T_1, possession of pedometers and other self-tracking tools at T_1, pedometer brand measured at T_1, number of persons living in the participants' household at T_2, living environment at T_1 (city center, outer city, village, countryside), amount of billing services preceding the prevention program at T_1, exchange with other participants of the prevention program at T_2, participation of a family member or friend at T_1, and observation of media coverage of the prevention program and possible impact on participants' physical activity at T_2.

Additional variables were measured to better understand the participants behaviour. These variables are participants' perception of the Web-based platform, perception of the insurance company (eg, perceived social responsibility), customer loyalty, participants' willingness to share data with their insurance company, willingness to donate (in the charitable incentive group), reasons for participating and not participating, reasons for opting out, and improvement suggestions to the program.

Data Analysis

Due to the nested structure of the data, mixed-effect models will be used for data analysis. As measurements are nested within participants, the step count measurements represent the level 1 unit of analysis, whereas the participants represent the level 2 unit of analysis. A recent article [73] discusses the problem of faking with regard to financial incentives, (eg, faking step counts in order to qualify for financial rewards). This problem applies to our study as step counts could be entered manually. Step count measurements that are unusually high and were manually entered are likely to represent a tendency of faking. Thus, univariate and multivariate outlier analysis [74] will be conducted in order to identify participants that are prone to faking. Changes on outcomes solely measured at T_1 and T_2 will be analyzed performing a repeated-measures analysis of variance (rmANOVA). The analyses will be conducted using the nlme-package [75] in R [76] and the typical significance level of $\alpha = 5\%$ will be applied.

Figure 1. Study design.



Results

Survey Participation

In total, 1319 persons participated in the survey at T_1. Of those, 47.46% (626/1319) belonged to the financial incentives group, 42.61% (562/1319) to the charitable incentives group, and 9.93% (131/1319) to the control group.

Baseline Characteristics

Table 1 presents the baseline characteristics of all T_1 survey participants for each of the different EGs. Unfortunately, participants' service billings with the health insurance company were not yet available at the time of writing. Between-group comparisons are based on one-way ANOVA for continuous variables and on chi-square tests for categorical variables. Due to the large number of participants, even small between-group differences are likely to become statistically significant. Hence, effect sizes are reported for between-group comparisons.

Participants were mostly Swiss (1195/1319, 90.60%), living in a village or on the countryside (836/1319, 63.38%), holding a university degree (597/1319, 45.26%), and were 43-years old on average (M=42.95, SD = 13.11). Slightly more men than women participated in the T_1 survey (638/1319, 48.14% vs 585/1319, 44.35%). A Fitbit pedometer or the Fitbit app was most often used for tracking physical activity (1116/1319, 84.61%) and more than half of the participants (709/1319, 53.75%) bought a pedometer in order to participate in the PHI.

While baseline characteristics show no meaningful group differences regarding age, gender, education, income, nationality, self-reported physical activity at work and during spare time, walking on the way to work, pedometer brand, prior possession of a pedometer, and participation of a family member or friend, group differences could be observed regarding residence of participants, self-reported physical activity and walking, and subjective health status. Differences regarding residence of participants indicate that matching groups according to population density may not be sufficient to account for residence differences.

Because these baseline characteristics are related to physical activity they are primarily relevant for the analysis of the secondary outcomes of the study. Consequently, residence of participants and subjective health status will be used as covariates in the statistical analyses of the secondary outcomes. Because mixed-effects models will be used for data analysis, group differences regarding baseline physical activity will be directly modelled by allowing different intercepts for the experimental groups.

Table 1. Demographics and baseline characteristics.

Charachteristic[a]	Total (*N*=1319)	Financial incentives/ EG1 (*n*=626)	Charitable incentives/ EG2 (*n*=562)	Control group/ CG (*n*=131)	*P*	Effect size[b]
Group characteristics						
Number of cantons	26	8	11	7		
Number of customers contacted	18,638	7487	8216	2935		
Population density[c] (residents/km^2, median)	233.56	255.15	173.45	221.08		
Demographic variables						
Age	42.95 (13.11)	43.06 (13.25)	42.50 (12.88)	44.37 (13.40)	.36	.002
Gender (%)					.89	.01
Female	585 (44.35)	285 (45.53)	244 (43.42)	56 (42.75)		
Male	635 (48.14)	301 (48.08)	270 (48.04)	64 (48.85)		
Not declared	99 (7.51)	40 (6.39)	48 (8.54)	11 (8.40)		
Education[d] (%)					.17	.10
University	597 (45.26)	301 (48.08)	244 (43.42)	51 (39.69)		
Professional School	421 (31.92)	194 (30.99)	188 (33.45)	39 (29.77)		
High School	219 (16.60)	95 (15.18)	95 (16.90)	29 (22.14)		
Secondary School	25 (1.90)	13 (2.08)	10 (1.78)	2 (1.53)		
Primary School	6 (0.45)	4 (0.64)	1 (0.18)	1 (0.76)		
Not declared	51 (3.87)	19 (3.04)	24 (4.27)	8 (6.11)		
Place of Residence (%)					< .001	.27
Town	156 (11.83)	92 (14.70)	49 (8.72)	15 (11.45)		
Outskirts of town	327 (24.79)	185 (29.55)	116 (20.64)	26 (19.85)		
Village	644 (48.82)	270 (43.13)	303 (53.91)	71 (54.20)		
Countryside	192 (14.56)	79 (12.62)	94 (16.73)	19 (14.50)		
Income in CHF (%)					.25	.11
< 2500	68 (5.16)	29 (4.63)	35 (6.23)	4 (3.05)		
2501–5000	203 (15.39)	90 (14.38)	91 (16.19)	22 (16.79)		
5001–7500	418 (31.69)	204 (32.59)	176 (31.32)	38 (29.01)		
7501–10,000	220 (16.68)	107 (17.09)	87 (15.48)	26 (19.85)		
>10,000	137 (10.39)	78 (12.46)	50 (8.90)	9 (6.87)		
Not declared	273 (20.70)	118 (18.85)	123 (21.89)	32 (24.43)		
Nationality (%)					.03	.13
Swiss	1195 (90.60)	554 (88.50)	520 (92.53)	121 (92.37)		
German	56 (4.25)	36 (5.75)	17 (3.02)	3 (2.29)		
Other	54 (4.09)	32 (5.11)	16 (2.85)	6 (4.58)		
Not declared	14 (1.06)	4 (0.64)	9 (1.60)	1 (0.76)		
Physical activity measures						
Self-reported moderate to vigorous physical activity[e] (hours/week)					< .001	.03
Mean (SD)	8.90 (11.10)	8.96 (11.38)	8.75 (10.59)	9.26 (11.25)		
Median	6.00	6.00	6.00	5.25		
Self-reported walking[e] (hours/week)					<.001	.03

Charachteristic[a]	Total (*N*=1319)	Financial incentives/ EG1 (*n*=626)	Charitable incentives/ EG2 (*n*=562)	Control group/ CG (*n*=131)	*P*	Effect size[b]
Mean (SD)	10.01 (13.70)	10.31 (13.44)	9.99 (15.55)	8.61 (10.87)		
Median	6.00	6.54	6.00	4.50		
Physical activity at work	3.45 (1.88)	3.37 (1.84)	3.48 (1.91)	3.67 (1.90)	< .001	.009
Physical activity during spare time	5.26 (1.17)	5.36 (1.19)	5.19 (1.13)	5.09 (1.22)	.06	.003
Walking on way to work (%)						
Yes	234 (17.74)	126 (20.13)	87 (15.48)	21 (16.03)	.10	.06
No	1085 (82.26)	500 (79.87)	475 (84.52)	110 (84.97)		
Other						
Subjective health status	3.60 (0.73)	3.66 (0.73)	3.55 (0.71)	3.53 (0.80)	<.001	.02
Pedometer brand (%)					.73	.09
Fitbit	832 (62.08)	387 (61.82)	359 (63.88)	86 (65.65)		
Fitbit App	284 (21.53)	141 (22.52)	121 (21.53)	22 (16.79)		
Garmin	138 (10.46)	69 (11.02)	55 (9.79)	14 (10.69)		
Jawbone	65 (4.93)	29 (4.63)	27 (4.80)	9 (6.87)		
Pedometer bought for participation (%)					.04	.07
Yes	709 (53.75)	316 (50.48)	325 (57.83)	68 (51.91)		
No	571 (43.29)	289 (46.17)	221 (39.32)	61 (46.56)		
Not declared	39 (2.96)	21 (3.35)	16 (2.85)	2 (1.53)		
Participation of family member or friend					.65	.03
Yes	251 (19.03)	122 (19.49)	108 (19.22)	21 (16.03)		
No	1068 (80.97)	504 (80.51)	454 (80.78)	110 (83.97)		

[a] Unless otherwise indicated, mean (SD) are displayed for continuous variables and absolute frequencies (relative frequencies) are displayed for categorical variables.

[b] η^2 is used as a measurement of effect size for one-way ANOVAs and Cramer's *V* is used as a measurement of effect size for chi-square test. Effect size conventions for η^2 are: .01 (small effect), .09 (medium effect), .25 (large effect). Effect size conventions for Cramver's *V* are: .10 (small effect), .30 (medium effect), .50 (large effect) for *df*=1 and .07 (small effect), .21 (medium effect), .35 (large effect) for *df*=2 [77].

[c] Based on information of the Swiss Federal Office for Statistics for the year 2013 [78].

[d] Categories with expected frequencies <5 were not considered for between-group comparison.

[e] Due to violation of normality a logarithmic transformation was applied for between-group comparison and the median is reported in addition to the mean.

Discussion

Strengths and Limitations

This study protocol describes the design and baseline characteristics of a longitudinal cluster-randomized controlled trial testing the effects of monetary and charitable incentives on the acceptance of and adherence to a pedometer-based health prevention program. To the best of our knowledge, this is the first study to systematically test the effects of different incentive strategies within a pedometer-based health intervention offered by a large health insurance company in western cultures. External validity has to be pointed out as a key strength of the described trial. Both study design and incentive strategies are tested in a real-world setting, thus ensuring the applicability of the results and conclusions.

When interpreting the results of this study, some limitations have to be considered: selection effects might affect the participation in the PHI. For example, by especially attracting highly motivated or physically active participants, those effects could potentially undermine the power of our analyses. However, we will be able to control our analyses for prior level of physical activity. Further, comparisons of T_2 measures between the groups have to be interpreted with caution, because T_2 reflects different time points for experimental and control groups. T_2 was set at 6 months after start of the intervention for the EGs and at 3 months for the CG. However, the main focus of this study is on the acceptance of the promotion program, which is operationalized using the participation rate, and is thus not dependent on any T_2 measurement. Lastly, the goal of reaching 10,000 steps per day on average might have detrimental motivational effects for some participants. It might be perceived as too challenging for very inactive participants or when

participants were not able to achieve sufficiently high step counts for several days in a month.

Conclusions

Considering the importance of physical activity for the course of various NCDs, this study yields important insights for insurance companies, public health institutions, and health practitioners alike. If the effectiveness of the examined incentive strategies is demonstrated, this study provides the basis for simple yet powerful health interventions that can easily be implemented by various health care institutions.

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The study protocol was approved by the Ethics Committee of the University of St. Gallen, Switzerland (reference number: HSG-EC-2015-04-22-A; date of approval June, 4th, 2015). Informed consent to participate was obtained from all participants of the study.

Conflicts of Interest

All authors have read and understood the editorial policies on competing interests. We declare the following possible competing interest: the study is partly funded by the CSS Insurance.

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Abbreviations

CG: control group
EG: experimental group
M: mean
NCD: noncommunicable disease
PHI: pedometer-based health intervention
rmANOVA: repeated-measures analysis of variance
SD: standard deviation

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Protocol

The Deckled Incision: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Scar visibility is multifactorial and skin closure technique is thought to play an important role. It is an established principle in plastic surgery that Z plasties generally reduce scar contracture by breaking up the lines of tension in a wound. As an extension of this principle, it is postulated that irregular “deckled” skin incisions made during tumor excision would produce aesthetically superior scars.

Objective: The primary objective of this study is to assess both the clinician and patient opinion of scar quality using the Patient and Observer Scar Assessment Scale (POSAS). Secondary objectives include the proportion of scars judged as good by the both the patient and clinician (less than or equal to 5 on the overall PSOAS scale), the number of adverse events, and the proportion of the scar visible at 1 meter.

Methods: The deckling study will be a patient-blinded, simple randomized controlled trial (RCT) at a single center institution. The two groups will be equally allocated on a 1:1 ratio into the control and treatment arms. All patients greater than 18 years of age undergoing a plastic surgery procedure involving excision of skin lesions will be enrolled. Any patients requiring re-excision through the wound or undergoing injectable corticosteroid therapy will be excluded. A total of 500 patients will be enrolled. The patients will be followed-up at 1 week, 3 months, and 6 months post-operatively.

Results: The study is expected to begin enrolment in August 2016. We anticipate that the deckling study group will have superior scar outcomes when compared to the straight line incision. From clinical experience this is especially true for lesions involving the face and in those areas of the skin that have undergone radiation therapy. The study will be funded by the Plastics and Reconstructive Surgery Department at St Vincent’s Hospital, Sydney, Australia. Ethics approval has been obtained for the study. Conclusion: We believe this will be an important study to assess a novel method to improve the appearance of post-operative scars. The deckling study is simple to master, can be applicable to almost any surgical procedure, and can have good generalizability to a large population cohort.

Conclusions: We believe this will be an important study to assess a novel method to improve the appearance of post-operative scars. The deckling study is simple to master, can be applicable to almost any surgical procedure, and can have good generalizability to a large population cohort.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12616000193471; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12616000193471 (Archived by Webcite at http://www.webcitation.org/6gmG8yf1A)

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KEYWORDS

scar improvement; post-operative

Introduction

Disease Background

Scar visibility is multifactorial and skin closure technique is considered to play an important role. It is an established principle in plastic surgery that Z plasties generally reduce scar contracture by breaking up the lines of tension in a wound. As an extension of this principle, it is postulated that irregular "deckled" skin incisions made during tumor excision would produce aesthetically superior scars. A previous unpublished pilot study at St Vincent's Hospital was conducted to look at deckled incisions versus straight incisions on head and neck lesions in 47 patients. It showed a statistically significant (P <.001) smaller detectable scar length ratio with the deckled incision compared to straight line incisions [1]. There are a limited number of studies that describe the use of the deckled incision in literature and they report improved scar formation and reduced contracture rates [2-4].

Study Rationale

The aim of the study is to assess and quote whether using the deckled incision improves post-operative scars compared to the standard straight line incision. We hypothesize that the deckled incision has superior scar outcomes. Previous studies have been underpowered and had a number of biases as they were not conducted in a randomized fashion. The deckling study will be a patient-blinded, simple randomized controlled trial (RCT) at a single center institution. The two groups will be equally allocated on a 1:1 ratio into the control and treatment arms.

Methods

Objectives

The primary objectives of the study are (1) to assess clinician opinion of scar quality using the observer component of the Patient and Observer Scar Assessment Scale (POSAS); and (2) to assess the patient's opinion of scar quality and/or sensation using the patient component of POSAS.

The secondary objectives are (1) to assess the proportion of scars described as good by the clinician (determined by ≤5 on the overall component of the POSAS); (2) determine the number of adverse events overall and by individual components (namely dehiscence infection, keloids); and (3) calculate the percentage of the scar visible as a percentage of the total length at 1 month.

Design

The deckling study will be a patient-blinded, simple RCT at a single center institution. The two groups will be equally allocated on a 1:1 ratio into the control and treatment arms. There will be two groups: those that receive the deckled incision and those that receive the standard straight line incision.

Participants

The study will be solely undertaken at St Vincent's Public Hospital. The care providers involved with the study will include plastics and reconstructive surgery consultants and registrars. A total of 500 patients will be recruited and divided evenly into the two treatment groups.

Duration

The study will be conducted over a period of 24 months with ongoing recruitment or until the total sample size required is reached.

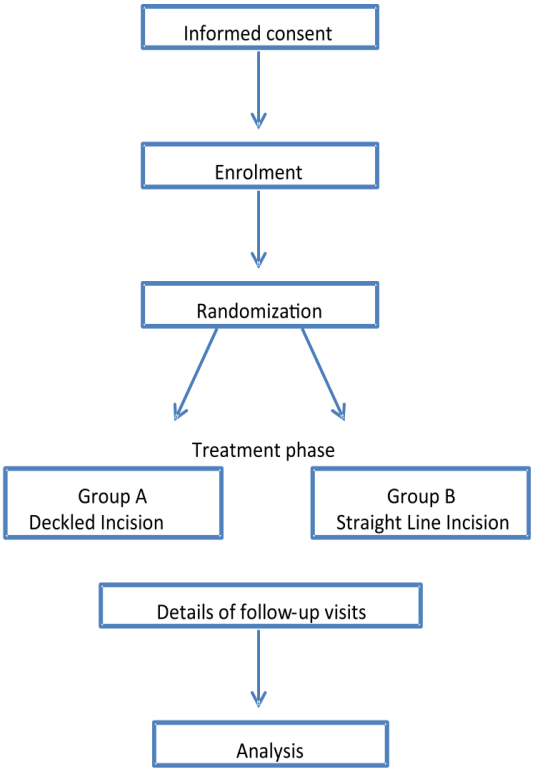
Inclusion and Exclusion Criteria

Inclusion criteria for the study include (1) greater than or equal to 18 years of age; (2) able to give informed consent and willingness to participate in follow-up; and (3) undergoing any plastic surgery procedure involving excision of skin lesions. Exclusion criteria include those requiring re-excision through the original wound and undergoing injectable corticosteroid therapy into the scar.

The patients will be randomly allocated to receive either the deckled incision or the straight line incision for their surgery. In patients with multiple (two or more) separate lesions requiring separate incisions, each lesion will be randomly allocated to receive either the deckled or straight line incision. Only the treating surgeon will be aware of which incision was used and the patient will be blinded to the type of incision. The surgeon will document in the operation note the number and site of lesions, whether they were deckled or not, the precise length of the scar, and whether the procedure was carried out by a registrar or consultant.

The patient will be followed-up in the outpatient clinic. Standard post-operative care with micropore tape will be given to both groups with respect to scar minimization. The scar and compliance with standard post-operative scar reduction will be assessed at 1 week, 3 months, and 6 months post-operatively using the POSAS [5]. The 6-month cut off was chosen as scars have usually matured by 6 months to reflect their final life-long appearance and to avoid a large number of patient attrition over a longer follow-up period (Figure 1).

Figure 1. Study flow chart.



Investigation Plan

The intervention plan is shown in Table 1.

Table 1. Intervention plan.

List interventions	Enrolment visit	1 Week	3 Months	6 Months
Informed consent	✓			
Inclusion/exclusion criteria	✓			
Medical history	✓			
Patient and observer scar assessment scale (POSAS)		✓	✓	✓
Adverse event and serious adverse event assessment		✓	✓	✓

The follow-up will be done in the outpatient setting. The POSAS requires at least three independent assessors to achieve a valid result and this will be done by a combination of medical and nursing staff. The results will be recorded in real-time on a tablet (iPAD), which has been pre-populated with the patient demographics and the unique study code identifier that can be cross referenced with the medical records. The data is automatically backed up to an online database via Dropbox. Selected photographs will be taken by a digital camera for future publication purposes.

The routine standard of follow-up will vary with each individual procedure and thus the above protocol is not the standard of care. The additional costs of the procedure will be covered by the Plastics and Reconstructive Surgery Department.

Study Procedure Risks

We anticipate minimal additional risks by undertaking the study. The deckled incision is fairly common practice among the Plastic Surgery Department and as previously illustrated in the pilot study, all other aspects of the post-operative care are standard.

Recruitment and Screening

The patient will be recruited from outpatient and inpatient referrals and the Emergency Department at St Vincent's Public Hospital.

Informed Consent Process

Once the patient is identified as suitable, informed consent will be obtained to be enrolled in the study. The patient will be explained how the procedure is conducted, the expected post-operative recovery time, and the follow-up time periods. The risks and benefits of the procedure will be explained and the patient will be made aware of suitable alternatives [6].

Enrolment Procedure

The participant will be enrolled into the study after the informed consent process has been completed, and the participant has met all inclusion criteria and none of the exclusion criteria. The patient's baseline characteristics will be recorded on a pre-populated A4 sheet and scanned via email to a single email address. The patient baseline characteristics that will be recorded are age, gender, smoking, Fitzpatrick classification of skin type and ethnicity, presence of vascular co-morbidities, diabetes, use of systemic and/or oral steroids or immunosuppressant's, previous poor scar results, site of lesions (face vs trunk vs limbs), and previous radiotherapy over the surgical site. An independent person will subsequently enter the patient data into an online database and allocate a study code, which will be documented in the patient records.

The final statistical analysis will be stratified and adjusted by the patients' baseline characteristics to adjust for their effects on wound healing. We are particularly interested in effects of previous radiotherapy and sites of lesions (face vs trunk vs limbs) as we believe that the deckling incision will offer the most benefit in those with previous radiotherapy and in lesions on the face.

Randomization Procedure

Following suitability for enrolment into the study and allocation of study code, the participants will be randomized to receive either the deckled incision or the standard straight line incision in a simple fashion using a random computer number generator. This will be done in the anesthetic bay after confirmation of patient suitability by checking the medical records. The surgeon will subsequently ring an external number and the study nurse will specify what treatment the individual lesions will receive.

Adverse Events

An adverse event is any untoward medical occurrence that results in the following: death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability and/or incapacity or congenital or birth defect, and any condition requiring medical or surgical intervention. An adverse event can therefore be any unfavorable or unintended sign, symptom, condition, and/or an observation that may or may not be related to the study treatment.

Blinding

In order to achieve allocation concealment an external third party will be used to assign the treatment group. The surgeon will document in the patient notes which incision was carried out for a specific lesion. This will be entered into the patient database by an independent third party.

The patient will be blinded to the type of incision that is done for any given lesion. However, it is impractical to blind the individual surgeon. In addition, the outcome adjudicators will also be blinded to the incision used. The data collectors and analysis will be centralized and remain independent of the outcome adjudicators at all times. Medical record numbers will also be recorded to enable tracking of progress over time.

Statistical Consideration

Sample size was calculated on the basis of a type I error of 5% (ie, P <.05) and a type II error of 10% (ie, power of 90%) with the aid of a statistician. Using formal sample size calculations we estimated a sample size of 250 patients for each treatment group. We anticipate an attrition rate of 10%, and subsequently, have increased our sample size by that amount for each treatment group.

Statistical analysis will be carried out by an external statistician. We intend to use independent two-sample t tests on primary endpoints and both chi-squared and independent two-sample t tests on secondary endpoints.

Confidentiality, Storage and Archiving

The patients will be allocated a study code and their data will be de-identified. Following completion of the study the data will be kept on a secure server for a minimum of 15 years in the Department of Plastics and Reconstructive Surgery.

Results

The study is expected to begin enrolment in August 2016. We anticipate that deckling will have superior scar outcomes when compared to the straight line incisions. From clinical experience this is especially true for lesions involving the face and in those areas of the skin that have undergone radiation therapy.

The study will be funded by the Plastics and Reconstructive Surgery Department at St Vincent's Hospital, Sydney, Australia. Ethics approval has been obtained for the study.

Discussion

The deckling study is a novel method for improving post-operative scar outcomes. Although this study mainly evaluates scar outcomes following excision of smaller lesions in plastic surgery procedures, its results can be applicable to a broad range of surgical procedures involving the skin. The learning curve associated with a new surgical procedure or technique can limit its uptake by surgeons. The deckling incision is simple to master with a minimal learning curve and has a small impact on the overall operating time.

Conclusion

The deckling incision is a unique, simple and cost effective technique for improving post-operative scar outcomes.

Acknowledgments

We would like to acknowledge James Southwell-Keely, Elias Moisidis, Kevin Ho, Fred Clarke, and Russell Aldred for their contribution in designing the protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Patient and Observer Scar scale - Observer.

[PDF File (Adobe PDF File), 177KB - resprot_v5i3e97_app1.pdf]

Multimedia Appendix 2

Patient and Observer Scar Scale - Patient.

[PDF File (Adobe PDF File), 172KB - resprot_v5i3e97_app2.pdf]

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Abbreviations

POSAS: Patient and Observer Scar Assessment Scale
RCT: randomized controlled trial

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Protocol

Effect of Sitagliptin and Metformin on Prediabetes Progression to Type 2 Diabetes - A Randomized, Double-Blind, Double-Arm, Multicenter Clinical Trial: Protocol for the Sitagliptin and Metformin in PreDiabetes (SiMePreD) Study

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Abstract

Background: The high prevalence and incidence of type 2 diabetes mellitus (DM), and its associated morbidity and mortality, has prompted growing international interest and effort in the primary prevention of this disease. Primary prevention is possible since type 2 DM is preceded by prediabetes, offering a window opportunity to treat patients, and prevent the emergence of advanced disease. Sitagliptin is an oral dipeptidyl peptidase-IV inhibitor that preserves existing beta cell function and increases beta cell mass. These two effects have been demonstrated both in vitro and in animal studies, and current clinical data show that sitagliptin is safe. Metformin, a biguanide, reduces insulin resistance and inhibits hepatic gluconeogenesis, and has an excellent safety profile. The combination of metformin and sitagliptin, targeting both characteristics of prediabetes (insulin resistance and progressive beta cell degeneration), may potentially slow or halt the progression from prediabetes to type 2 DM. This paper describes the rationale and design of the Sitagliptin and Metformin in PreDiabetes (SiMePreD) study.

Objective: The aim of this study is to determine the effect of sitagliptin and metformin on progression from prediabetes to type 2 DM. The objectives of the study are to determine the effects of metformin and placebo on glycemic endpoints, the effects of sitagliptin and metformin on glycemic endpoints, the effects of metformin and placebo on incidence of cardiovascular disease and death, and the effects of sitagliptin and metformin on incidence of cardiovascular disease and death.

Methods: This is a randomized, double-blind, multicenter clinical study that will determine if the combination of metformin and sitagliptin is effective in preventing the progression from prediabetes to type 2 DM. The study will contain two arms (metformin/sitagliptin and metformin/placebo). Primary endpoints include the number of subjects progressing from prediabetes to type 2 DM, the number of cardiovascular events, and the number of deaths. The planned duration of the study is five years, and 410 subjects will be included in each group. Data analyses will include clinically relevant measures (eg, numbers needed to treat and numbers needed to harm) and will be performed according to the intention-to-treat principle.

Results: This study is currently in the process of acquiring research funding.

Conclusions: The SiMePreD study is the first study to investigate the utility of sitagliptin in combination with metformin for the primary prevention of type 2 DM.

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KEYWORDS

primary prevention; type 2 diabetes mellitus; prediabetes; dipeptidyl peptidase-IV

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, lipid, and protein metabolism, resulting from defects in insulin secretion, insulin action, or both [1]. The World Health Organization estimates that between 120 and 140 million people suffer from DM worldwide, and that this number could double by the year 2025 [2]. Most of the increase will occur in developing countries and will be due to population aging, diet, obesity, and a sedentary lifestyle [2,3]. DM is associated with a significant decrease in life expectancy and is a risk equivalent to established coronary artery disease [4]. In patients who develop DM, cardiovascular morbidity and mortality are increased by 2-to-6 fold [5,6].

Prediabetes is a metabolic condition characterized by insulin resistance and primary or secondary beta cell dysfunction, which increases the risk of type 2 DM [7]. The American Diabetes Association defines prediabetes as either impaired glucose tolerance (IGT; 2-hour postprandial glucose of 7.8-11.0 mmol/L) or impaired fasting blood glucose (FBG; value of 5.6-6.9 mmoI/L), or both [1]. Risk factors for prediabetes include family history of diabetes, excess body weight (particularly abdominal adiposity), age >45 years, gestational diabetes, high birth weight children, certain ethnic groups, hypertension, and physical inactivity [8]. Glucose levels above the normal, but below the threshold diagnostic for diabetes, are associated with a substantially increased risk of developing cardiovascular disease and death [9,10].

Subjects that eventually develop type 2 DM progress from normal glucose tolerance to IGT, and finally to type 2 DM [11]. Edelstein et al [12] investigated the predictors of progression from IGT to type 2 DM in data from six prospective studies. This study concluded that individuals with IGT have an increased risk of developing type 2 DM.

The progression of the disease is related to deterioration in beta cell function and increased insulin resistance [1]. IGT precedes type 2 DM, providing an attractive target for intervention, and thus entertains the possibility of slowing down or preventing progression to type 2 DM.

The growing prevalence of type 2 DM and its high associated mortality and morbidity make the prevention of this disease an important public health intervention [13]. Patients with type 2 DM and those with prediabetes are at an increased risk for the development of cardiovascular diseases [14]. Halting the progression from IGT to type 2 DM is therefore an important health intervention strategy.

Interventions to delay or even prevent type 2 DM have the potential to improve the health of populations, and reduce health care costs associated with the management and prevention of diabetic complications [15]. Various interventions have been used to prevent or delay the progression from IGT to type 2 DM [16], including pharmacological agents, lifestyle modification (LSM), and herbal remedies. Pharmacological interventions have included oral antidiabetic drugs and antiobesity drugs.

Nonpharmacological and Pharmacological Interventions for Prediabetes

During the conception of the Sitagliptin and Metformin in PreDiabetes (SiMePreD) study, we discussed various interventions for prediabetes. A summary of selected clinical trials on prediabetes is presented below. The rationale for the choice of drugs for the SiMePreD study will be detailed in the discussion section.

Nonpharmacological Interventions

Lifestyle Modification and the Prevention of Diabetes Mellitus

Three randomized studies [17-19] have demonstrated a positive effect of LSM on DM prevention. The Da Qing IGT and Diabetes Study [17] screened 110,660 men and women for IGT and DM, of whom 577 had IGT (as per World Health Organization criteria for IGT). Subjects with IGT were randomized either to a control group or to one of three active treatment groups: diet only, exercise only, or diet-plus-exercise. Follow-up evaluation examinations were conducted at 2-year intervals over a 6-year period to identify subjects who developed type 2 DM. The cumulative incidence of diabetes at 6 years was 67.7% (95% CI 59.8-75.2) in the control group compared with 43.8% (95% CI 35.5-52.3) in the diet group, and 41.1% (95% CI 33.4-49.4) in the diet-plus-exercise group (P<0.05). The relative decrease in rate of development of diabetes in the active treatment groups was similar when subjects were stratified as lean or overweight. After adjustment for differences in baseline body mass index (BMI) and fasting glucose, the diet, exercise, and diet-plus-exercise interventions were associated with 31% (P<0.03), 46% (P<0.05), and 42% (P<0.05) reductions in risk of developing diabetes, respectively. The study demonstrated that the diet alone, exercise alone, or the combination of the two interventions resulted in the reduced incidence of DM over a 6-year period in subjects with IGT.

The Finish Diabetes Prevention Study [18] randomly assigned 522 middle-aged, overweight subjects (172 men and 350 women; mean age 55 years; mean BMI 31 kg/m^2) with IGT to either the intervention group (individualized counseling aimed at reducing weight and total intake of saturated fat, and increasing intake of fiber and physical activity) or the control group. An oral glucose-tolerance test was performed annually; the diagnosis of diabetes was confirmed by a second test. The mean duration of the follow-up was 3.2 years. The cumulative incidence of diabetes after four years was 11% (95% CI 6-15%) in the intervention group and 23% (95% CI 17-29%) in the control group. The risk reduction was 58% (P<0.001) in the intervention group. The reduction in the incidence of diabetes was directly associated with changes in lifestyle.

The Diabetes Prevention Program Research Group [19] randomly assigned 3234 nondiabetic subjects with elevated fasting and postload plasma glucose concentrations to placebo, metformin treatment, or an LSM program. The average follow-up was 2.8 years. The incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person years in the placebo, metformin, and lifestyle groups, respectively. The lifestyle intervention reduced DM incidence by 58 percent (95% CI

48-66%) and metformin reduced incidence by 31 percent (95% CI 17-43%), as compared with placebo. To prevent one case of diabetes during a period of three years, 6.9 persons would have to participate in the lifestyle intervention program, and 13.9 would have to receive metformin. The American Diabetes Association [20] recommends exercise as a component of DM prevention. Diet and exercise interventions improve insulin resistance and decreases the incidence of diabetes and cardiovascular events, although long term weight loss is difficult to maintain [17,18,21,22].

Pharmacological Interventions

Metformin and the Prevention of Diabetes Mellitus

Metformin has been studied for more than 50 years and has been shown to be safe, even with long term use [23,24]. Observational and randomized studies have shown that metformin is the most effective oral hypoglycemic agent for reducing cardiovascular morbidity and mortality in patients with DM, and is considered first line treatment [24-27]. A meta-analysis of metformin treatment in persons at risk for DM has concluded that metformin treatment results in substantial reductions in the development of type 2 DM (odds ratio 0.6 [0.5-0.8]) [28].

Ramachandran et al [22] investigated the effect of LSM and metformin on the prevention of type 2 DM in Asian Indian subjects with IGT. Study subjects (n=531) with IGT were randomly allocated to four groups: control, advice on LSM, metformin alone, and LSM combined with metformin. The primary outcome measure was type 2 DM. The median follow-up period was 30 months, and the 3-year cumulative incidences of diabetes ranged between 39.5-55.0%.

The relative risk reduction was 28.5% with LSM (95% CI 20.5-37.3, *P*=0.018), 26.4% with metformin (95% CI 19.1-35.1, *P*=0.029) and 28.2% with LSM and metformin (95% CI 20.3-37.0, *P*=0.022), as compared to the control group. To prevent one case of diabetes, 6.9 persons would need to be treated with metformin, and 6.5 persons for LSM combined with metformin. The investigators concluded that both LSM and metformin significantly reduced the incidence of diabetes in Asian Indians with IGT. The lifestyle intervention was more effective than metformin. However, the intense LSM group had to endure a program that is unlikely to be sustained in real world settings.

Thiazolidinediones and the Prevention of Diabetes Mellitus

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication trial [29] enrolled 5269 adults with impaired fasting glucose or IGT, or both. These study subjects were followed for a median of 3 years and the primary outcome was a composite of incident diabetes or death. Three hundred and six (11.6%) individuals given rosiglitazone and 686 (26.0%) given placebo developed the composite primary outcome (hazard ratio 0.40, 95% CI 0.35-0.46; *P*<0.001); 1330 (50.5%) individuals in the rosiglitazone group and 798 (30.3%) in the placebo group became normoglycemic (median 1.71, 1.57-1.87; *P*<0.001). Fourteen (0.5%) participants in the rosiglitazone group and two (0.1%) in the placebo group developed heart failure (*P*=0.01). Rosiglitazone was associated with greater incidence of heart failure.

The Troglitazone in Prevention of Diabetes (TRIPOD) study, a randomized double-blind study, investigated the effect of troglitazone (400 mg/day; n=133) versus placebo (n=133) in women with previous gestational diabetes [30]. The average annual diabetes incidence rates in women who returned for follow-up were 12.1% in the placebo group and 5.5% in the troglitazone group. There was a significantly lower cumulative incidence of diabetes in the troglitazone group. The hazard ratio for diabetes was 0.45 (95% CI 0.25-0.83) and was unchanged (hazard ratio=0.44) by adjustment for differences in baseline and on-trial. The hazard ratio for diabetes in the troglitazone group was 0.50 (95% CI 0.28-0.89) and 0.44 with adjustment for differences in baseline and on-trial characteristics. Thus, troglitazone reduced the incidence of diabetes in women who returned for follow-up by at least 50%.

The Pioglitazone in Prevention of Diabetes (PIPOD) study [31] was an open-label observational study to determine the effects of pioglitazone in women with prior gestational diabetes who had completed the TRIPOD study. The PIPOD study consisted of 3 years of drug treatment and 6 months of postdrug washout. The average dropout rate for the study period was 9.6% (n=24). Of the 24 patients that did not complete the study, 19 women moved away from the study area, 10 withdrew consent for personal reasons, and none of these patients had diabetes. Five women failed to come for scheduled appointments either immediately after enrolment (n=3) or after a period of active participation (n=2), and attempts to contact them failed, so their diabetes status at the time of drop out was unknown. Incidence rates of diabetes were calculated from 86 women (42 from the active treatment arm of the TRIPOP study). Eleven participants had diabetes at one or more oral glucose tolerance tests during a median of 35.9 months of pioglitazone treatment. No new cases of diabetes were observed during the post-drug wash-out, which lasted a median of 5.7 months.

Average annual incidence rates of diabetes were 5.2% during pioglitazone treatment and 4.6% during the entire observation period, including the postdrug washout. The final cumulative incidence of diabetes during treatment and postdrug follow-up was 17%. These rates were similar to analogous rates observed during a median of 31 (standard deviation [SD] 8) months of troglitazone treatment and posttrial washout in the TRIPOD study (5.7% and 25% per year, respectively) and lower than rates observed during a median of 28 (SD 8) months of placebo treatment and posttrial washout in the TRIPOD study (13.1% and 52% per year, respectively).

Combination of Thiazolidinediones and Biguanides in Diabetes Prevention

Thiazolidinediones and biguanides have different modes of pharmacological action. Metformin inhibits hepatic glucose production, while thiazolidinediones produce a greater effect on peripheral glucose uptake. Basal insulin concentrations are not raised with metformin or thiazolidinediones, thus there is a minimal risk of hypoglycemia, and metformin can reduce the weight gain associated with thiazolidinediones [32]. The combination of biguanides and thiazolidinediones has been used

to treat type 2 DM [33,34]. Fonseca et al [33] investigated the effect of metformin and rosiglitazone combination therapy in patients with type 2 DM using a randomized, double-blind, placebo controlled trial. The study concluded that combination treatment with once-daily metformin/rosiglitazone improved glycemic control, insulin sensitivity, and beta cell function more effectively than treatment with metformin alone. Dose-dependent increases in body weight and total and low-density lipoprotein cholesterol levels were observed (P<0.001) for both rosiglitazone groups versus placebo. The proportion of patients reporting adverse events was comparable across all groups.

Rosenstock et al [34,35] compared treatment with rosiglitazone/metformin fixed-dose combination therapy with monotherapy of either rosiglitazone or metformin in patients with uncontrolled type 2 DM. This study found that the rosiglitazone/metformin therapy achieved significant reductions in glycosylated hemoglobin (HbA1c) and fasting plasma glucose compared with either drug used as monotherapy.

The Canadian Normoglycemia Outcomes Evaluation (CANOE) study [35], a randomized double-blind controlled trial with a median duration of 3.9 years, investigated whether low dose combination therapy with rosiglitazone and metformin would prevent type 2 DM. One hundred and three subjects with IGT were assigned to rosiglitazone/metformin, and 104 to placebo. The CANOE study demonstrated that low dose therapy with rosiglitazone/metformin effectively prevented the onset of DM, and 4.0 persons would need to be treated with this combination to prevent one case of DM. A significant increase in diarrhea was observed in the active arm compared to placebo (16% vs 6%, P=0.0253).

Sitagliptin and the Potential in Diabetes Prevention

Dipeptidyl peptidase-IV (DPP-IV) inhibitors are a new class of antidiabetic drugs. These drugs enhance the body's ability to regulate blood glucose by increasing the active levels of incretins, glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) [36]. Sitagliptin is a DPP-IV inhibitor that increases insulin release and decreases glucagon levels by preventing the deactivation of GLP-1 and GIP [37]. Sustained receptor activation is associated with insulin biosynthesis and stimulation of beta cell proliferation [37].

Cumulative clinical trials with sitagliptin have enrolled >2600 patients with type 2 DM [36]. In these trials, study subjects received sitagliptin in doses of 100 mg/day for at least 12 weeks; >1000 patients received sitagliptin in doses of 100 mg/day for 24 weeks, and >500 patients were exposed to sitagliptin 100 mg/day for 52 weeks [34,38-44]. In phase III studies [34,40-42], adverse events were reported in 5% of patients treated with sitagliptin and were reported more than in patients who received placebo, regardless of causality. Such adverse events included upper respiratory tract infections (6.3%), nasopharyngitis (5.2%), and headaches (5.1%) [45]. The incidence of hypoglycemia with sitagliptin and placebo were comparable (1.2% of patients treated with sitagliptin and 0.9% given placebo) [46]. The prevalence of abdominal pain was 2.3% and 2.1% in sitagliptin and placebo arms, while the prevalence of nausea was 1.4% and 0.6% in sitagliptin and placebo arms, respectively [46]. Patients treated with sitagliptin demonstrated no significant increase in body weight from baseline [46].

A Cochrane review [47] of DPP-IV inhibitors found that all-cause infections (eg, nasopharyngitis, upper respiratory tract infection, urinary tract infection) showed a statistically significant increase after sitagliptin treatment (risk ratio 1.15, 95% CI 1.02-1.31; P=0.03). Furthermore, discontinuation due to adverse effects did not differ significantly between sitagliptin intervention and control arms. The risk ratios of serious adverse events did not show statistically significant differences between groups. The Cochrane review concluded that, overall, sitagliptin was well tolerated [47]. There is, however, no data on the adverse effects associated with long term use of sitagliptin.

Based on the mode of action of sitagliptin, it is plausible that the drug may reduce beta cell apoptosis and preserve beta cell functioning, thereby preventing the progression from prediabetes to type 2 DM. Animal and *in vitro* studies suggest that activation of GIP and GLP-1 receptors promotes beta cell resistance to apoptosis, proliferation, and neogenesis, resulting in enhanced beta cell function [37]. GLP-1 and GIP also promote beta cell proliferation and survival, and DPP-IV inhibitors exert similar effects in rodents with type 2 DM [48]. Sitagliptin prolonged islet graft retention in streptozotocin-induced diabetic mice [48]. Of the 56 studies that are currently investigating sitagliptin in diabetes, there are no studies investigating the effect of sitagliptin on the prevention of type 2 DM (Table 1).

Table 1. Summary of diabetes prevention studies.

Study	n	Study Arms	Duration	Endpoint	Results
Lifestyle modification and diabetes prevention					
The Finish Diabetes Prevention Study [18]	522	Lifestyle counselling, control group	3.2 years	Development of type 2 diabetes	Cumulative incidence of diabetes was 11% (95% CI 6-15%) in the intervention group and 23% (95% CI 17-29%) in control group
The Da Qing IGT and Diabetes Study [17]	577	Control group, diet only, exercise only, diet-plus-exercise	6 years	Development of type 2 diabetes	Cumulative incidence of diabetes at 6 years was 67.7% (95% CI 59.8-75.2) in control group compared with 43.8% (95% CI 35.5-52.3%) in diet group, 41.1% (95% CI 33.4-49.4) in exercise group and 46% (95% CI 37.3-54.7) in diet-plus-exercise group
Metformin and diabetes prevention					
The Diabetes Prevention Program Research Group [19]	3234	Placebo, metformin, lifestyle modification	2.8 years	Development of type 2 diabetes	Lifestyle intervention reduced incidence by 58% (95% CI 48-66%) and metformin by 31% (95% CI 17-43%), as compared to placebo
Ramachandran et al [22]	531	Control, lifestyle modification, metformin alone, lifestyle modification and metformin	30 months	Development of type 2 diabetes	Relative risk reduction 28.5% with lifestyle modification (95% CI 20.5-37.3%, *P*=0.018), 26.4% with metformin (95% CI 19.1-35.1, *P*=0.029), 28.2% with lifestyle modification and metformin (95% CI 20.3-37.0, *P*=0.022)
Thiazolidinediones and diabetes prevention					
The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication [29]	5269	Rosiglitazone, placebo	3 years	Development of type 2 diabetes	Diabetes mellitus incidence in 49.5% of individuals in the rosiglitazone group (hazard ratio 0.40, 95% CI 0.35-0.46; *P*<0.001) and 69.7% in the placebo group (1.71, 1.57-1.87; *P*<0.001)
The Troglitazone in Prevention of Diabetes (TRIPOD) study [30]	133	Troglitazone, placebo	30 months	Development of type 2 diabetes	Average annual diabetes incidence rates in women who returned for follow up were 12.1% and 5.4% in placebo and troglitazone groups, respectively The hazard ratio for diabetes was 0.45% (95% CI 0.25-0.83) in the control group and 0.50 (95% CI 0.28-0.89) in the troglitazone group
The Pioglitazone in Prevention of Diabetes (PIPOD) study [31]	95	Pioglitazone, placebo	3 years	Development of type 2 diabetes	Average annual incidence rates of diabetes were 5.2% during pioglitazone treatment and 4.6% during the entire observation period, including the post-drug washout The final cumulative incidence of diabetes during treatment and post drug follow up was 17%

Motivation for the Study

The high global prevalence of type 2 DM, and its associated morbidity and mortality, place major demands on health care resources (both human and financial). Developing countries are faced with a high prevalence of both infectious diseases and diseases of lifestyle. Reducing the incidence of type 2 DM will reduce the demand on limited health care resources.

Type 2 DM is predated by a condition known as prediabetes, which offers an opportunity for targeting preventative measures. There is currently great interest in the search for interventions to prevent type 2 DM. Various pharmacological and nonpharmacological agents have been used with various degrees of success. Since DPP-IV inhibitors and biguanides have differing pharmacological modes of actions, we propose that combining these agents may have additive and possibly synergistic effects on preventing the progression from prediabetes to type 2 DM. The combination of the aforementioned drugs will allow for the reduction in the prescribed doses of each agent, and thus may limit the probability for adverse drug effects.

Sitagliptin is a novel antidiabetic agent that theoretically possesses the ability to preserve existing beta cell function by preventing beta cell apoptosis, and also increases beta cell mass. These effects have been shown *in vitro* and in animal studies. Furthermore, current clinical data indicate that sitagliptin is safe in the short term. This will be the only study investigating the effect of the combination of sitagliptin and metformin on prediabetes progression.

Developing Country Dynamics and Clinical Trials

Conducting a trial of this magnitude in a developing country encompasses numerous challenges, including the availability of human and financial resources. Clinicians involved in this study will be those that are currently in training or employed in the public sector, and are affiliated with a teaching hospital

and medical university. The trial will also allow for the exposure of medical doctors to clinical trials, and will allow for their training in good clinical trial practice.

The use of resources for the prevention of type 2 DM is an opportunity cost for HIV/AIDS and other chronic disorders. However, we propose that resources spent in the short term for diabetes prevention may, in the long term, allow for more resources to be allocated to competing disease conditions.

Currently, we plan to obtain funding from the pharmaceutical industry, endocrine societies, University of Witwatersrand, University of Cape Town, University of Pretoria, Medical University of South Africa, University of KwaZulu-Natal, and South African Department of Health. The trial will be registered on the National Institutes of Health (NIH) clinical trial database, subsequent to approval by the university ethics review boards and confirmation to the regulations of National Health Authority.

Limitation of the Study

The study is only 5 years in length, and thus cannot truly determine the effect of interventions on progression from prediabetes to type 2 DM.

Methods

The aim of the study is to determine the effect of sitagliptin and metformin on progression from prediabetes to type 2 DM.

Objectives

This study has seven primary objectives, namely to determine: (1) the effect of metformin and placebo on glycemic endpoints; (2) the effects of sitagliptin and metformin on glycemic endpoints; (3) the effects of metformin and placebo on incidence of cardiovascular disease and death; (4) the effects of sitagliptin and metformin on incidence of cardiovascular disease and death; (5) the incidence of adverse effects associated with metformin and placebo; (6) the incidence of adverse effects associated with sitagliptin and metformin; and (7) the quality of life (QOL) of subjects using metformin and sitagliptin.

Study Population

The study population will consist of subjects referred from *peripheral sites* within Johannesburg, Pretoria, Durban, and Cape Town. These *peripheral sites* will include general practitioners, primary health care clinics, and other facilities in which screening glucose tests are performed. High risk subjects will be screened for IGT. Subjects with high risk for prediabetes, in whom screening may be warranted, include the following groups: age >45 years and overweight (BMI >25 kg/m^2); cardiovascular events (eg, myocardialinfarction); age <45 years and overweight with a first degree relative with DM, previous gestational diabetes or macrosomia in one or more children, or have hypertension or dyslipidaemia; patients of Asian descent with a lower BMI (>23 kg/m^2); and patients with thyroid dysfunction.

Study Timeline

Visit 1 - Study Start

Subjects referred from *peripheral sites* to the study sites will be briefed about the study and invited to participate. Thereafter, informed consent will be obtained. Appropriate tests will be performed to determine if subjects meet the criteria for inclusion in the study (eg, liver function tests [LFTs], urea and electrolytes, HbA1c, FBG, fasting blood insulin [FBI] level, physical examination, urate levels, and blood gases for pH determination). See Textbox 1 for inclusion, exclusion, and withdrawal criteria for the study. Drug history will be obtained and anthropometric measures determined. Subjects will be told that they must return the following week for their results and for appropriate counseling.

Textbox 1. Inclusion, exclusion, and withdrawal criteria for the study.

Inclusion Criteria

- Informed consent
- Subjects with impaired glucose tolerance as defined by American Diabetes Association
  - Impaired glucose tolerance (2-hour postprandial glucose of 7.8–11.0 mmol/L)
  - Impaired fasting blood glucose (fasting glucose of 5.6-6.9 mmol/L)
- Age 18-65 years
- No history of liver disease
- Negative pregnancy test

Exclusion Criteria

- Impaired liver function tests
- Cardiac failure or history of congestive heart failure in the close family
- Medication that may affect insulin resistance (eg, oral hypoglycemic agents, thiazide diuretics)
- Contra-indications to exercise
- Pregnancy
- Patients planning to move residence within the next 5 to 10 years
- History of hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema

Withdrawal Criteria

- Withdrawal of informed consent
- Congestive cardiac failure
- Impaired liver function
- Lactic acidosis
- Clinical or biochemical evidence of hypoglycemia
- Drug usage should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function
- Excessive rapid weight gain, dyspnea, and/or edema
- Renal disease or renal dysfunction
  - Serum creatinine levels >1.5 mg/dL (males), >1.4mg/dL (females)
  - Abnormal creatinine clearance, which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma
- Pregnancy

Visit 2 - 2 Weeks Later

Subjects meeting the inclusion criteria will be invited to join the study. Study subjects not meeting the inclusion criteria will be counseled and a detail letter will be sent to the initial referring site for further treatment. Patients unable or unwilling to return to their initial referring site will be treated at the study sites. All subjects will be given dietary advice and a standard exercise protocol from the Sports Science Department, and will be allowed access to the university gym. Subjects will be randomized to either metformin extended release (500 mg daily) and placebo (daily), or metformin extended release (500 mg daily) and sitagliptin (25 mg daily), for one month.

Visit 3 - 2 Weeks Later

Measures for determining safety and measures of glycemic control will be examined. The dose of metformin and sitagliptin will be increased to 1000 mg and 50 mg daily, respectively (provided that the patients have tolerated the initial trial of drug). Subjects who have progressed to type 2 DM (based on indicators of glycemia such as FBG) will be referred to the diabetic clinic for management. LSM advice will be reenforced.

Visit 4 - 1 Month Later

Measures of glycemia (FBG and HbA1c) will be repeated, along with biochemical and clinical tests for safety. Anthropometric

measures, lipid profiles, QOL forms, and FBI levels will also be examined.

Visits 5 Through 25

Every two months, the parameters examined in Visit 4 will be repeated, until the 1-year time point after study initiation. Subsequent study visits will occur every three months and the investigations will be repeated. A total of 25 visits will occur over a period of 5 years. During the second last visit, all trial medication will be stopped and subjects will return to the clinic two weeks later for further assessment. Measures of glycemia, LFTs, renal function, anthropometric measures, lipid profiles, QOL forms, safety data (biochemical and clinical), and FBI levels will all be assessed. An outline of the study assessments and visits are contained in Table 2 and Table 3, respectively.

Table 2. Study assessment during various visits.

	Visit number																							
Assessments	1[a]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver function test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urea and electrolytes	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Glycosylated hemoglobin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting blood glucose	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting blood insulin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anthropometric measures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a]Screening after documented informed consent obtained

Table 3. Study time period and study procedures.

Visit	Time interval	Study procedures	Cumulative time period
1	Study start	Patients referred from peripheral sites	0
		Patients interviewed and informed consent obtained	
		Tests to determine if subjects fulfil inclusion criteria	
		Drug history and anthropometric measures	
		Patients informed to attend next visit after one week for results and appropriate counselling	
2	2 weeks	Subjects fulfilling inclusion criteria will be invited to partake in the study	2 weeks
		Subjects not fulfilling the inclusion criteria will be counselled and directed back to initial referral center	
		All subjects will be given dietary advice and a standard exercise protocol, and will be allowed access to the university gym	
		Randomized to either metformin (500 mg daily) and placebo (daily) or metformin 500 mg daily and sitagliptin (25 mg daily) for one month	
3	2 weeks	Efficacy and safety measures	1 month
		Dose escalation to metformin 1000 mg and sitagliptin 50 mg daily	
		Subjects that have progressed to type 2 DM will be referred for management	
		Lifestyle modification advice reenforced	
4	1 month	Glycemic measures repeated	2 months
		Tests for safety (biochemical and clinical), anthropometric measures, lipid profiles, quality of life forms, safety data, FBI levels	
5	2 months	Repeat	4 months
6	2 months	Repeat	6 months
7	2 months	Repeat	8 months
8	2 months	Repeat	10 months
9	2 months	Repeat	1 year
10	3 months	Repeat	1 years and 3 months
11	3 months	Repeat	1 years and 6 months
12	3 months	Repeat	1 years and 9 months
13	3 months	Repeat	2 years
14	3 months	Repeat	2 years and 3 months
15	3 months	Repeat	2 years and 6 months
16	3 months	Repeat	2 years and 9 months
17	3 months	Repeat	3 years
18	3 months	Repeat	3 years and 3 months
19	3 months	Repeat	3 years and 6 months
20	3 months	Repeat	3 years and 9 months
21	3 months	Repeat	4 years
22	3 months	Repeat	4 years and 3 months
23	3 months	Repeat	4 years and 6 months
24	3 months	Repeat and medication stopped	4 years and 9 months
25	3 months	Glycemic measures and safety tests	5 years
		Patients referred to appropriate clinics	

Blinding

Blinding will be achieved by formulating a product that is identical to sitagliptin in appearance, but does not contain the pharmacologically active agent .

Endpoints

Primary endpoints include the number of subjects progressing from prediabetes to type 2 DM, the number of cardiovascular events, and the number of deaths. Secondary endpoints include lipograms, urea and electrolytes, LFTs, full blood count, FBG,

FBI, weight and other anthropometric parameters, and blood pressure.

Safety Considerations

Pharmacological agents are not without adverse effects, and in designing this study the probability and severity of adverse effects were considered. The safety of the interventions was very important due to the long duration of the study. We thus had to ensure the inclusion of agents that were pharmacologically rational and safe. Metformin has been used for many decades and is relatively safe, and we have developed inclusion criteria to ensure that subjects susceptible to lactic acidosis (a rare but serious adverse effect of metformin) would be excluded from the study. Sitagliptin has been used for the therapy of type 2 DM and has been associated with minimal adverse effects. This drug has only been on the US market for approximately six years and has proven safe thus far. The current study will have a duration of 5 years, and the frequent evaluation and close monitoring over the 5-year study period will enable monitoring of any serious adverse effect.

Safety measures have been incorporated into the study, including LFTs, renal function tests, and the regular clinical evaluation of patients for adverse effects. Subjects suspected of having study-drug related adverse effects will be aggressively investigated and managed at the cost of study team. Furthermore, we will monitor the use of sitagliptin for diabetes in the global market, with particular note of its adverse effect profile. If the safety benefit ratio of sitagliptin becomes unacceptable, the study will be stopped. To further augment safety, we will use low doses of both sitagliptin and metformin.

Ethical Considerations

The study protocol will be submitted to the ethics committee at the University of the Witwatersrand. Permission to conduct the study at public sector health care sites will be obtained from the managers of the named institutions, and the Director General of Health in the provinces in which the study is to be conducted. The study will be conducted in accordance with the Declaration of Helsinki [49] and its amendments, and the Patients' Rights Charter. Subjects will be asked to provide written informed consent to participate as a criterion for entry into the study.

Value of the Study

This study aims to determine the efficacy of pharmacotherapy in preventing the progression from prediabetes to type 2 DM, and thus may add to the armamentarium of agents utilized for the management of prediabetes.

Data Management

The clinicians at the study sites will fill out all study forms. Study coordinators at the various study sites will check the forms for completeness. The data manager will then also check all forms for completeness and enter the data onto a database. Lists of the subjects who need to be called back will be printed by the data manager, and faxed and emailed to the study sites to ensure that study participants are reminded of their study visit dates and times. Confidentiality will be maintained by allocating a code number to each participant, and original data collection forms for each patient will be kept safe and strictly confidential.

Statistical Analysis

This study will compare two groups, one of which will receive metformin and sitagliptin, and the other metformin and placebo. The primary end point is progression from prediabetes to type 2 DM at the end of the 5-year study period. Sample size, determined by a statistician, is based on the following assumptions: the rate of development of type 2 DM will be, at most, 50% after a 5-year follow-up in the group that receives placebo and metformin; the rate of development of type 2 diabetes will be 30% (20% reduction) after a 5-year follow up in the group that receives sitagliptin and metformin; and at most, the dropout rate of participants will be between 10-20% per year.

For a 5% significance level and 90% power, 134 participants are required in each group (268 participants total) at the end of the study. This value translates to between 228 and 410 participants in each group at the beginning of the study to allow for 10-20% loss to follow-up in each year. We thus chose to include 410 subjects in each group. Data analyses will include clinically relevant measures (eg, numbers needed to treat and numbers needed to harm) and will be done according to the intention-to-treat principle.

Results

This study is currently in the funding phase.

Discussion

The high morbidity and mortality associated with type 2 DM [2,4-6,50], and its ability to consume health care resources, make it an important target for primary prevention [51]. Various studies [17-19] have demonstrated that lifestyle intervention is effective in preventing type 2 DM. However, lifestyle interventions comparable to those used in the aforementioned studies would require significant investments by the subject and the community [14,52,53]. Adherence to lifestyle interventions in clinical trials, in which subjects are given extensive support, is generally poor [52,53]. Medication, although less effective than LSM, may have the added benefit of improved compliance. Valensi et al [8] in their European Consensus statement, recommend that pharmacological intervention combined with diet and exercise counselling may be the most realistic option for achieving real reductions in diabetes incidence.

Ameliorating insulin resistance could influence the progression from IGT to type 2 DM. The combination of a biguanide with a thiazolidinedione is pharmacologically rational [32-34] since these agents target insulin resistance via different mechanisms. However, this combination does not address beta cell dysfunction, which is an important factor in the progression from prediabetes to type 2 DM. Currently, the literature does not contain the results of any trials investigating the effect of combining a biguanide and thiazolidinedione on the progression of prediabetes to type 2 DM. However, the NIH has registered a clinical trial that is investigating the effect of combining rosiglitazone and metformin to determine their effects on

individuals with IGT. Rosiglitazone has more adverse effects compared to pioglitazone, leading to our hypothesis that the combination of pioglitazone and metformin may be associated with fewer adverse effects. The current study registered in the NIH clinical trial database is not blinded or randomized, thus reducing its quality. However, poor publicity, and the association of the thiazolidinediones with fatal hepatic failure [54], was a deterrent to their use. Furthermore, having three study arms meant that a greater number of patients would need to be recruited into the study, thereby increasing the resources required. Finally, motivating patients to use a combination of drugs for a disease that they do not actually have, with a drug that has been associated with life-threatening adverse effects [54], was unacceptable and ethically unjustifiable. As such, we decided to exclude the combination of thiazolidinedione and biguanide, based on an unacceptable safety benefit ratio when considered for prediabetes.

The development of DPP-IV inhibitors has added to the armamentarium of pharmacological agents available for the treatment of type 2 DM [36]. The efficacy of these drugs in type 2 DM treatment compares favorably to other oral antidiabetic agents [47]. Sitagliptin, an orally administered DPP-IV inhibitor, has been shown to preserve beta cell function [37], thus having the theoretical potential to prevent the progression from prediabetes to type 2 DM. This clinical trial will determine whether the promising results in animal studies will translate to clinical utility.

The combination of sitagliptin and metformin is pharmacologically rational since each drug has a different mode of action and good safety profile [23-27,34,36,40-42,45-47]. This combination will target both insulin resistance and beta cell dysfunction, which are key pathological hallmarks of prediabetes. We postulate that the beneficial effects of this combination on prediabetes will be greater than that of metformin alone. Further rationale for combining metformin with sitagliptin supposes that patients using this combination will have the benefit of proven metformin efficacy [28], and further possible protective effects of sitagliptin. Furthermore, this approach enables us to determine the potential benefit of this untested combination.

Blinding is not always practical, and clinicians can sometimes determine which therapy is which (ie, *break the code)*. Blinding in this study will be accomplished by using metformin in both arms, and having sitagliptin in one arm and a preparation with the appearance of sitagliptin (but without the active ingredient) in the other arm. This tactic will make *breaking the code* more difficult, thereby limiting potential for bias.

This study is designed to include clinically relevant endpoints, and the strength of the study design will facilitate appropriate conclusions. The study is designed to include blinding, intention-to-treat analysis, and randomization in a homogenous population. The study has a sufficient follow-up period and uses clinically relevant parameters to determine the magnitude of the treatment effect (control event rate, experimental event rate, relative risk reduction, absolute risk reduction, and numbers needed to treat). The precision of the estimate of treatment effect will be gauged by the calculation of confidence intervals. Furthermore, the applicability of the results to patients with prediabetes encountered in clinical practice was also considered; in doing so, we considered whether patients in clinical practice would be similar to those in our study, feasibility of treatment in our setting, and potential benefits and harms. Consequently, this study is in keeping with the trend to design clinical trials to ensure conformity to evidence-based medicine.

Conducting this study in a resource-poor setting is challenging. The cost of bringing many experts together and harnessing their skills is high, so we chose to make the study a collaboration in which experts throughout the country would be engaged. The incentives for these experts to join the study are that (1) they will apply their knowledge to answering a clinically relevant study question for not only South Africa and Africa, but the entire world, and (2) they will share authorships in the publications, provided that they make contributions that will make them eligible for coauthorship. Most importantly, we envisage that the multidisciplinary team will improve the quality of the study. Diabetes is a disease that requires a multidisciplinary approach and this study will require the expertise of individuals from diverse fields, including internal medicine, endocrinology, sports science, pharmacology, diabetes, chemical pathology, psychology, and biostatistics. A coordinated team approach will harness individual strengths to help build a team of experts that will propel the study in the face of financial and human resource challenges.

Another challenge of the study is that the interventions in this study may also control glycemia and thus *mask* the biochemical evidence of type 2 DM. One method of overcoming this limitation would entail the use of washout periods at regular intervals. However, this approach would be resource-intensive and inconvenient to study participants, as it would interrupt the routine and may jeopardize compliance. Based on this consideration, we decided to have a single washout period at the end of the study period to determine how many subjects have actually become diabetic.

Evidence favoring the use of LSM and holistic approaches to the treatment of diabetes and prediabetes has inspired us to include LSM in both arms of the study. Furthermore, the proven efficacy of metformin in prediabetes has influenced our decision to include this agent in both of the study arms, thus allowing study participants the full benefit of the best current evidence-based practice. The addition of sitagliptin to the metformin arm attempts to take advantage of the beta cell sparing effects of sitagliptin, and it is hoped that this combination will have greater effects than metformin alone. The exclusion of the thiazolidinedione drugs is based on their poor safety record and the long duration of the study (even relatively mild adverse effects over a protracted period of time may compromise compliance). It was paramount to ensure that study subjects received safe drugs to ensure a favorable safety/risk benefit.

In summary, DM is associated with high morbidity and mortality that places major demands on health care resources. It is important to reduce the incidence of type 2 DM by preventing progression from prediabetes to diabetes. LSM remains the gold standard to prevent progression from prediabetes to diabetes,

but adherence to LSM is challenging, even in the controlled environments of clinical trials. This study investigates the potential of a low dose combination of a biguanide (metformin) and DPP-IV inhibitor (sitagliptin) to prevent progression from prediabetes to type 2 DM. The choice of the aforementioned pharmacological combination is based on good safety profiles for each drug, and their complementary modes of action.

Conflicts of Interest

None declared.

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Abbreviations

BMI: body mass index
CANOE: Canadian Normoglycemia Outcomes Evaluation
DM: diabetes mellitus
DPP-IV: dipeptidyl peptidase-IV
FBG: fasting blood glucose
FBI: fasting blood insulin
GIP: glucose dependent insulinotropic peptide
GLP-1: glucagon-like peptide 1
HbA1c: glycosylated hemoglobin
IGT: impaired glucose tolerance
LFT: liver function tests
LSM: lifestyle modification
NIH: National Institutes of Health
PIPOD: Pioglitazone in Prevention of Diabetes
QOL: quality of life
SD: standard deviation
SiMePreD: Sitagliptin and Metformin in PreDiabetes
TRIPOD: Troglitazone in Prevention of Diabetes

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Original Paper

The Effectiveness Of Social Media (Facebook) Compared With More Traditional Advertising Methods for Recruiting Eligible Participants To Health Research Studies: A Randomized, Controlled Clinical Trial

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Abstract

Background: Recruiting participants for research studies can be difficult and costly. The popularity of social media platforms (eg, Facebook) has seen corresponding growth in the number of researchers turning to social networking sites and their embedded advertising frameworks to locate eligible participants for studies. Compared with traditional recruitment strategies such as print media, social media advertising has been shown to be favorable in terms of its reach (especially with hard-to-reach populations), cost effectiveness, and usability. However, to date, no studies have examined how participants recruited via social media progress through a study compared with those recruited using more traditional recruitment strategies.

Objectives: (1) Examine whether visiting the study website prior to being contacted by researchers creates self-screened participants who are more likely to progress through all study phases (eligible, enrolled, completed); (2) compare conversion percentages and cost effectiveness of each recruitment method at each study phase; and, (3) compare demographic and smoking characteristics of participants recruited through each strategy to determine if they attract similar samples.

Methods: Participants recruited to a smoking cessation clinical trial were grouped by how they had become aware of the study: via social media (Facebook) or traditional media (eg, newspaper, flyers, radio, word of mouth). Groups were compared based on throughput data (conversion percentages and cost) as well as demographic and smoking characteristics.

Results: Visiting the study website did not result in individuals who were more likely to be eligible for (P=.24), enroll in (P=.20), or complete (P=.25) the study. While using social media was more cost effective than traditional methods when we examined earlier endpoints of the recruitment process (cost to obtain a screened respondent: AUD $22.73 vs $29.35; cost to obtain an eligible respondent: $37.56 vs $44.77), it was less cost effective in later endpoints (cost per enrolled participant: $56.34 vs $52.33; cost per completed participant: $103.66 vs $80.43). Participants recruited via social media were more likely to be younger (P=.001) and less confident in their quit attempts (P=.004) compared to those recruited via traditional methods.

Conclusions: Our study suggests that while social media advertising may be effective in generating interest from potential participants, this strategy's ability to attract conscientious recruits is more questionable. Researchers considering using online resources (eg, social media advertising, matrix codes) should consider including prescreening questions to promote conversion percentages. Ultimately, researchers seeking to maximize their recruitment budget should consider using a combination of advertising strategies.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN 12614000329662; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=365947l (Archived by WebCite at http://www.webcitation.org/6jc6zXWZI)

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KEYWORDS

Facebook; recruitment methods; smoking; clinical trial

Introduction

Background

One of the greatest challenges for researchers is recruiting eligible and representative participants to their studies. Traditionally, commonly used recruitment strategies include print media, radio, and informal channels such as word of mouth. More recently, researchers have turned to social media as an additional, or in many cases primary, recruitment strategy [1-3]. Compared with traditional recruitment strategies, social media appears attractive for its potential reach, apparent cost effectiveness, usability, and capacity for targeting hard to reach, isolated, and/or minority populations (eg, people with HIV [4,5], LGBT (lesbian, gay, bisexual, and transgender) populations [6], young women [7-10]). Ultimately, however, the utility of a recruitment strategy is defined by its ability to effectively attract people representative of the target population who are not only willing to participate in the study as per protocol but also to see the study to completion. Despite its popularity, data on social media recruitment's effectiveness compared with more traditional methods is limited [11].

Perceived Advantages of Social Media Advertising

Social media sites are vessels of vast amounts of personal data (based on user profiles) and are therefore extremely attractive to researchers, who can specifically target the audience of their advertisements (eg, users younger than 18 years living within a certain distance of a certain city). Indeed, Facebook and other social media platforms offer specifically generated and embedded advertising frameworks providing researchers more advanced, user-friendly, and data-generating recruitment platforms.

The enormous reach of social media platforms is another advantage of this recruitment strategy, with users all over the world representing a range of demographics. Facebook, for example, is one of the most visited sites on the Internet and the most popular social media site, with more than 1.5 billion monthly active users worldwide [12]. In years past the average Facebook user was a young woman under the age of 30, but there is evidence that the disparity in age and gender among Facebook users is lessening [13].

Another advantage of social media advertising platforms for recruitment is that researchers can exercise greater control over advertising duration and day-to-day expenditure compared to traditional recruitment strategies. Researchers can typically generate an ad, elect where (eg, mobile newsfeed, right-hand ad banners) and to whom it will be shown, predetermine how much they are willing to pay each time someone clicks on the ad, and indicate the overall daily budget they wish to spend on this advertising. Further, researchers can manipulate (eg, turn the ad on and off, increase the amount they are willing to pay per click) how many individuals are exposed to the advertising in near real time, controlling the flow of potential participants. In part because of this flexibility, social media has been suggested by a number of studies to be a cost-effective recruitment strategy [3,14,15] even if more expensive than other more traditional forms of advertising [16-18].

Finally, since people who click on an advertisement are redirected to a study website which may include more specific information about the study, eligibility criteria, full information sheet and/or further screening questions, individuals recruited via social media may be better informed. Our group [18] hypothesized that, by presenting detailed study information to interested individuals before they elect to participate, we attract individuals who are more likely to be eligible when contacted by researchers for screening, resulting in a higher conversion percentage both in terms of study completion and cost per participant. Testing these conversions is one of the main aims of this study.

Potential Disadvantages of Social Media Advertising

In spite of the apparent potential benefits, social media advertising can only be considered a viable recruitment method if it is able to recruit representative samples of the target populations. For example, while social media advertising has been demonstrated to be extremely effective at recruiting participants to health studies specifically targeting young adults [9,14,19], other studies seeking to recruit a broader demographic sample (eg, for smoking cessation trials [18] or obtaining normative data for questionnaire development [20]) reported obtaining samples skewed to the younger demographic when using social media recruitment strategies. This reflects the fact that the average social media user is still at the younger end of the demographic spectrum and as such, may question social media's ability to recruit more general population samples for health research and its overall effectiveness compared with more traditional recruitment strategies.

To date, however, few studies have compared the demographic characteristics of samples collected via social media to those recruited via traditional strategies. In a previous study [18], our group reported that participants recruited via social media were significantly younger than those recruited via traditional media and thus cautioned against solely relying on social media advertising to recruit for studies targeting more diverse population samples. As we noted in the original study, however, this finding needs to be replicated.

Finally, we have previously reported that the cost of participants recruited via social media was almost twice as expensive as

those recruited via traditional recruitment strategies; however, we cautioned that this was not a true indication of cost-effectiveness because other contributing factors could not be accounted for in this calculation (eg, cost of personnel screening participants, conversion percentages of enrolled and completed participants [18]).

This Study

In light of the popularity and reporting of social media advertising for health research, this study aims to replicate our 2014 research [18] by considering whether social media is more cost-effective than traditional strategies in recruiting for health research and whether samples recruited via social media reflect those recruited via traditional avenues. Since the success of a study is not determined by how many participants are recruited but by how many actually comply with study protocol and complete the study, we compare the conversion percentages of participants at each phase of the study (screened, eligible, enrolled, and completed) with how they were recruited. This way, we offer a more detailed interpretation of the effectiveness of social media (Facebook) as a recruitment strategy to health research compared with traditional media (newspaper, radio, flyers, word of mouth). Specifically, we aim to:

Examine whether individuals who visit the study website are more likely, due to self-screening, to be eligible for, enroll in, and complete the study.

Compare conversion percentages and cost effectiveness of individuals recruited through social media with those recruited through traditional media at each study phase (ie, screened, eligible, enrolled, and completed) to determine if either method is more efficacious.

Compare demographic and smoking characteristic data of participants recruited through social media with traditional media to determine if representativeness of the target sample is comparable between recruitment strategies.

Methods

Overview

Data for this study are a subset drawn from a larger study investigating the mechanism through which smoking cessation medications promote abstinence [21]. Results of this randomized, open-label controlled clinical trial will be reported elsewhere. Here we describe the recruitment process and present data on the effectiveness of social media advertising compared with traditional media advertising methods in recruiting a representative sample of interested quitters to a smoking cessation trial.

Target Participants

Participants were adult smokers who reported smoking 10 or more cigarettes per day (CPD) for the past 3 years and indicated no intention to quit within the next month. Participants were excluded if they reported current or recent (within the last 3 months) participation in a smoking cessation program or had existing medical conditions (eg, epilepsy, diabetes, depression) that deemed them unsuitable for treatment using nicotine patches or varenicline. Participants were recruited between September 23, 2014, and November 9, 2015. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0013619).

Recruitment Strategies

A combination of traditional media advertising strategies including newspaper ads, flyers, radio, word of mouth, and paid social media advertising on Facebook were used concurrently to recruit participants to this study. Both newspaper and flyer ads contained brief information about the study including contact details of researchers and a matrix barcode which could be scanned to direct interested people to the study website if they wanted more information. Flyers were distributed at University of Tasmania campuses and surrounding shopping districts.

Multiple Facebook ads were created using a combination of wording and images and were rotated and switched on and off in response to recruitment flow. Facebook ads were set up to target adults (18 years and older) living within 25 kilometers of the recruitment site. Interested individuals who clicked on the Facebook advertisement were automatically redirected to a study website containing a brief description of the study and a link to the study information sheet. Interested individuals were then prompted to enter their contact details, which were automatically forwarded to the study researchers who subsequently contacted these individuals for participation screening. We set social media daily spending targets—typically capped at AUD $30 per day—with advertisements regularly turned on and off over the course of the week in an attempt to reduce advertisement fatigue.

Procedure

The process of recruitment occurred in four phases. Individuals screened were all those who registered interest in the study (eg, via phone, internet, word of mouth) and who were subsequently contacted by the researchers via a telephone call to confirm eligibility. During the screening process, data were collected including how they had heard of the study, whether they had seen the ad themselves or someone had told them about it, and whether they had visited the study website prior to contacting/being contacted by the research team. Screening criteria were then assessed (eg, intention to quit, conflicting medical condition, agreement to use treatment) and person's eligibility determined. Interested individuals were considered *eligible* for the study if they met the eligibility criteria. Individuals were *enrolled* once they had completed an enrollment session and were considered a participant of the study. At enrollment, participants provided baseline demographic and smoking characteristic data before completing subsequent study procedures. Participants had *completed* the study once they had finished the full study protocol, which included study visits over 6 weeks, 4 to 6 weeks of either nicotine patch or varenicline treatment to assist with quitting smoking, and 2 weeks of ecological momentary assessment to track affect/craving/behavior (full details of the trial are reported elsewhere [21]). Thus, data detailing participants who completed the study are presented as retention percentages in the present paper.

Table 1. Screened individuals by recruitment strategy (N=414).

Recruitment strategy		n (%)
Social media	Facebook	228 (55.1)
Traditional media		148 (37.5)
	Newspaper	92 (22.2)
	Word of mouth	33 (8.0)
	Flyer	22 (5.3)
	Internet[a]	4 (1.0)
	Radio	1 (0.2)
	Unknown[a]	34 (8.2)

[a]Internet and Unknown were excluded from further comparisons.

Data Reduction and Analytical Plan

In total, 414 interested individuals were screened for study eligibility. To explore differences between individuals reached by different recruitment methods, screened individuals were grouped by how they had heard of the study (Table 1): Facebook, Internet, newspaper, radio, flyer, and word of mouth.

A total of 34 individuals did not indicate how they had heard of the study, allowing 380 to be categorized by recruitment method. Individuals who reported hearing about the study via flyer, radio, word of mouth, and newspaper were categorized as being reached via traditional media; individuals who heard about the study via Facebook were categorized as being reached via social media. Four individuals indicated becoming aware of the study via the Internet. Because it could not be determined whether this was indeed Facebook or another website, these data were not included in the traditional media versus social media comparisons, thus resulting in a final sample of 376 (with 38 of the original 414 excluded).

To examine the first aim of the study, all individuals screened for eligibility who had visited the website prior to contacting researchers were compared at each phase of the study (eligible, enrolled, and completed) using a series of chi-square tests. Similarly, the number of and cost per participant at each study phase were compared in order to explore conversion percentages and cost effectiveness of social media versus traditional media (Aim 2). Finally, to determine whether participants recruited via social media generally reflected those recruited via traditional media (Aim 3), the demographic (age, gender, income, and education) and smoking characteristics (CPD, motivation and confidence to quit, Heaviness of Smoking Index [HSI], and number of past quit attempts) of each group were compared using independent samples *t* tests and chi-squares.

Results

Objective 1: Comparison of Individuals Visiting the Study Website by Proportion Who Are Eligible for, Enroll in, and Complete the Study

Table 2 compares the proportions of individuals who visited the study website at each phase of the study to those who did not. Those who visited the website prior to contacting the research team were not more likely to be eligible (*P*=.24), be successfully enrolled (*P*=.20), or complete the study *(P*=.25). In addition, we examined the proportion of individuals who visited the study website within each recruitment method. Not surprisingly, fewer participants recruited through traditional media (52/148, 35.5%) reported visiting the study website compared to social media–recruited participants (228, 100%) (*P*<.001).

Table 2. Proportion of recruited interested individuals (n=353) who visited the study website prior to screening.

	Visited website prior to contacting researchers	
	Yes n (%)	No n (%)
Overall (screened)[a]	284 (80.5)	69 (19.5)
Eligible[b]	176 (62.0)	48 (69.6)
Enrolled[b]	128 (45.1)	37 (53.6)
Completed[b]	75 (26.4)	23 (33.3)

[a]n=61 did not report whether they had visited website.

[b]Proportion of overall who had and had not visited the website.

Objective 2: Comparison of Conversion Percentages and Cost Effectiveness of Each Recruitment Method

Table 3 provides a breakdown of proportions of individuals interested in the study by recruitment phase (screened, eligible, enrolled, and completed) and media strategy as well as cost per participant at each of these study phases. Costs associated with Facebook advertising were drawn from the study's Facebook advertising manager matrices and cross-checked with monthly credit card expenditure as charged and invoiced to the study's account. Total cost of Facebook advertising over the course of the study was $5183.13. Traditional media costs comprise 12 individual ads to a local newspaper at $313.80 plus production costs ($288.75) for the two ads, totaling $4343.10. Cost associated with the printing and distribution of flyers was not recorded, and radio interviews were conducted free of charge. As such, the total cost of traditional media advertising reflects only the cost associated with newspaper advertising. Compared with individuals recruited through social media, a greater proportion of those who became aware of the study via traditional media were eligible, enrolled into, and completed the study (Table 3). Furthermore, while social media advertising captured more initial recruits at a lower cost, the cost per participant was less at the enrolled and completed stages for traditional media recruited participants.

Table 3. Cost of participant by recruitment strategy and study phase.

	Social media		Traditional media	
Total cost	AUD $5183.13		AUD $4343.10	
	n (%)	$	n (%)	$
Screened	228 (100)	22.73	148 (100)	29.35
Eligible	138 (60.5)	37.56	97 (65.5)	44.77
Enrolled	92 (40.4)	56.34	83 (56.1)	52.33
Completed	50 (21.9)	103.66	54 (36.5)	80.43

Objective 3: Comparison of Demographic Profile of Enrolled Participants

Significant differences between recruitment groups were found for age and quitting characteristics (Table 4). Participants recruited via social media were more likely to be younger and self-report as less confident in their ability to quit in comparison with those recruited through traditionally media. There were no differences in gender, education, income, CPD, motivation, HSI, or number of past quit attempts.

Table 4. Demographic and smoking characteristics of enrolled participants: traditional media versus social media.

	Overall n=182	Social media n=92	Traditional media n=83	*P* value
Demographics				
Age, years, mean (SD[a])	42.3 (12.0)	39.3 (10.9)	44.9 (12.6)	.01
Gender (female)[b], n (%)	71 (40.8)	43 (46.7)	28 (34.1)	.09
Education[c], n (%)				
High school or less, n (%)	74 (45.4)	39 (45.9)	35 (44.9)	.90
Certificate or trade, n (%)	60 (36.)	34 (40.0)	26 (33.3)	.38
College, n (%)	29 (17.8)	12 (14.1)	17 (21.8)	.20
Income[d], n				
<$21,000	18 (10.9)	6(7.1)	12(15.0)	.10
$21,000-$51,999	38 (23.0)	19 (22.4)	19 (23.8)	.83
$52,000-$77,999	38 (23.0)	24 (28.2)	14 (17.5)	.10
$78,000-$103,999	31 (18.8)	16 (18.8)	15 (18.8)	.99
>$104,000	40 (24.2)	20 (23.5%)	20 (25.0)	.83
Smoking characteristics				
CPD, mean (SD)	18.2 (7.0)	19.1 (8.0)	17.4 (5.8)	.14
Motivation to quit, mean (SD)	89.5 (10.8)	89.2 (8.0)	91.1 (8.8)	.23
Confidence to quit, mean (SD)	72.6 (19.3)	69.2 (19.7)	77.3 (16.4)	<.01
HSI, mean (SD)	3.0 (1.2)	3.2 (1.3)	2.9 (1.2)	.19
Number of past quit attempts, mean (SD)	3.8 (3.9)	4.1 (4.4)	3.3 (2.8)	.14

[a]SD: standard deviation.

[b]n=174 (8 missing).

[c]n=163 (19 missing).

[d]n=165 (17 missing).

Discussion

Principal Findings

The main findings of this study were that visiting the study website did not result in individuals who were more likely to be eligible for, enroll in, or complete the study. While using social media drew more interest and was more cost effective than traditional methods when we examined earlier endpoints of the recruitment process (ie, screened and eligible), it was less cost effective in later endpoints (enrolled and completed). Participants recruited via social media were more likely to be younger and less confident in their quit attempts compared to those recruited via traditional methods. There were no other demographic or smoking characteristic differences between individuals by recruitment strategy.

Although the popularity of social media recruitment for health research is increasing, data (including cost effectiveness and conversion and retention percentages) on this strategy's effectiveness and efficiency compared with more traditional recruitment are limited [11]. Here we address this by reporting on the conversion and retention percentages of participants in a smoking cessation study. Specifically, we examined whether participants recruited via social media are more likely to be eligible, enroll in, and complete the study due to self-screening. The apparent cost effectiveness of social media over traditional media advertising was also examined. Finally, the study compared the demographic characteristics of participants recruited via social media and traditional media.

The first finding of the study was that interested individuals who visited the study website, regardless of the recruitment method, prior to contacting the research team were not more likely to be eligible for participation in our study. As such, using social media advertising like Facebook or including tools such as matrix codes on more traditional recruitment mediums as we did in our study did not appear to promote participant self-screening or study conversion. One explanation for this may be that while interested individuals are automatically directed or self-direct (using the matrix code) to study information via a website, they do not necessarily read the materials and thus effectively self-screen. Researchers contemplating using a study website to boost self-screening should consider incorporating prescreening questions requiring interested people to answer a series of questions correctly (based on the embedded study information) before being allowed to enter their contact details.

Interestingly, while all participants recruited via Facebook in this study were coded as having visited the website prior to contacting researchers (by clicking on the Facebook ads, these individuals were automatically directed to the study website), when asked by the researcher during the screening telephone call whether they had indeed visited the website, only approximately two-thirds (146/228, 64.0%) indicated that they had. This suggests that these participants were not aware of having been directed to the website and had not read the study information. Future studies should explore methods of improving the use of online resources such as prescreening questions prior to allowing interested individuals to enter their contact details to ensure those not eligible are identified as early as possible.

The second finding of our research was that while social media advertising captured more individuals interested in the study, they were not more likely to be eligible, enrolled into, or complete the study compared with those recruited through traditional media. This was surprising given these individuals were automatically directed to the study website where it was assumed they would read some information before providing details to researchers for follow-up screening and enrolment. This result implies that the use of social media does not lead to better informed and potentially self-screened participants compared with traditional media. In terms of cost effectiveness, while social media provided recruits at a lower cost at the screening and eligibility phases of the study, the cost per participant was more at the enrolled and completed phases of the study. Overall, not only did traditional media capture a greater proportion of participants who were eligible, enrolled into, and completed the study, this medium was also more cost effective in the latter two phases of the study. Similar findings were reported by Rait et al [17] who also compared cost and conversion rates of participants recruited to a smoking cessation study. They found that although Facebook attracted higher numbers of interested individuals to the study, Facebook recruitment had a higher ineligibility rate and was less cost effective to enroll participants than using traditional media.

It is possible that social media attracts individuals who click on an ad in the spur of the moment. Facebook advertisements reach their audiences by popping up in user newsfeeds and thus, if interested, the individual has to click on the advertisement there and then or it disappears. As such, social media advertising may attract people who have not otherwise given quitting that much thought but on the spur of the moment decide to enter their details allowing the researchers to contact them (as is the case for traditionally recruited participants who scan the matric code, are directed to website, and if interested, enter their contact details). This is in part supported by our finding that participants recruited through social media advertising were less confident in their ability to quit compared to those recruited through traditional media. Further, interested people who see a newspaper advertisement, hear a radio advertisement, or see a flyer may be more likely to contact the researchers themselves (eg, leave a message on answering machine) and may have put more thought and deliberation into their decision to participate, potentially resulting in a more conscientious participant.

It has also been suggested that social media users are more likely to suffer from mental health conditions [22], and we might expect that respondents via this medium would be more likely to be deemed ineligible for the study (as per study protocol, participants with existing mental health conditions were not eligible to participate), providing some explanation to the differing conversion percentages. However, no differences were found between the participants recruited by social media (44/228, 19.3%) and traditional media (27/148, 18.2%) who indicated having an existing mental health condition.

The third finding of this research was that the demographic profile and smoking characteristics of participants recruited via social media largely mirrored that of those recruited through traditional media. While individuals recruited and enrolled through social media were more likely to be younger and less confident in their quit attempt, no differences were found in other demographic or smoking characteristics. This in part supports the findings of other studies [18,20] which have shown that participants recruited via social media were more likely to be young and female. That this study did not find a significant difference in the proportion of males to females recruited by recruitment strategy supports the trend of social media user profiles increasingly representing a broader demographic. This finding therefore provides optimism for the utility of social media sites like Facebook to recruit more representative samples in the future.

Limitations

While informative, this study is not without limitations. First, while the direct cost of newspaper advertising is known, the actual cost of participants recruited through other traditional means like flyers is unknown. For example, the time spent and associated researcher costs of distributing flyers and screening interested individuals via telephone is unknown. Similarly, researcher time spent (and thus cost) of monitoring and managing Facebook advertising was not recorded but is likely comparable to that of managing recruitment flow of more traditional recruitment strategies. In addition, it is noted that 8% (34/414) of participants did not indicate how they became aware of the study and were not able to be categorized into either social media or traditional media. However, the proportion is relatively small and hence unlikely to influence the results.

This study limited its social media advertising to Facebook, and while this was a deliberate choice because Facebook is the most popular and far-reaching social media site on the Internet, our results may not be as readily generalized to other social media platforms. It is possible although unlikely that other social media platform users may provide more conscientious participants. Furthermore, we only used paid Facebook advertising. Other studies have reported on the efficacy of social media and specifically Facebook as a free advertising and recruitment tool (eg, placing ads on certain social pages or creating a free Facebook page for the study) [23,24]. Researchers considering using social media for health research may like to consider both paid and unpaid methods of advertising to fully exploit the benefits these frameworks offer.

Future Research

As Lane and colleagues [11] state, this study stands alone in its attempts to report on the effectiveness and efficiency, using empirical data as evidence, of social media advertising compared with more traditional means in recruiting participants who will complete the health studies to which we recruit them. As such, the findings we have presented here should be interpreted with regard to the target sample sought (Australian smokers wishing to quit) and advertising methods used. Until other studies provide empirical data (retention and cost conversation rates/percentages) on the effectiveness and efficiency of social media recruitment compared with traditional media recruitment, we encourage health researchers wishing to maximize recruitment to their studies to use a combination of social media and traditional recruitment advertising strategies. However, we also caution that while social media platforms such as Facebook may be effective in recruiting large numbers of participants to a study, these individuals may represent less conscientious participants, resulting in lower conversion rates and more expensive participants compared to traditional media platforms. Future studies should consider including embedded prescreening questions to check if people directed to study websites actually read the information they are assumed to. Future research should also explore the earlier suggestion and implications that participants recruited through social media may have higher rates of mental health issues.

Conclusions

Social media advertising is an effective and user-friendly recruitment strategy for reaching a large sample at a comparatively lower cost than traditional media recruitment strategies. However, researchers must be aware that samples recruited solely through social media may be demographically skewed. In the long term, social media–recruited participants may not be as representative of the target population or as conscientious as participants recruited via traditional media. To our knowledge, this study is the first to report on the efficacy of social media advertising compared with more traditional media recruitment strategies to attract demographic samples who will cost effectively and successfully complete study participation. Until further studies are reported, we would advise researchers to use a combination of recruitment strategies to maximize reach, retention, and target-sample representativeness.

Acknowledgments

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Conflicts of Interest

Dr. Ferguson has worked as a consultant to GlaxoSmithKline Consumer Healthcare and Chrono Therapeutics on matters relating to smoking cessation, received researcher-initiated project grant funding from Pfizer (through the GRAND initiative), and served on an advisory board for Johnson & Johnson. These organizations were not involved in this study in any way.

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Abbreviations

CPD: cigarettes per day
HSI: Heaviness of Smoking Index
SD: standard deviation

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Protocol

A Cluster-Randomized Controlled Trial Evaluating the Effectiveness and Cost-Effectiveness of Tobacco Cessation on Prescription in Swedish Primary Health Care: A Protocol of the Motivation 2 Quit (M2Q) Study

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Abstract

Background: In Sweden, the prevalence of tobacco use is disproportionately high among socioeconomically disadvantaged groups. Previous research and clinical experience suggest that prescribed lifestyle interventions in the primary health care (PHC) setting such as Physical Activity on Prescription are effective in changing behavior. However, there is a lack of evidence for if and how such a prescription approach could be effectively transferred into the tobacco cessation context.

Objective: The aim of this trial is to evaluate the effectiveness and cost-effectiveness of Tobacco Cessation on Prescription (TCP) compared to current practice for tobacco cessation targeting socioeconomically disadvantaged groups in the PHC setting in Sweden.

Methods: The design is a pragmatic cluster-randomized controlled trial. The sample will consist of 928 daily tobacco users with Swedish social security numbers and permanent resident permits, recruited from 14-20 PHC centers located in socioeconomically disadvantaged areas in Stockholm County. The primary outcome will be measured in self-reported 7-day abstinence at 6 and 12 months after the intervention. The secondary outcomes will be measured in daily tobacco consumption, number of quit attempts, and health-related quality of life at 6 and 12 months after the intervention. Data will be collected through questionnaires and review of electronic medical records. Cost-effectiveness will be estimated through decision analytic modeling and measured by the incremental cost per quality-adjusted life year.

Results: In the first set of PHC centers participating in the study, eight centers have been included. Recruitment of individual study participants is currently ongoing. Inclusion of a second set of PHC centers is ongoing with expected study start in September 2016.

Conclusions: If TCP is found effective and cost-effective compared to standard treatment, the method could be implemented to facilitate tobacco cessation for socioeconomically disadvantaged groups in the PHC setting in Sweden.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 11498135; http://www.isrctn.com/ISRCTN11498135 (Archived by WebCite at http://www.webcitation.org/6kTu6giYQ)

(JMIR Res Protoc 2016;5(3):e188) doi:10.2196/resprot.6180

KEYWORDS

tobacco use cessation; primary health care; vulnerable populations; randomized controlled trial; pragmatic clinical trial; cost-effectiveness analysis; Sweden

Introduction

Smoking is a major risk factor for more than 60 different diseases, out of which cardiovascular diseases, lung diseases and cancers are the most common [1]. In Sweden, tobacco use is estimated to cause approximately 12,000 deaths and 100,000 new cases of tobacco-related diseases each year [2], corresponding to 8% of the total disease burden in the country [3]. In addition to the negative effects that tobacco use has on the health and quality of life of the population [4], it is also associated with increased costs for the health care system and for society at large [5]. Currently, 20% of the general adult population in Sweden are daily tobacco users [6]. However, the prevalence of tobacco use is unequally distributed as it is almost twice as high in lower socioeconomic groups compared to higher socioeconomic groups [7].

Since tobacco cessation has been found to reduce the risk of premature morbidity and mortality caused by tobacco-related diseases [8], it is a prioritized area in Swedish public health policy [9]. Treatment guidelines for tobacco cessation in the health care setting have been issued both on the national level in Sweden [1] and the regional level, eg, in Stockholm County [10]. The guidelines recommend that health care providers should offer cessation support to all daily smokers [1]. Although tobacco cessation interventions are one of the most cost-effective interventions available in health care [11], the treatment intensity for tobacco cessation is relatively low in Sweden [12]. In addition, high-risk groups that have an increased need of support are often not reached by such health promoting activities [1]. This could partly be explained by a lower motivation, self-efficacy and social support for quitting, a limited understanding of the harmful effects of tobacco use, and a stronger addiction to tobacco among tobacco users in lower compared to those in higher socioeconomic groups [13]. Other influencing factors include targeted marketing by the tobacco industry and lower adherence to treatment [13]. Moreover, there is a lack of awareness in this target group regarding available treatment options and misconceptions regarding the use and effectiveness of such services [14]. In addition, costs related to seeking and completing treatment for tobacco cessation present particular barriers for socioeconomically disadvantaged tobacco users [14,15]. The need for a more systematic approach and improved access to cessation support for socioeconomically disadvantaged groups has recently been emphasized [16]. There is also a need for more knowledge and training for PHC staff in how to communicate with and empower disadvantaged groups for efficient health promotion [17,18].

Studies conducted on health care consumption in Stockholm in different social groups show that individuals with foreign background, low educational level and low income visit primary health care (PHC) more often than their counterparts [19]. The public has confidence in the health care system [20] and most tobacco users seek care for different health problems at PHC centers. In addition, 87% of patients are positive towards receiving advice on lifestyle changes from health care providers [20]. According to the Swedish Healthcare Act, PHC has the main responsibility for health promotion and disease prevention in the Swedish health care system [21]. Therefore, PHC can be seen as a potential platform to improve the reach of health promoting activities, such as tobacco cessation support, to socioeconomically disadvantaged groups.

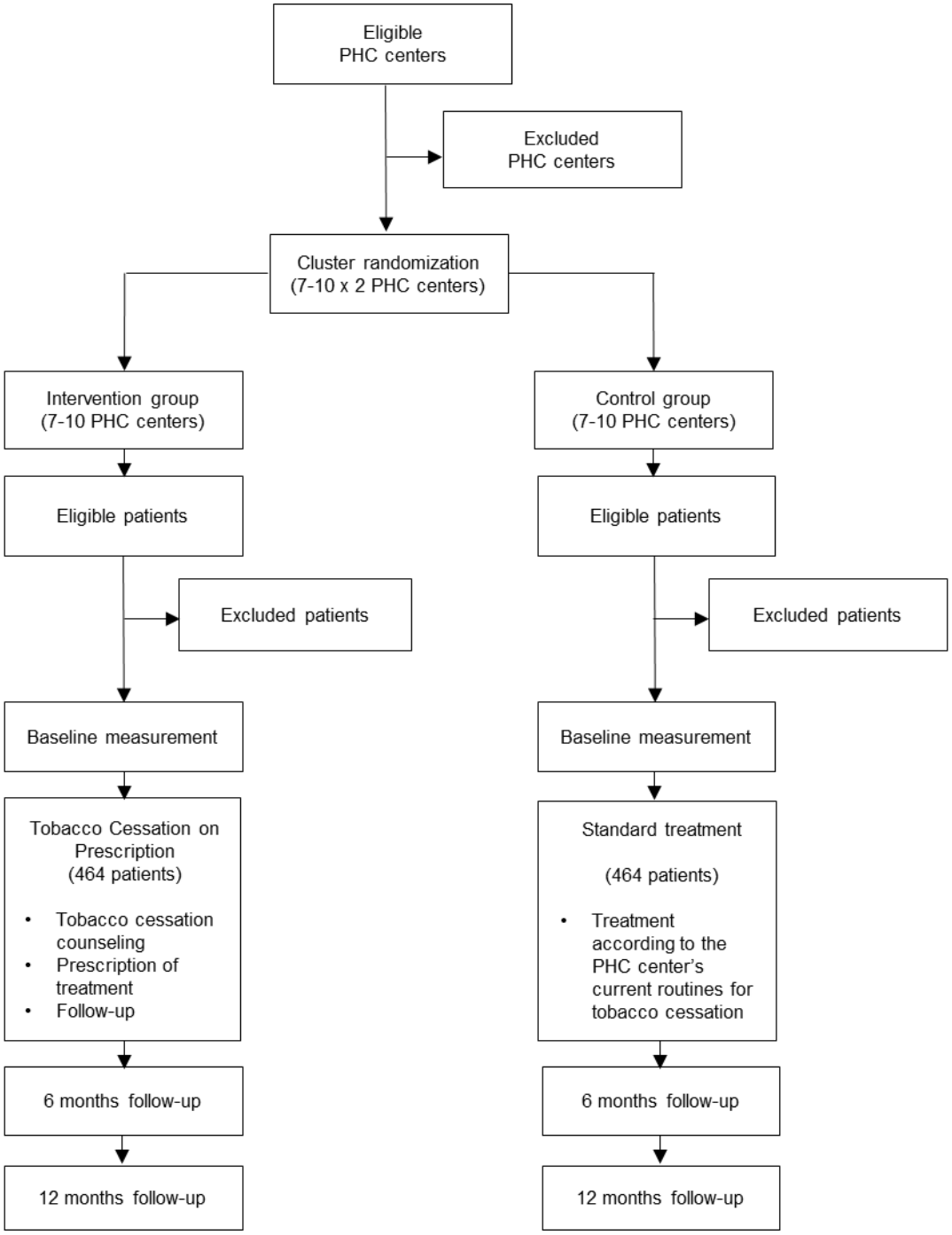
In a recent study, the perceived feasibility and optimal design of Tobacco Cessation on Prescription (TCP) as a PHC intervention targeting disadvantaged groups in Sweden, was explored [22]. The study found that TCP was perceived as a useful tool for tobacco users and health care providers and that it could facilitate a more structured and effective approach to tobacco cessation in the future compared to current tobacco cessation practices in PHC [22]. Based on these findings, there is now a hypothesis that TCP could be implemented and prescribed in a similar manner as Physical Activity on Prescription (PAP). PAP has been found effective in changing behavior and improving health and quality of life and is already in use in the PHC setting in Sweden to prevent disease and promote health in the general population [23]. A prescription approach to tobacco cessation could potentially increase the treatment intensity of tobacco cessation in the PHC setting and thus lead to decreased tobacco use and improved health in the target population. The aim of this study is to evaluate the effectiveness and cost-effectiveness of TCP as PHC intervention targeting socioeconomically disadvantaged groups in Stockholm, Sweden.

Methods

Study Design

In order to evaluate the effectiveness and cost-effectiveness of the intervention, a two-armed pragmatic cluster-randomized controlled trial [24], with an economic evaluation as a component, has been chosen as the study design. In total, 14-20 PHC centers will be randomized to either intervention or control conditions with a 1:1 ratio. Study participants in the control arm will be offered standard treatment, while study participants in the intervention arm will be offered TCP as a complement to current treatment practices for tobacco cessation at the PHC center. Measurement of patient outcomes will be conducted at baseline and 6 and 12 months after the intervention. The trial has been approved by the Regional Ethical Review Board in Stockholm (ref: 2015/207-31, 2015/1226-32). The study details in this protocol are presented according to the SPIRIT 2013 Statement to ensure high quality in reporting [25]. The study design is presented in Figure 1.

Figure 1. Flow chart of the study design.



Study Setting and Participants

Study participants will be recruited from participating PHC centers located in socioeconomically disadvantaged areas in Stockholm County, Sweden. Eligible PHC centers will be identified based on a socioeconomic index, which takes into account the income, educational level, ethnicity and health status of the population in a PHC center's catchment area [26]. Daily tobacco users over 18 years of age with Swedish social security numbers and permanent residence permits, fluent in one of the two most common languages in the study setting, Swedish or Arabic, will be eligible for inclusion in the study. Daily tobacco use will be defined as daily use of cigarettes, snus (smokeless tobacco) or other tobacco products for at least the last year. Ongoing treatment for tobacco cessation and cognitive impairment affecting ability to participate in the study on a voluntary basis will be applied as exclusion criteria.

Sampling and Recruitment

PHC centers located in areas with low socioeconomic status in Stockholm County will be identified through the previously mentioned socioeconomic index [26], purposively sampled by the researchers and invited to participate in the study. The managers at the PHC centers will be contacted via telephone by the researchers and offered further information via email and a physical meeting before agreeing to participate in the study.

Study participants will be recruited by one to three appointed providers employed at each of the participating PHC centers.

However, all staff at the participating PHC centers will be able to refer patients to recruiting staff for more information about the study. In order to reduce selection bias, eligible participants will be identified through a short screening questionnaire before being invited to participate. Further information about the study will be administered by the recruiting staff at the participating PHC centers and written informed consent to participate sought before invited participants will be included in the study. Staff responsible for the recruitment of study participants will receive a brief training in the study design and recruitment procedure before the study start. Recruiting staff will also receive posters to help facilitate the recruitment of individual study participants. The recruitment period is expected to last for 18 to 24 months.

Interventions

Tobacco Cessation on Prescription (Intervention)

The TCP method is based on the PAP concept, which consists of person-centered counseling on physical activity, individualized prescription of physical activity, co-operation between prescribers and providers of physical activity, follow-up of the prescription, and a comprehensive manual that describes for which indications and how the method should be used [27]. In the TCP method, the components in PAP have been adjusted to the tobacco cessation context (see conceptual model in Figure 2 and full description of the core components below). The initial TCP prescription form was drafted by the researchers based on the national guidelines for tobacco cessation treatment in Sweden [1] and the results from the qualitative study that explored the perceived feasibility and optimal design of TCP [22]. The prescription form was then further developed based on an iterative process of feedback from waiting room interviews with patients, as well as workshops and written correspondence with health care providers, researchers and experts on tobacco cessation and lifestyle interventions already available by prescriptions in Sweden. The intervention design was also adjusted based on feedback from PHC providers that pilot tested the TCP method during a 6-week period at a PHC center located in a socioeconomically disadvantaged area in Stockholm.

Prior to the administration of the intervention, one to three PHC providers per center, responsible for the treatment of patients in the intervention group, will receive 4 hours of training by representatives from the Swedish National Tobacco Quitline (SNTQ) [28] and the Stockholm County Council (the regional authority and health care provider) in available treatment options for tobacco cessation and the TCP method. A manual which summarizes the training and describes how the prescription form should be filled out and how it can be used in tobacco cessation counseling, has been developed and will be distributed in connection with the education of PHC providers in the intervention group.

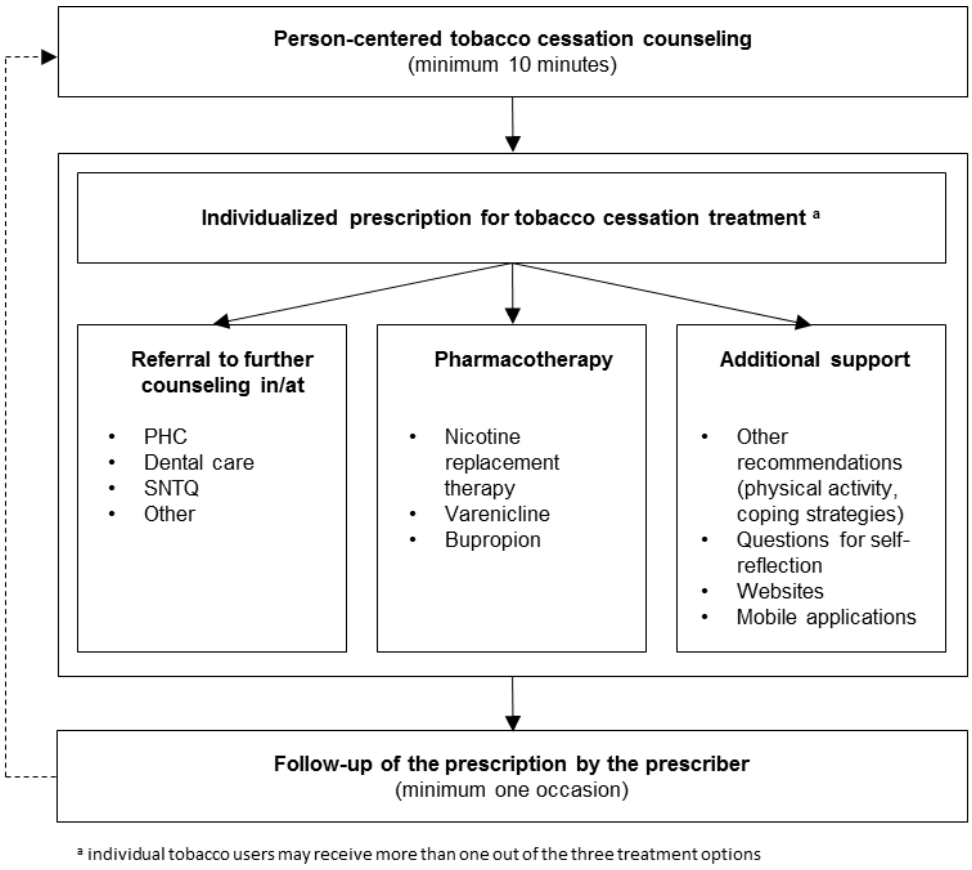
The core components of the intervention consist of tobacco cessation counseling of tobacco users according to the TCP method. This is defined as tobacco cessation counseling (minimum 10 minutes) provided by a qualified health care professional in combination with a prescription for individualized tobacco cessation treatment, including options for (1) further counseling (referral to a health care provider with more competence or SNTQ), (2) pharmacotherapy (nicotine replacement therapy, varenicline, bupropion), (3) other measures for tobacco cessation (physical activity and other strategies to cope with withdrawal symptoms), (4) follow-up (by telephone or revisit) and (5) support for self-management (questions for self-reflection, reference to mobile applications, Web-based counseling and websites for more information and support). The approach will be individualized in the sense that providers will discuss the available treatment options, contraindications, preferences, and other relevant circumstances with the patient and then decide together which treatment alternative(s) suit the individual best. The TCP method also includes follow-up of the prescription by the prescriber on at least one occasion.

Standard Treatment (Control)

Standard treatment is defined as treatment for tobacco cessation according to current practices at the PHC center. Since the choice of tobacco cessation treatment varies depending on individual characteristics and preferences of tobacco users and it is up to each PHC center to decide for themselves how their tobacco cessation services should be organized, the treatment components (eg, type of counseling and pharmacotherapy) are expected to vary both within and between the study arms. Thus, the provided treatments will be documented by one to three PHC providers per center in the control group responsible for the treatment of study participants and further defined retrospectively. Since the same treatment components are likely to be present in both study arms, it is important to state that the major difference between them is how the counseling is administered (with or without a prescription form). The minimum intervention for the control group is a brief advice (<5 minutes).

To ensure that the difference between the trial conditions is dependent on the prescription form and not on the training of PHC staff, the PHC providers responsible for the treatment of patients in the control group will receive 3.5 hours of training by representatives from SNTQ and the County Council in available treatment options for tobacco cessation prior to the study start (the same training as the intervention group, excluding the 30 minute TCP component). A manual identical to the one developed for the intervention group, excluding all information about the TCP method and summarizing the training, has been developed and will be distributed in connection with the education of PHC providers in the control group.

Figure 2. Conceptual model for TCP.



Outcomes

The primary outcome of the intervention will be measured in self-reported point prevalence of 7-day abstinence (total abstinence from tobacco use during the 7 days preceding follow-up) at 6 months after the intervention. The secondary outcomes are self-reported point prevalence of 7-day abstinence at 12 months after the intervention and 3-month continued abstinence, daily tobacco consumption (number of cigarettes), number of quit attempts (periods of total abstinence from tobacco use for more than 24 hours) and health-related quality of life (on a scale from 0-1 where 0 represents death and 1 represents perfect health) at 6 and 12 months after the intervention. All outcomes will be based on patients' self-reports. Cost-effectiveness will be measured as the incremental cost per quality-adjusted life year.

Data Collection

Data on sociodemographic characteristics, tobacco use, and nicotine dependence, previous quit attempts, self-efficacy and motivation to quit, health status and health-related quality of life will be collected through patient questionnaires. The questionnaires are based on questions from the Swedish Public Health Survey 2014 [29], a questionnaire that was used in a previous study that evaluated the effectiveness of brief advice for tobacco cessation in dental practices in Sweden [30] and the Swedish and Arabic (Lebanon) version of the EQ-5D-5L instrument [31]. Questions not included in the EQ-5D-5L questionnaire were translated from Swedish to Arabic and back by two different professional translation agencies and critically reviewed by a research assistant fluent in both Swedish and Arabic. The questionnaires were pilot tested in Swedish prior to the study start and in Arabic prior to the recruitment of Arabic speaking participants.

The measurements will be conducted at baseline (before the intervention) and 6 and 12 months after the intervention. In the follow-up questionnaires, questions regarding the tobacco cessation-related care the patients have received during the study period have been added. The baseline questionnaires will be administered by staff responsible for the treatment of patients at the participating PHC centers. The PHC providers administering the treatment will also document what treatment the patients have received (duration, content, intensity and number of visits, mode of counseling, referrals, any recommended and prescribed pharmacotherapy, follow-ups, etc) in the electronic medical records and in study specific documentation protocols. Staff will be educated in the documentation procedures before the start of the study. The follow-up questionnaires will be sent to the participants via mail by the researchers to avoid attrition caused by additional costs and administrative burden of revisits for the study participants. A reminder with a new follow-up questionnaire attached will be sent out via mail by the researchers if the follow-up questionnaire is not returned within ten days. If the reminder questionnaire is not returned, additional reminders to return the questionnaire will be sent out via mail, email and SMS text messaging (short message service, SMS) by the researchers. In connection with the second reminder, the participants will be offered the opportunity to answer the questionnaire in a telephone interview. Multiple reminders and forms of contact

have been found essential in promoting high retention rates among disadvantaged research participants who are often highly mobile [32]. The strategy above is expected to be sufficient in reaching study participants who are willing to respond to the follow-up questionnaires. Arabic speaking staff will assist the researchers in contacting and collecting data from the Arabic speaking participants.

Additional data on the characteristics of participating PHC centers and providers delivering the intervention will be collected through questionnaires and interviews. This includes data on organizational aspects such as number of listed patients, number of employees, and type of professions and routines for tobacco cessation at the PHC center level and data on age, sex, profession, qualifications, and personal experiences of tobacco use and tobacco cessation at the PHC provider level. Data on structural changes in the PHC centers during the study period (eg, staff turnover) will also be collected retrospectively. This data will be collected by the researchers.

Sample Size

The required sample size was calculated based on the primary outcome, assuming a 7% rate of 7-day prevalence in abstinence from tobacco use at 6 months follow-up in the control group, significance level of 5% and 80% power to detect a 2.0 relative risk of successful quit attempts in the intervention group compared to the control group. The estimated prevalence of abstinence in the control group corresponds to the success rate of brief advice [33] which is the minimum intervention for the control group in this study. The estimated relative risk corresponds to the relative risk of abstinence from tobacco use for combined pharmacotherapy and counseling, as recommended for the intervention group in this study, compared to minimal intervention or usual care [34]. The unadjusted sample size was found to be 300 per arm. Assuming an intra-cluster coefficient (ICC) of 0.01 according to Adams et al [35] the sample size was adjusted for design effect using the formula: $1 + (m - 1)\rho$, where m represents the mean number of participants in each cluster and ρ is the ICC. Having 7 clusters per arm and 43 participants per cluster, the adjusted sample size will be 426 per arm. Finally adjusted for an attrition/drop-out of 8%, the final sample size will be 464 per arm or 928 in total. The estimated attrition rate of 8% is based on reported attrition rates from two other tobacco cessation trials with similar study designs, both conducted in the Swedish health care setting [30,36]. A higher number of participating PHC centers could decrease the required number of study participants without compromising the power to detect a statistically significant difference in the outcomes between the groups at follow-up, wherefore the aim is to recruit a total of 20 PHC centers. A total sample size of 840 would then be needed.

Randomization

A computer generated random allocation sequence will be applied to randomize the PHC centers to either intervention or control conditions with a 1:1 ratio. Cluster-randomization will be employed at the PHC center level, meaning that all individual study participants recruited from a particular PHC center will receive the same treatment. This will be done due to feasibility reasons and to avoid contamination of the trial conditions. The PHC centers will be paired based on their socioeconomic index and allocated to the treatment conditions from each pair after they have agreed to participate, approximately one month before the PHC provider training. Each set of participating PHC centers will be randomized separately. The randomizations will be conducted by a statistician.

The PHC providers and study participants will not be blinded. However, the study participants will not be informed about the difference between the trial conditions until after the study. This will be done in order to avoid attrition and preconceptions regarding the treatment effectiveness that could affect the study results (risk that study participants in the control group could perceive standard treatment as less effective compared to TCP).

Statistical Analysis

In order to describe the setting and the effectiveness of the randomization, descriptive statistics of the study population's baseline characteristics at both individual and cluster level will be presented separately for the intervention and control arm, as proportions for categorical variables and as mean values with corresponding standard deviation (SD) for continuous variables.

The association between the treatment and the outcomes post-intervention will be analyzed using multiple regression models. A logistic regression model will be used for binary outcomes, including the primary outcome, 7-day abstinence. The result will be presented as an odds ratio (OR) and corresponding 95% confidence interval (CI). The association between the treatment and continuous/count outcomes, including the secondary outcomes, daily tobacco consumption, number of quit attempts and health-related quality of life, will be analyzed using multiple linear and Poisson regression models. All analyses will be conducted according to the intention to treat principle [37], meaning that the individual study participants will be analyzed according to how the PHC centers where they were recruited and treated were randomized, regardless of which intervention they received. Inference will be targeted at the individual level and hierarchical models will be used to handle potential clustering on the PHC center level. Model covariates will include age, sex, educational level, nicotine dependence, motivation and readiness to quit, previous quit attempts, previous use of pharmacotherapy, and diagnosis of chronic disease. For main analysis no missing data will be imputed. However, classical multiple imputation methods will be used for an additional sensitivity analysis if any of the included variables have more than 5% missing observations. The analyses will be conducted by the research team, including a statistician.

Process Evaluation

A process evaluation will be conducted to measure implementation outcomes such as service delivery of tobacco cessation at the PHC center level and self-reported fidelity to the intervention at the PHC provider level and the participant level [38]. Data will be collected through review of electronic medical records, PHC provider documentation protocols and patient questionnaires. Semi-structured interviews with PHC providers and tobacco users will also be conducted and qualitatively analyzed with content analysis to explore the

acceptability, appropriateness, adoption [38], and general experiences of TCP.

Economic Evaluation

A health economic evaluation will be conducted alongside the trial to evaluate the cost-effectiveness of the intervention compared to standard treatment. This will be done by incorporating the trial results on effectiveness and data from other sources into a decision analytic model specifically developed to estimate the future costs and outcomes of tobacco cessation interventions. Decision analytic models are often used in health economic evaluations since they allow for synthesis of data from different sources and extrapolation of events beyond a clinical trial [39]. The analysis will be conducted from a societal perspective with a lifetime horizon where the incremental cost-effectiveness ratio (difference in cost, divided by the difference in effectiveness between the treatment alternatives), is defined as the additional cost in Swedish Krona (SEK) per quality-adjusted life year. Cost (resource use) and epidemiological data will be collected from the trial as well as from registers, reports, and previously published scientific articles. Cost data will include indirect costs of production loss and direct health care costs of PHC staff, pharmacotherapy, and other resources used in the delivery of tobacco cessation treatments and overhead costs in both study arms throughout the entire study period. Future health care costs will be calculated as average annual costs of health states included in the evaluation. Epidemiological data will include population data on life expectancy and relative risk of tobacco related diseases among tobacco users and former tobacco users. The evaluation, including discounting, sensitivity analysis, and reporting will be conducted based on best practice guidelines for health economic evaluations in Sweden [40].

Results

From April to November 2015, eight PHC centers were recruited and randomly assigned to the trial conditions. The PHC providers responsible for the treatment of study participants were trained in February and April 2016. Recruitment of individual study participants is currently ongoing. Recruitment of a second set of PHC centers is also ongoing. The expected study start of the second set of PHC centers is in September 2016.

Discussion

This study aims to evaluate the effectiveness and cost-effectiveness of a novel intervention that builds on previous research and experiences of prescribed lifestyle interventions in the PHC setting in Sweden that could potentially facilitate a more structured approach to tobacco cessation for socioeconomically disadvantaged groups compared to current practice. The method is based on clinical guidelines for tobacco cessation treatment in the Swedish health care setting [1] and has been developed in close collaboration with a variety of relevant stakeholders including the target population [32]. Stakeholders that have been involved in this process include researchers and experts on tobacco cessation and lifestyle interventions on prescription in Sweden (researchers experienced in intervention research, tobacco control and PAP, as well as representatives from the Swedish Professional Agency Against Tobacco and SNTQ), PHC providers (mainly nurses and physicians but also dieticians and occupational therapists) and tobacco users of various ages and sexes from PHC centers located in socioeconomically disadvantaged areas in Stockholm. Since community involvement in intervention design has been found to have positive effects on the uptake of an intervention [32], this is expected to have a positive effect on the effectiveness and acceptability of TCP. Results from the previously mentioned study that explored the perceived feasibility and optimal design of TCP suggest that there is support for the method [22].

A key concern when conducting the study is reaching the intended target population. For example, language barriers may limit the access to the most disadvantaged groups. However, the two most common languages in the target population, Swedish and Arabic, are considered in the study. It is important that the participating PHC centers have access to interpretation services, or staff fluent in these languages, and that the materials are available in both languages to enable recruitment of participants and delivery of the intervention as intended [32]. It is also important to consider that not all tobacco users who visit PHC centers located in socioeconomically disadvantaged areas have a low socioeconomic status. However, recruitment of patients to health interventions has been found much more effective in the PHC setting in socioeconomically disadvantaged areas compared to community approaches [41]. For feasibility and ethical reasons, a common research approach is to focus on socioeconomically disadvantaged areas rather than individuals when recruiting such populations. Since the intended target population may be difficult for outsiders of the community to reach [32], PHC staff will be responsible for recruitment of individual study participants. As in other studies conducted on disadvantaged populations, the participants will receive a gift certificate worth 100 SEK to promote their partaking in the research and increase retention rates [32]. In order to describe the study population and assess whether it is representative for the intended target population, data on socioeconomic status will be collected on the individual level at baseline.

A possible limitation of the study is due to self-reported tobacco-related outcomes. The accuracy of self-reported tobacco use tends to be lower compared to biochemical markers such as cotinine measurements and may lead to underestimates of tobacco use due to underreporting as a consequence of social desirability [42]. However, self-reported tobacco use is a common research approach and was chosen in this study due to budget restrictions and feasibility reasons. In addition to higher costs for equipment and training, cotinine measurement would require two more compulsory revisits per study participant which could compromise the retention rate due to an increase in administrative burden and costs for the study participants who have to pay out-of-pocket for their visits. This is expected to have a particularly negative impact on the retention of the participants in this study as they are recruited from socioeconomically disadvantaged areas. Cotinine measurements are also expected to decrease the willingness among PHC to participate due to the increased administrative

burden of additional compulsory revisits. However, a correction factor may be used to adjust for underreporting which is expected to be lower than 10% [42].

Another potential limitation is that the education of PHC providers is relatively brief (4 hours). However, data collected at the PHC center level prior to the study start showed that the majority of the PHC providers responsible for the treatment of patients had previous training in tobacco cessation treatment, motivational interviewing or lifestyle counseling. Given this fact, the length of the education was considered sufficient by the participating PHC centers and the representatives from SNTQ and the County Council that were involved in designing the training of the PHC providers in the study.

A major strength of the study is the robustness of its design. The pragmatic approach will provide high external validity under real world conditions in the context under study [24] and lead to useful results for policy making and health systems development. Furthermore, the inclusion of data on cost-effectiveness will facilitate policy decisions on wider use of the program [24,39]. Another strength of the study is that it focuses on socioeconomically disadvantaged groups who have a greater need for tobacco cessation support due to the higher prevalence of tobacco use and difficulties in reaching this target group with health promoting interventions compared to groups with higher socioeconomic status. To the authors' knowledge, this is the first study to evaluate the effectiveness and cost-effectiveness of tobacco cessation services targeting socioeconomically disadvantaged groups in the PHC setting in Sweden. The study is expected to offer valuable insights regarding how such services are currently organized. If TCP is proven to be effective and cost-effective, it will be a valuable tool for tobacco prevention that can be readily implemented to promote health among socioeconomically disadvantaged populations in the PHC setting in Sweden.

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Authors' Contributions

TT conceived the study and led procurement of funding assisted by AL. AL drafted study protocol supervised by TT with assistance by PL, CJS and MP. The latter provided statistical expertise. AL wrote first draft of study protocol manuscript, all provided input. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

PAP: Physical Activity on Prescription
PHC: primary health care
SNTQ: Swedish National Tobacco Quitline
TCP: Tobacco Cessation on Prescription

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Proposal

Using Competency-Based Digital Open Learning Activities to Facilitate and Promote Health Professions Education (OLAmeD): A Proposal

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Abstract

Background: Traditional learning in medical education has been transformed with the advent of information technology. We have recently seen global initiatives to produce online activities in an effort to scale up learning opportunities through learning management systems and massive open online courses for both undergraduate and continued professional education. Despite the positive impact of such efforts, factors such as cost, time, resources, and the specificity of educational contexts restrict the design and exchange of online medical educational activities.

Objective: The goal is to address the stated issues within the health professions education context while promoting learning by proposing the Online Learning Activities for Medical Education (OLAmeD) concept which builds on unified competency frameworks and generic technical standards for education.

Methods: We outline how frameworks used to describe a set of competencies for a specific topic in medical education across medical schools in the United States and Europe can be compared to identify commonalities that could result in a unified set of competencies representing both contexts adequately. Further, we examine how technical standards could be used to allow standardization, seamless sharing, and reusability of educational content.

Results: The entire process of developing and sharing OLAmeD is structured and presented in a set of steps using as example Urology as a part of clinical surgery specialization.

Conclusions: Beyond supporting the development, sharing, and repurposing of educational content, we expect OLAmeD to work as a tool that promotes learning and sets a base for a community of medical educational content developers across different educational contexts.

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KEYWORDS

medical education; competency frameworks; technical standards; open learning activities; massive open online courses; learning management systems

Introduction

In the past 20 years there has been a growing momentum among higher education institutions to take part in the provision of open educational resources, or teaching, learning, and research resources that reside in the public domain or have been released under an intellectual property license that permits their free use or repurposing by others [1,2]. The recent massive open online courses (MOOC) initiatives have provided insights into how such open material may be scaled up to reach a large number of users. Other initiatives such as the open educational resources programs in the United Kingdom and the IMS global learning consortium [3] have enabled the design and development of teaching and learning resources to be made freely available worldwide ‘’using copyright licenses that promote their use, reuse, and repurposing’’ [1,4]. This process has run concurrently with the emergence of digital learning making substantial advances in medical education [5]. Furthermore, the development and sharing of digital educational and training material has the potential to offer more economically viable options [6]. Most recently and perhaps most notably, the emergence of MOOC platforms has enabled open educational resources that can reach massive numbers of students enabling engagement in learning across professional, social, and geographical borders. This, we believe, also has the potential to foster and scale up medical education by addressing some of the current challenges identified by Mehta et al [7] such as test grades that reflect students’ test performance without verifying the acquired skills and attributes that build the desired competencies [8]. However, one of the challenges to useful open educational resources is the lack of a shared language or sense of purpose between professionals; in addition, material developed in one context may not be readily useful in another [9].

From the instructor's perspective, developing digital learning material usually involves numerous challenges such as cost, time, and resources restrictions [6,10]. Furthermore, the outreach may be limited or local [11], and the variety of learning management systems (LMSs), defined as enterprise-wide and Internet-based systems that integrate a wide range of pedagogical and course administration tools [12]; educational platforms; and technological infrastructures limits reusability, which could reduce the cost of developing the same material at various places in the world and the time spent on lecturing [13]. Technical standards, online content sharing, and content metadata exploitation have partially addressed these challenges [14-17]. It is clear that there is interest in supporting the community in the design process of online educational material for MOOCs and LMSs [18], and the medical education community could benefit from this as well. However, to the best of our knowledge there has been no initiative yet for supporting, exchanging, and displaying this material holistically with a solution that could readily be adopted to address all the stated challenges.

In this proposal we present an idea for how medical education institutions can (1) identify commonalities across competency frameworks, or organized and structured representations of a set of interrelated and purposeful competencies [19]; (2) design open learning activities based on common, identified competencies; and (3) utilize generic technical standards to provide health care professionals with the opportunity to develop and share material in health care professions education.

We propose the development of competency-based digital open learning material, here called OLAmeD (Open Learning Activities for Medical Education). OLAmeD would allow faculty to develop material that could be used in multiple medical education contexts and would be fully functional, either as stand-alone learning modules integrated into a MOOC or as part of an LMS. We expect that OLAmeD, when developed using common competencies and generic technical standards, will promote student learning and support instructors in the process of material production that can be used across borders. With that in place, we believe the incentive to use and reuse material is likely to increase. The use of generic technical standards will give faculty and researchers an opportunity to perform and evaluate interventions on a scale not formerly associated with learning design [6]. Additionally, the development of OLAmeD could promote sharing and professional networking, where the disciplinary community begins to develop OLAmeD in the local context but for global spread, enabling new opportunities for collaboration within disciplines across competency frameworks. The development of OLAmeD will be based on two equally important pillars: identifying commonalities across competency frameworks and using generic technical standards that allow for sharing and reusability.

Methods

Identifying Commonalities Across Competency Frameworks

As a first approach, we believe that the comparison of two different competency frameworks, one in the US and one in Europe, which are used to address a common specialization in an undergraduate medical education program, could place us in a position to decide the feasibility of identifying generic outcomes that could be used as the first pillar of OLAmeD.

A first step would compare in a small scale pilot competency frameworks for outcomes used to teach urology as a part of clinical surgery specialization. Our hope is to identify commonalities between competency frameworks that will allow us to identify common outcomes that are applicable across competency frameworks and also to examine the potential to scale up from this initial pilot context to a number of competency frameworks. The urology competency frameworks from two medical schools, one in the United States and one in Europe, have already been mapped and one of the goals we identified to be applicable across both urology frameworks was “Students should have knowledge about the management and treatment of urogenital tumor diseases.” For the comparison between competency frameworks, we will use technical standards developed by the Medbiquitous Consortium [20]. Medbiquitous standards are accredited by the American National Standards Institute and have been implemented by the Association of American Medical Colleges; they are open source and constantly updated to facilitate and advance the health

professions education. This provides an integrated approach to expressing, comparing, and verifying the consistency of competencies used through the different standards. We suggest using the Curriculum Inventory standard [21], which is "intended to facilitate the exchange and aggregation of data about health professions curriculum across the continuum of professional education and training" and the Competency Framework standard [22], which "enables users to search for resources addressing a specific competency and determine where competencies are addressed in the curriculum." We expect to enable comparisons that will eventually promote decisions and actions concerning the potential to identify and target common outcomes.

Identifying Technical Standards to Allow Reusability and Sharing

To introduce the sharing and reusability of OLAmeD and its integration into different educational platforms, it is essential that OLAmeD includes technically standardized learning activities and content descriptions. For this purpose we see potential in identifying standards that allow the learning content to be organized and distributed with seamless connection of the OLAmeD with different LMS and MOOC platforms, a secure data flow between OLAmeD and other learning environments on predefined standard data elements, and a single sign-on mechanism [14-17]. Further, the identified standards would provide insights into user experiences and record their activities to enable the development and incorporation of metadata that will fully outline OLAmeD.

Practical Steps Involved in Developing OLAmeD

To summarize the process of developing OLAmeD, we suggest the following steps. First, it would be vital to identify commonalities in competencies from a broad range of curricula (frameworks). As a second step and in order to design a specific learning activity based on the common identified set of competencies it would be necessary to define the learning outcome and choose content, design the digital learning activity that promotes the selected competencies, digitize the learning activity using generic technical standards, and tag the digital learning activity with metadata. In the final step the digital learning activity is ready to be promoted and shared locally and internationally in subject or professional networks.

Results

Following is a hypothetical case reflecting the expected results and workflow when developing OLAmeD with the above steps. We exemplify using urology as a part of clinical surgery specialization where in the first step we compare urology competency frameworks of curricula in the United States and Europe to identify commonalities. In the second step we design the learning activity based on the common set of competencies where we (1) select the content for the common learning outcome, "Students should have knowledge about the management and treatment of urogenital tumor diseases;" (2) design the digital learning activity using the selected content; (3) digitize the learning activity with a selected technical standard; and (4) tag the digital learning activity with metadata elements that adequately describe it (eg, activity title, activity summary, type of activity, duration, and competency addressed). Finally, we promote and share locally and internationally through established online repositories for OLAmeD exchange.

Discussion

Today we have the ability to examine medical education curricula and identify overlapping competencies that could be targeted when developing digital learning material. We also have the ability to utilize common technical standards which allow educators to extend the reach of these open learning activities of high quality educational material and make them readily available to multiple users around the globe. These generic technical standards also allow us to monitor student learning and gain insights into the key aspects of learning in medical education. The effort to develop OLAmeD is a worthwhile endeavor if there is a possibility to reach a much broader community of learners and if teachers gain from using learning material produced by others. Current use of existing educational technologies and interoperability standards individually within the context of an institution or organization promotes local development and exploitation but a more collective use is missing. We believe that OLAmeD will add to the current use of educational technology, interoperability standards, and open educational resources because it has the potential to support the efforts of development, sharing, and repurposing of online learning activities and content in medical education and sets a strong base for synergies among collaborating institutions. Additionally, we consider OLAmeD to be an important method for faculty to identify opportunities to develop learning activities for a broader community of learners and potentially engage in a community of faculty education material developers.

Conflicts of Interest

None declared.

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Abbreviations

LMS: learning management system
MOOC: massive open online course
OLAmeD: Open Learning Activities for Medical Education

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Protocol

Telemedicine Versus Standard Follow-Up Care for Diabetes-Related Foot Ulcers: Protocol for a Cluster Randomized Controlled Noninferiority Trial (DiaFOTo)

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Abstract

Background: This paper presents the protocol for an ongoing study to evaluate a telemedicine follow-up intervention for patients with diabetes-related foot ulcers. Diabetes-related foot ulcers represent challenges for patients and the health services. The large increase in the prevalence of diabetes, combined with the aging population, means that the absolute number of patients with diabetes-related foot ulcers is likely to continue to increase. Health care services therefore need to provide close clinical follow-up care for people with diabetes both in primary and specialist care. Information and communication technologies may enable more integrated treatment and care pathways across organizational boundaries. However, we lack knowledge about the effect of telemedicine follow-up and how such services can be optimally organized.

Objective: To present the design and methods of a study evaluating a telemedicine follow-up intervention for patients with diabetes-related foot ulcers.

Methods: The study is designed as a cluster randomized controlled trial (noninferiority trial) involving municipalities or municipality districts (clusters) belonging to one clinical site in Western Norway. The study includes patients with type 1 and type 2 diabetes presenting with a new foot ulcer at the initial visit to the clinic. Patients in the intervention group receive telemedicine follow-up care in the community. The key ingredient in the intervention is the close integration between health care levels. The intervention is facilitated by the use of an interactive wound platform consisting of a Web-based ulcer record combined with a mobile phone, enabling counseling and communication between nurses in the community and specialist health care. Patients in the control group receive standard hospital outpatient care. The primary endpoint in the trial is healing time; secondary outcomes include amputation and death, patient-reported outcome measures, and follow-up data on the recurrence of foot ulcers. In addition, qualitative substudies are being performed to provide a more comprehensive evaluation of the ongoing processes during the trial

with the patients in the intervention and control groups and those health care professionals either working in primary care or in specialist care delivering the intervention.

Results: The project has been funded. The inclusion of patients started in September 2012. Because recruitment goals were not met in the initial period, two more clinical sites have been included to meet sample size requirements. Patient recruitment will continue until June 2016. Data collection in the qualitative substudies has been completed.

Conclusions: This telemedicine trial operates in a novel setting and targets patients with diabetes-related foot ulcers during a 12-month follow-up period. The trial addresses whether integrated care using telemedicine between primary and specialist health care can be an equivalent alternative to standard outpatient care.

Trial Registration: ClinicalTrials.gov NCT01710774; https://clinicaltrials.gov/ct2/show/NCT01710774 (Archived by WebCite at http://www.webcitation.org/6im6KfFov).

(JMIR Res Protoc 2016;5(3):e148) doi:10.2196/resprot.5646

KEYWORDS

diabetes; diabetic foot; foot ulcer; telemedicine; randomized controlled trial; primary care; delivery of health care, integrated; complex intervention; patient-reported outcomes; Norway; cluster RCT

Introduction

Background

The prevalence of diabetes is expected to increase both in Norway and globally [1]. In Norway, about 200,000 people have been diagnosed with diabetes [2] with an annual increase of 8000 to 10,000 forecast. In addition, an estimated 150,000 people have undiagnosed type 2 diabetes [2,3]. The increasing prevalence of diabetes, especially type 2 diabetes, combined with an increasing proportion of older people in the population present great challenges for the health care services [2,4,5]. An epidemiologic study of diabetes-related foot ulcers among community-dwelling adults and older people based on data from the Nord-Trøndelag Health Study (HUNT2) showed that a history of foot ulcer was significantly associated with increased mortality and that about 10% of people with diabetes reported a history of foot ulcer [6-8]. Other studies have shown that a foot ulcer is associated with reduced quality of life, social limitations, and pain [9]. The cost of treating foot ulcers is also considerable [10]. It is therefore important to start treatment early and have a close, well-organized follow-up for patients with diabetes-related foot ulcers to improve the management of the diabetic foot [11].

State of the Evidence, Relevance, and Innovation Potential

The main goal for the Norwegian Coordination Reform in the health care sector in January 2012 was to obtain coordinated and integrated health care for patients, especially for those with complex conditions [12]. In this reform, electronic communication and use of telemedicine is emphasized. Qualitative studies of diabetes-related foot ulcers [13-15] have shown that using telemedicine can result in follow-up care of similar quality to standard outpatient care while at the same time enabling more flexible organization and greater patient satisfaction. Patients with diabetes foot ulcers are prone to adverse outcomes because of rapid deterioration of the ulcer or the onset of infection. To date, randomized controlled studies have not confirmed that telemedicine follow-up care for patients with diabetes-related foot ulcers results in equivalent healing time when compared with standard outpatient care in specialist health care [16,17]. Therefore, there is a need for such studies to document the safety and effectiveness of a telemedicine-based follow-up. This project is expected to increase the focus on research related to integrated care [3,12].

This paper presents the protocol for an ongoing cluster randomized controlled noninferiority trial, DiaFOTo (Diabetic Foot and Telemedical Images Project). The trial is designed to compare the effect of telemedicine follow-up in primary care to standard hospital outpatient care on ulcer healing time. In addition, qualitative data were collected to evaluate ongoing processes and further elaborate the experiences of patients and health care professionals during the intervention period. These qualitative studies are part of a larger program supported by the Norwegian Research Council (DiaHEALTH-221065/F40) to promote patient and professional competencies in diabetes care and management.

Aims and Research Questions

The main aim of this trial is to evaluate whether follow-up of patients with diabetes-related foot ulcers in primary care, in collaboration with hospital outpatient specialist care, is noninferior to standard outpatient care in terms of ulcer healing time.

Our primary research question is whether healing time (within 12 months) of diabetes-related foot ulcers treated in primary care in collaboration with telemedicine consultations with a hospital outpatient is no worse than with standard hospital outpatient care. The corresponding null hypothesis: mean difference in healing time is 1.5 months or less for diabetes-related foot ulcers with telemedicine follow-up in primary care, compared to standard hospital outpatient care.

We will also evaluate whether the incidence of amputation and mortality, sickness absence, clinical measures (number of consultations, complications directly related to the foot ulcer as indicated by use of antibiotics), recurrence of a new foot ulcer (within 48 months), and patient-reported outcome measures (PROMs) are different for telemedicine follow-up in primary care compared with standard hospital outpatient care.

We conducted supplementary qualitative studies to provide a more comprehensive description and evaluation of the ongoing

processes during the intervention. Individual interviews with patients in the intervention and control groups aimed to explore patient experiences with telemedicine follow-up or standard outpatient care delivered in the DiaFOTo trial. Focus group interviews with health care professionals either working in primary care or in specialist care delivering the intervention aimed to explore health care professional experiences when they adopt this new technology in caring for patients with diabetes foot ulcers.

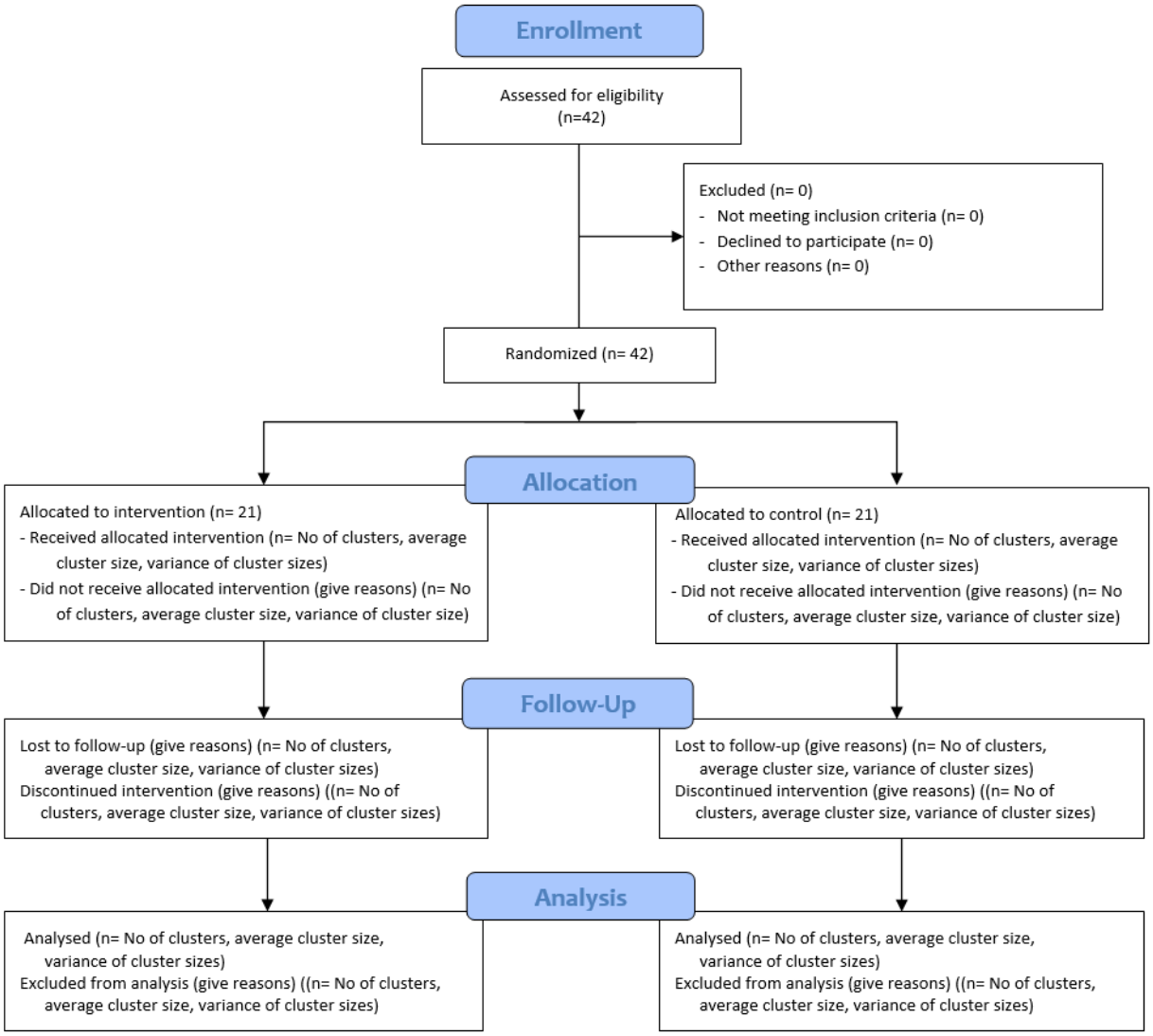
Methods

Trial Design

In this pragmatic randomized controlled trial (RCT) [18], we evaluate the effectiveness of the intervention on patient health using the Model for Assessment of Telemedicine criteria [19] and the complex intervention framework developed by the Medical Research Council in the United Kingdom [20]. We used a noninferiority parallel cluster design. The flow and attrition diagram is shown in Figure 1 and based on the CONSORT 2010 statement: extension to cluster randomized trials [21]. Reporting will adhere to the guidelines of the Consolidated Standards for Reporting Trials (CONSORT) [22]. The trial is in accordance with the CONSORT EHEALTH checklist [23]. The study has been registered with ClinicalTrials.gov [NCT01710774].

Quantitative data are being collected at the time of inclusion (baseline) after informed consent has been obtained and before randomization (t1), and the patient is monitored every second week until the foot ulcer has either healed or until the end of follow-up (maximum 12 months after baseline) (t2). Additional information will be retrieved 36 months after the initial follow-up period about the occurrence of new foot ulcers, amputation, or death. Maximum follow-up for each patient is therefore 48 months.

Figure 1. Flow diagram of clusters and patients in the cluster randomized controlled noninferiority trial, DiaFOTo.



Trial Population and Recruitment

We are currently including all patients with diabetes-related foot ulcers from the southern part of Rogaland County referred to the endocrinology unit of Stavanger University Hospital (Stavanger HF) between September 2012 and June 2016 at the initial visit to the clinic.

The trial includes patients with type 1 or type 2 diabetes if they are 20 years or older and present a new foot ulcer to the clinical

site. A foot ulcer is defined as a skin lesion below the ankle on a diabetic foot. The exclusion criteria include (1) an ulcer on the same foot treated during the past 6 months in specialist health care (because chronic ulcers can interfere with the primary outcome in the study protocol); (2) mental disorders or cognitive impairment (including schizophrenia, other psychotic disorders, and dementia); (3) inability to complete questionnaires in Norwegian, or (4) life expectancy of less than 1 year. Patients are being assessed for primary diagnosis and treatment at the clinical site according to standard protocols based on national guidelines [3].

Randomization and Blinding

The southern part of Rogaland County in the western part of Norway was divided into 26 clusters based on municipalities or districts within municipalities. These were matched in pairs according to population size and rural/urban characteristics. Within each of the 13 pairs, the two clusters were randomly allocated to intervention or standard treatment. The randomization sequences were generated by an independent person using SPSS version 21 statistical software (IBM Corp). All patients in each cluster/municipality are in the same treatment group. All participants are informed by the study nurse about the allocated type of treatment after enrollment in the study and after providing baseline data. The intervention is designed to evaluate a change in health service provision; therefore blinding of the intervention is not possible. The study staff monitors whether pictures are submitted as planned and follows up to ensure compliance. We also assess how closely the nurses follow the protocol. The outcome is assessed by health care professionals at the outpatient clinics, who are not blinded to study arm but are trained to follow and assess wounds using a standardized protocol. The numbers of patients who do not meet the inclusion criteria, decline to participate, or drop out of the trial are recorded by age and gender.

Development of the Intervention

The intervention consists of a Web-based ulcer record to facilitate asynchronous communication between primary and specialist health care and includes a database and an application to communicate images and text between participants. The Web-based ulcer record (Dansk Telemedicin AS) has been adapted to Norwegian legislation and is described in a previous publication [24]. We carried out a preliminary project in spring 2011 to develop and adjust the telemedicine tools to patients with diabetes-related foot ulcers receiving care in the community. In a pilot project between autumn 2011 and spring 2012, the data collection forms and telemedicine tools were tested on five patients. A standard procedure protocol was developed in brochure form to ensure that photographic documentation of ulcers was taken at optimal resolution, with adequate lighting and good contrast, from specified angles. The brochure also included instructions for use of the Web-based ulcer record, the integrated infrastructure, and legal and data security aspects.

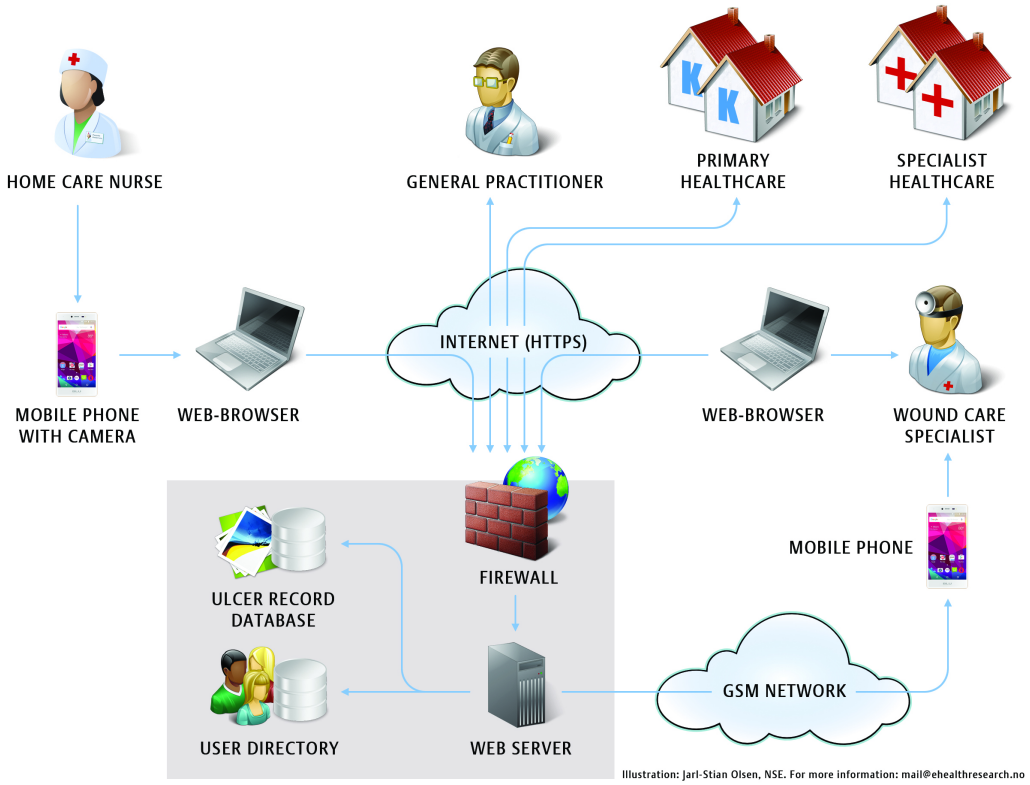
Telemedicine Intervention

Patients in the intervention group receive telemedicine follow-up care in the community. The key ingredient in the intervention is the close integration between health care levels. The intervention is facilitated by the use of an interactive wound platform consisting of a Web-based ulcer record combined with a mobile phone, enabling counseling and communication between nurses in the community and specialist health care. Foot ulcer data including images are sent by mobile phone to the Web-based ulcer record for asynchronous consultation with specialist health care. Images are recorded throughout the trial, stored in the Web-based ulcer record, and transferred encrypted to a server. General practitioners in the intervention group can get access to the Web-based ulcer platform if required (Figure 2).

The nurses are trained to use the Web-based ulcer record and mobile phone using written information. Individual teaching and training of the nursing staff in primary care is offered at the specialist clinic or in primary care to secure equivalent and competent handling of patients. The diabetes specialist nurse and/or podiatrist in the multidisciplinary project team provide the latter. The written information also includes a section defining the delegation of responsibility at each level of health care providers with respect to the treatment of diabetic ulcers. Follow-up procedures are set up for each participant. The nurses review the images at the Web-based ulcer record and discuss them with the specialists if there is any uncertainty. Nurses in the specialist health care communicate with community care nurses at least once a week. In addition, nurses in specialist health care can check and contact community nurses on an ongoing basis. Discussions are mainly about wound care but could also include earlier referral if required. The home care nurse or general practice nurse will initiate contact with specialist health care regardless of prior agreements if the ulcers do not improve or get worse.

We have not made important changes to the intervention or control arm during the trial. Functionality has been evaluated every year and minor adjustments have been performed; however, this has not involved system failures/downtimes, etc. We have used the same photo documentation (smartphone/camera) throughout the project.

Figure 2. Diagram illustrating the general use of the telemedicine tool.



Control Group

The control group receives standard hospital outpatient consultations with health care professionals at the endocrinology unit of Stavanger University Hospital. The medical treatment given to the control and intervention group is based on the same procedures. Foot ulcer data including images are recorded throughout the trial but only at the outpatient clinic. Like in the intervention group, the data are stored in the Web-based ulcer record and transferred in encrypted form to the same server.

Evaluation Measures

The trial includes self-reported questionnaire data and information collected from the electronic patient journal and the clinical diabetes system at the outpatient clinic. The quantitative measures in our trial are described in detail below.

Primary Outcome Measure

The primary outcome is healing time measured from the time the person presents the ulcer at the clinical site (included in the trial) until the foot ulcer is healed.

Secondary Outcome Measures

Time to amputation (foot, below, through, or above the knee) and death during the patient follow-up period as well as self-reported questionnaire data will be used as secondary outcome measures in this trial. This questionnaire package will include standardized instruments measuring patient-reported outcomes as problem areas in diabetes, quality of life, symptoms of anxiety and depression, and satisfaction with treatment (see Table 1 for details).

Table 1. Summary of measures.

Outcome	Data collection instrument	Time points[a]
Primary outcome		
Healing time	Time to healing. Data from electronic medical journals at the clinical sites.	t2
Secondary outcomes		
Amputation (before healing)	Time to amputation. Data from electronic medical journals at the clinical sites.	t2
Death (before healing)	Time to death. Data from electronic medical journals at the clinical sites.	t2
Well-being during the previous 2 weeks [25-27]	The World Health Organization well-being index (WHO-5). Scale 0-5; higher scores indicating greater emotional distress.	t1, t2
Symptoms of anxiety and depression during the past week [28-30]	Hospital Anxiety and Depression Scale (HADS). Two subscales, 0-3 (scored 0-21); higher scores indicate more symptoms.	t1, t2
Diabetes-related problem areas [31-33]	Problem Areas in Diabetes (PAID). Scale 0-4 (scored 0-100); higher scores indicate more problems.	t1, t2
Impact of diabetic peripheral neuropathy and foot ulcers on patient's quality of life [34,35]	Neuropathy- and Foot Ulcer–Specific Quality of Life Instrument (NeuroQoL). Five subscales 1-5; higher scores indicate lower quality of life.	t1, t2
Health status reflecting an individual's subjective perception of health conditions [36-38]	Perceived health (or self-rated health). Scale 1-4; higher scores indicate better perceived health.	t1, t2
Health-related problems and health related quality of life [39,40]	Euro-Qol (EQ-5D-5L). Scale 1-5; 1 represents "no problem." Overall health, VAS-Scale, 0-100, higher scores indicate better health.	t1, t2
Patient experiences [41]	Nordic Patient Experiences Questionnaire.	t1, t2
The occurrence of new foot ulcers and amputation (after the initial follow-up period)	Data from electronic medical journals at the clinical sites.	t3
Sickness absence	Norwegian sick leave registry (FD-Trygd registry).	t4
Death (after the initial follow-up period)	Time to death (months). Cause of death registry.	t4
Other measures		
Demographic characteristics (age, sex, ethnicity, education, cohabitation, marital status, working status and smoking, travel distance to hospital)	Patient questionnaire.	t1
Clinical data related to diabetes and diabetes foot ulcer	Data from electronic medical journals at the clinical sites.	t1, t2,
Consultations	Number in specialist care and primary care.	t2
Wound classification [42,43]	University of Texas Diabetic Wound Classification System. Higher grade classified increasing wound depth (0-3). Higher stage classified the presence of infection and/or ischemia (A-D).	t1, t2

[a]t1: baseline assessment, t2: end of the initial follow-up period, t3: 36 months after end of the initial follow-up period, t4: will be merged with registry data after the trial is closed.

Long-term data on the time elapsing before a new foot ulcer appears and the incidence of amputation will be collected for 36 months after the initial follow-up period from the electronic patient journal at the clinical sites. Information on death (date and cause) will be retrieved from the Norwegian Cause of Death Registry.

Other Measures

We collect self-reported demographic data on age, sex, ethnicity, education, cohabitation, marital status, working status, and smoking status of the participant. In addition, clinical data are collected. For all participants, we store a picture and measure the wound area in the Web-based ulcer record system at the time of inclusion in the trial, after 8 weeks, and at the end of follow-up. The foot ulcers are classified according to the University of Texas Diabetic Wound Classification System [42], which combines grade and stage, is descriptive, and predicts clinical outcomes well (risk of amputation and healing time) [43]. At baseline, we collect data on blood pressure and measurements of neuropathy. Biological data include hemoglobin A_{1c} concentration and measurements of renal function (serum-creatinine, glomerular filtration rate, and microalbuminuria). Data from the medical records include type of diabetes, onset of diabetes, microvascular complications

(retinopathy, neuropathy, and nephropathy) and macrovascular complications (myocardial infarction, stroke, claudication, and angina pectoris). Furthermore, we calculate the number of consultations, both in specialist health care and primary care.

Sample Size

A statistical power analysis based on the primary outcome measure (healing time) was performed to decide the number of participants to be included using PASS sample size software, version 11 (NCSS, LLC). We powered the study to detect a difference in mean healing time larger than the selected noninferiority margin of 1.5 months [44,45], assuming 80% power, a significance level of .025, and a standard deviation of 3.6 months [46]. The analysis showed that on an individual level, a total sample size of 184 is needed. Considering an intraclass correlation coefficient of .02 and an average cluster size of 10 participants (design effect of 1.18), this number increased to 217 participants. As we expect an attrition rate of 5%, we aim to include 114 patients in each treatment group.

Statistical Analysis

We will report descriptive statistics of baseline characteristics for the treatments groups including means and standard deviations (medians and interquartile ranges for continuous variables and numbers and percentages for categorical variables).

Noninferiority of the telemedicine intervention will be confirmed if the lower limit of the 95% confidence interval for the mean difference in healing time is less than 1.5 months. To account for correlated data introduced by the study design, we will apply the linear mixed-effects model [47] for this analysis. In addition, we will analyze group differences in time to healing with a proportional hazards model with adjustment of the standard error for clustered observations. Secondary outcome measures will be analyzed with superiority hypothesis tests. These tests will be based on either (generalized) mixed-effects models [47] or proportional hazards models (cluster) depending on the type of the outcome measure investigated. Estimated effect measures (absolute and relative) will be presented with 95% confidence intervals and *P* values.

Because our trial has a maximum follow-up period of 48 months, we expect some dropouts. We will perform intention-to-treat analyses and additional analyses based on the participants who actually participated actively in our trial during the 12-month follow-up period.

Qualitative Substudies

Patient Experiences

Some participants with diabetic foot ulcers receiving either the telemedicine follow-up in primary care in collaboration with outpatient specialist care or standard outpatient care were individually interviewed to explore their experiences with telemedicine follow-up or standard outpatient care delivered in the DiaFOTo trial. Interviewees were selected to ensure a diverse sample in terms of group (intervention vs control), age, gender, marital status, setting, and comorbid diseases. The study nurses at the clinical sites organized recruitment of the patients. Patients were included if their foot ulcers had healed or after the intervention was completed.

Data were collected using individual semistructured interviews. The interview guide contained eight overall topics with subthemes for the intervention group and seven overall topics with subthemes for the control group. The topics were similar for both groups, except the control group were not asked questions related to the telemedicine equipment and the health care professional's attitudes on using images in wound care (Textbox 1).

Textbox 1. Main topics in the interview guide (patient experience).

Intervention group

- Patient experience with the foot ulcer and what he/she did when he/she discovered the ulcer
- Patient experience of receiving telemedicine treatment and follow-up from the home care nurse
- Patient experience of being followed up in specialist health care
- Patient experience of being involved in wound management and decisions that concerned his/her treatment
- Patient experience with health care professional use of the telemedicine equipment and health care professional's attitude on using images in wound care
- Patient-observed telemedicine collaboration between the home care nurse and specialist health care service during follow-up
- Patient perception of whether he/she takes more responsibility for his/her own health
- Patient perception of the most important task home care nurses and experts at the outpatient clinic have in treatment and care of patients with diabetic foot ulcers

Control group

- Patient experience with the foot ulcer and what he/she did when he/she discovered the ulcer
- Patient experience of receiving traditional treatment and follow-up from the home care nurse
- Patient experience of being followed up in specialist health care
- Patient experience of being involved in wound management and decisions that concerned his/her treatment
- Patient-observed collaboration between the home care nurse or general practitioner and specialist health care services during follow-up
- Patient perception of whether he/she takes more responsibility for his/her own health
- Patient perception of the most important task home care nurses and experts at the outpatient clinic have in treatment and care of patients with diabetic foot ulcers

Data were collected and interviews carried out until saturation was achieved, in line with recommendations existing for qualitative research [48]. Transcribed interview text was analyzed by developing codes, grouping similar codes together in larger groups, and exploring these for patterns in terms of similarities and differences. As relationships became apparent, we interpreted them from a clinical and theoretical perspective. Several researchers were involved to support reflexivity of researchers throughout all phases of the qualitative study. Researchers analyzed data separately first and then compared and contrasted their analyses to reach a consensus on main themes and subthemes. Interpretive description was used as a strategy in this study. This approach to qualitative knowledge development for applied clinical fields aims to produce new knowledge and a contextual understanding that can be put to direct applied use when implementing the intervention in future clinical practice [49,50].

Health Care Professional Experiences

Interpretive description was also used as a research strategy for this study. Health care professional experiences with the intervention were explored and Donabedian's framework was used to structure essential components of health services to be addressed in the study [51,52]. Information on health care professional experiences was collected through focus group interviews among those working in primary care or in specialist care delivering the intervention. We mixed different health care professions within their own working context so that different perspectives within their context could be explored and discussed. The focus groups were conducted by a moderator and comoderator among health care professionals in the initial stages of introducing telemedicine in their work. The semistructured interview guide covered topics related to our study aim (Textbox 2).

Textbox 2. Main topics in the interview guide (health care professional experience).

- Participant experience using telemedicine and how it was organized where they work
- Participant experience using telemedicine as a new tool in documentation and communication
- Participant experience of communication and collaboration between outpatient clinic (physicians, nurses, and foot therapists) and nurses in home care through telecommunication and among professions
- Participant perception of changes in competence in caring for people with diabetes foot ulcers during the intervention
- Participant perception of changes in job satisfaction while using telemedicine

Ethical Considerations

All participants receive written information about the project and its aims with a description of the procedures of the project before inclusion. We inform participants that their privacy will be protected and all data will be coded and processed anonymously to protect confidentiality and that they can withdraw from the project at any time without this affecting their treatment. All patients are required to provide written informed consent before participation. We do not believe that the project has any negative effects for the patients involved that would raise problematic or specific ethical issues. Completing the questionnaire might be a burden, but we do not consider this burden to exceed the potential new knowledge and evidence the study will produce. The project is approved by the Western Norway Regional Committee for Medical and Health Research Ethics (2011/1609), which also has given approval for merging our data with the Norwegian cause of death and sick leave registries.

The Norwegian Centre for Integrated Care and Telemedicine lent its expertise in data security and legal aspects to the planning of this project. In line with Norwegian legislation and security services, data controller agreements were performed between all parties. We performed risk assessment analyses after the pilot project and after years 1 and 2 of the trial. Information about the project has been disseminated in collaboration meetings at different administrative levels in the involved municipalities. Qualitative substudies were performed to include the perspective of health care users. In addition, a representative from the Norwegian Diabetes Association is participating in the project group. We have established standardized procedures for transfer of data, security, and storage of data in collaboration with the Norwegian Centre for Integrated Care and Telemedicine.

Results

The study has been successfully funded. The inclusion of patients started September 2012 from 26 municipalities or districts. Because recruitment goals were not met in the initial period, two more hospitals from the Western Norwegian Health Region have been included to meet sample size requirements. Patients from Sunnhordland County referred to the department of surgery at Stord Hospital (Helse Fonna HF) were included from September 2013 (6 districts), and patients from Hordaland County referred to the department of orthopedics or endocrinology unit at Haukeland University hospital (Helse Bergen HF) were included from November 2014 (10 districts), for a total of 42 districts before randomization (Figure 1). Furthermore, patient recruitment has been extended through June 2016. We expect to present results of the study in 2017.

Data collection in the qualitative substudies has been completed. Information on patient experiences was collected between March 2014 and May 2015 from 24 participants with diabetic foot ulcers receiving either the telemedicine follow-up in primary care in collaboration with outpatient specialist care or standard outpatient care. Information on health care professional experiences was collected through 10 focus group interviews from 7 home-based care services, 2 outpatient clinics, a medical center, and a nurse-led primary care clinic during 2014 and 2015 (n=43). Focus group interviews lasted from 70 to 90 minutes, included 3 to 7 health care professionals, and were audiotaped. The results of these studies are submitted and will be available in 2016.

Discussion

This project will contribute to increased focus on integrated care and is in accordance with national strategies [12]. By transferring the follow-up care to the lowest effective service level, we anticipate that results of this trial will improve the motivation and awareness of health care professionals in the community to implement disease prevention measures. We believe that telemedicine can become a tool to raise the competence of nurses in the community and facilitate better communication and closer collaboration between health care levels, improving both foot ulcer care and general diabetes care. In this project, patients are not sending pictures directly to specialist health care services because it would be difficult for patients with diabetic foot ulcers to take pictures themselves due to location of the ulcers, frailty, age, and impaired vision. However, we expect that telemedicine-based ulcer follow-up can positively influence patient competence and involvement in diabetes self-management, including using preventive strategies to avoid or delay new foot ulcers. If the study finds evidence of positive health gains for the individuals with diabetes and contributes to a higher quality of care, this new model may be applicable to other hospital trusts and health care regions.

An important concern due to internal validity is whether the intervention is working similarly in all communities and within the community itself. The nurses in the community are trained by using written information. Individual teaching and training of the nursing staff in primary care is offered at the specialist clinic or in primary care to secure equivalent and competent management of patients. We have not made important changes to the intervention or control arm during the trial, and we used the same photo documentation (smartphone/camera) throughout the project. When designing the study we stressed the internal validity. The rationale for choosing a cluster-randomized trial was that classic randomization could threaten the internal validity because nurses in the municipalities would treat patients in both the intervention and control groups. During the study, we have used qualitative studies to explore in detail how this complex intervention is working from a patient and provider perspective. Results from the trial as well as results from the qualitative studies will be published in peer-reviewed journals to the international audit. All studies will emphasize internal and external validity in line with the Model for Assessment of Telemedicine criteria [19].

One of the concerns of this complex intervention study is whether the patients included in the trial are representative of the majority of patients with diabetic foot ulcers. Patients with more complex illness living in nursing homes or having mental problems and those having difficulties traveling to a hospital may benefit from this type of intervention the most but will be excluded from participation in the present trial due to their

vulnerability. In addition, we excluded patients with a previous ulcer within 6 months of presentation since repeated chronic ulcers may interfere with the primary outcome. Therefore, our cohort does not fully reflect the total population with diabetic foot ulcers attending the participating clinics. To increase the number of patients included in the trial, the study is embedded in daily clinical practice at three clinical sites. This will contribute to increasing the external validity and generalizability of the results and thus make them more applicable to a realistic clinical setting.

We expect this project to provide evidence about alternative care pathways for the treatment of diabetic foot ulcers that may reduce the cost of health care services by delivering a larger proportion of services in municipal primary care. This study may also contribute to setting priorities for patient needs for flexible health services and enable more patients to be treated near their homes.

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Authors' Contributions

MMI and MFH were responsible for the study concept. MMI, TØ, GST, MG, BE, and BR designed the study, applied for funding, and drafted the protocol. MMI, JGC, MFH, SS, HD, and BG contributed in developing and improving the delivery of the intervention. MG, MMI, TØ, SS, and BR applied for additional funding and, in collaboration with MK, HSS, and BCHK, designed the additional qualitative studies. MMI, TØ, BE, MG MK, BG, SS, and BR contributed to editing of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DiaFOTo: Diabetic Foot and Telemedicine Images Project
PROM: patient-reported outcome measure
RCT: randomized controlled trial
CONSORT: Consolidated Standards for Reporting Trials

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Original Paper

Voice-Message–Based mHealth Intervention to Reduce Postoperative Penetrative Sex in Recipients of Voluntary Medical Male Circumcision in the Western Cape, South Africa: Protocol of a Randomized Controlled Trial

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Abstract

Background: There is an increased risk of transmission of sexually transmitted infections (STIs), including HIV, in the postoperative period after receiving voluntary medical male circumcision (VMMC). In South Africa, over 4 million men are being targeted with VMMC services but the health system is not able to offer quality counseling. More innovative strategies for communicating with and altering behavior in men and their partners in the postoperative period after VMMC are needed.

Objective: This paper presents a study protocol to test the effectiveness of an mHealth intervention designed to task-shift behavior change communication from health care personnel to an automated phone message system, encouraging self-care.

Methods: A single-blind, randomized controlled trial will be used. A total of 1188 participants will be recruited by nurses or clinicians at clinics in the study districts that have a high turnover of VMMC clients. The population will consist of men aged 18 years and older who indicate at the precounseling session that they possess a mobile phone and consent to participating in the study. Consenting participants will be randomized into either the control or intervention arm before undergoing VMMC. The control arm will receive the standard of care (pre- and postcounseling). The intervention arm will received standard of care and will be sent 38 messages over the 6-week recovery period. Patients will be followed up after 42 days. The primary outcome is self-reported sexual intercourse during the recovery period. Secondary outcomes include nonpenetrative sexual activity, STI symptoms, and perceived risk of acquiring HIV. Analysis will be by intention-to-treat.

Results: Enrollment is completed. Follow-up is ongoing. Loss to follow-up is under 10%. No interim analyses have been conducted.

Conclusions: The intervention has the potential of reducing risky sexual behavior after VMMC. The platform itself can be used for many other areas of health that require task shifting to patients for better efficiency and access.

Trial Registration: Pan-African Clinical Trial Registry: PACTR201506001182385

(JMIR Res Protoc 2016;5(3):e155) doi:10.2196/resprot.5958

KEYWORDS

protocol; RCT; male circumcision; HIV; mHealth; VMMC

Introduction

Background

Voluntary medical male circumcision (VMMC) has been shown to reduce risk of male acquisition of HIV by as much as 60% [1-3]. Based on this evidence, in 2007 the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) stated that "male circumcision should now be recognized as an efficacious intervention for HIV prevention" and that male circumcision should be promoted as an additional strategy in the prevention of HIV in men [4]. Thirteen countries in eastern and southern Africa with high HIV prevalence and low rates of male circumcision were prioritized for VMMC scale-up [5]. Significant technical and financial resources were provided by various funding and technical agencies, and the governments of these countries began a process of conducting situation analyses, drafting policies and protocols, and rolling out VMMC [5]. As a result of these efforts, by the middle of 2014 over 5.8 million VMMCs had been performed, more than half of which occurred in 2013 [6].

Early Resumption of Sexual Intercourse After VMMC

Expert guidelines for VMMC recommend a 6-week period of abstinence from penetrative sex after VMMC in order to avoid the spread of sexually transmitted infections, including HIV [7]. The risk of early resumption of sex exists without proper counseling, education, and follow-up. In the Rakai, Uganda trial, about 11% of HIV-positive and HIV-negative participants reported having intercourse before certified wound healing, defined in this study as "when there was an intact healthy scar with no residual exudate or scab formation, and all sutures had been completely absorbed" [8]. Married men were more likely to resume sexual intercourse before certified wound healing whether or not they were HIV positive (28%) or HIV negative (29%). This was despite intensive pre- and post-VMMC counseling within the trial, indicating strong sociocultural desire for quick resumption of marital sexual relations. In the same study, it was observed that more female HIV-negative partners of HIV-positive VMMC recipients enrolled in the trial acquired HIV when the couple resumed sex early (more than 5 days prior to certified wound healing) as opposed to those who did not [9]. In an observational study more approximating realistic clinical VMMC situations in Nyanza, Kenya, 30.7% of all participants resumed sexual intercourse before wound healing, usually in the first 3 to 4 weeks after VMMC [10]. Again, being married or cohabiting was the strongest predictor of having early sex: 65.7% of married participants resumed sex before healing despite counseling efforts by clinicians. Finally, a recent study from Zambia found that 24% of circumcised men resumed sex early, nearly half of whom (46%) did so in the first 3 weeks [11].

Cultural norms play an important role in expectations surrounding sexuality, and this has implications for health education messaging. Qualitative research from Nyanza, Kenya, indicates that the postoperative abstinence period is spontaneously cited by uncircumcised men as a barrier to obtaining VMMC; in particular, the 6-week period was considered too long to abstain [12]. Younger men were worried that their female partners would seek sex elsewhere, while older men worried that it would not be possible to sleep in the same bed as their wives and abstain. In the formative phase of the current project, we used qualitative methods to understand how newly circumcised men and their female partners feel about the 6-week abstinence period after VMMC. Our results confirm that it is not always easy for couples to navigate this period [13]. They live in close quarters so cannot avoid sleeping in the same bed, alcohol (and drug) use sometimes impairs their judgment, and there are expectations of sexual activity among married couples that men say they feel obliged to live up to.

Pre- and Postoperative Counseling and Education

All of the studies above have reiterated the need for proper counseling and education about the efficacy of VMMC and the need to maintain or adopt proper risk avoidance behavior after the procedure, particularly during the healing period. In the Rakai, Uganda, trial the authors concluded that "the association between resumption of sexual intercourse before complete wound healing and increased risk of male-to-female HIV transmission makes it imperative that circumcised men and their female partners are clearly instructed to abstain from intercourse until the wound is healed" [9]. In a pooled analysis of the three original efficacy trials, Mehta et al (2009) found that men reporting early sex did not have increased risk for HIV after 3 or 6 months [14]. However, the authors acknowledged that the intensive counseling involved in the context of the three studies is not likely to be replicated in real life, indicating the importance of continued vigilance regarding actual counseling practices and resulting behaviors. Further, more intensive counseling of married men, due to their increased likelihood of resuming sex early, was recommended by the authors.

A recent study indicated the effectiveness of a 180-minute theory-based risk reduction group counseling session in reducing sexual risk behavior following VMMC, although the study did not report on early resumption of sex [15]. This is a promising intervention for informing VMMC programs. However, there is also recognition that the lack of human resources in the VMMC scale-up countries presents a barrier to such intense services, particularly if repeated messaging is to occur [16]. This is particularly the case when countries turn to independent partners to carry out mass, one-off VMMC campaigns outside of the normal constellation of services. Clearly, more innovative strategies for communicating with and effectively altering behavior in men and their partners are needed. Further, given evidence of greater risk for resumption of sexual activity in married/cohabiting men, strategies for nonpenetrative sexual activity should be developed and included in such education.

mHealth As a Self-Care Strategy

Mobile health (mHealth)—the use of mobile phone technology to deliver health care—has emerged as an important and appreciated complement to health care education delivered

through traditional channels. Such technology may include the use of text messaging, video messaging, voice calling, and Internet connectivity. The potential for mHealth interventions to partially compensate for interpersonal services in resource-poor areas is enormous [17]. Although mHealth has been shown to be effective in medication adherence, clinical management, and behavior modification [18], the use of mHealth has primarily been restricted to developed countries. To date, there are few studies of the use of voice messages to reduce risky sexual behaviors. In fact, a Cochrane Review from 2013 found only one RCT of a telephone-delivered intervention (use of postexposure prophylaxis for rape victims) for preventing HIV infection in HIV-negative persons [19]. Further, most mHealth interventions are not theory-based, leading to poor results [20].

South Africa

South Africa holds the dubious title of being the country with the highest number of HIV positive individuals – over 6 million – and it accounts for 16% of all new HIV infections in the world [21]. Based on antenatal data, HIV prevalence in the general population is estimated at 17.3% in South Africa [22], with incidence estimated at 1.43%. Transmission of HIV in South Africa is almost exclusively through heterosexual sex, thus heightening the importance of VMMC as a form of prevention [23].

South Africa has committed to rolling out medical circumcision as one source of protection from HIV [24]. Circumcision is available as part of a comprehensive service at district hospitals, and, in theory, HIV testing, counseling, and HIV education are provided before the procedure. However, the South African health system is struggling to maintain high-quality counseling services around male circumcision due to human resource issues [5].

The Coloured community, which accounts for 48.8% of the Western Cape's population [25], has a growing HIV prevalence rate—7.5% according to 2012 antenatal data [22]. The heightened HIV risk to this population group lies at least partly in high illicit drug and alcohol use, which is associated with risky sexual behavior [26].

Mobile phone ownership in South Africa is nearly universal—97% of households have a mobile phone, with greater concentrations of ownership in the urban centers. Particularly within the urban setting there is little difference by income level in terms of access to phones [27]. Given this near-universal ownership, mobile phone technology has been found to be acceptable and feasible for HIV- and AIDS-related prevention and services [28,29] and is now used in several health-related text-reminder projects in South Africa [30].

Objectives

The objective of this study was to test the effectiveness of a customized relay of audio clips on safe sexual behavior in consenting, recently circumcised men.

Methods

Overview

The study is a randomized controlled trial (RCT) with two arms. The control arm consists of standard of care for pre- and postoperative counseling offered to VMMC recipients by the South African Department of Health VMMC services. In the intervention arm, VMMC recipients will receive voice messages for 6 weeks following the operation in addition to the standard of care. Data collection began January 21, 2015, and is ongoing.

Study Setting and Participants

The research will be done in seven clinics in Cape Town, in the Western Cape Province of South Africa. The study sites were chosen in conjunction with the provincial health department. The communities in each of the seven catchment areas are almost exclusively Afrikaans-speaking Coloured. The term Coloured refers to an official South African race group used in research and census data that is predominantly mixed ancestry. The term originated in the apartheid era but remains an important descriptor and label for a distinct community. More than 48% of the people who live in the Western Cape are classified as Coloured, mostly still living in defined communities that are at least 90% Coloured. Inclusion criteria are men aged 18 years and older who present for VMMC at one of the study clinics and indicate at the precounseling session that they possess a mobile phone and consent to participate in the study. There are no exclusion criteria.

Standard of Care (Control Group)

The standard of care offered by the provincial circumcision team consists of the counseling session during the HIV testing and counseling procedure and a brief postsurgery counseling session where men are advised on how to care for the wound and ordered to go to their local clinic at 2 days and 7 days following surgery. They are reminded not to engage in penetrative sex until the mandatory wound-healing period of 6 weeks has passed. No further contact is sought other than if there are health complications such as swelling or infection.

Intervention Group

The intervention group gets the standard of care plus the intervention program which consists of 38 audio messages delivered over the 42 days following surgery. Once men are randomized into the intervention group, the project manager passes on the participants' mobile phone numbers, personal identification numbers, and dates of enrollment to the mHealth platform operator (the South African company Health Information Systems Program [HISP]). The mobile system will automatically call participants twice a day for the first 2 days, once a day for the next 4 weeks, and on alternative days in the last 2 weeks. Using the last 4 digits of their mobile number as their password, participants can listen to the message and, using their keypad, replay it if they do not understand the message. It is not possible to respond to the message. The platform is programmed to redial unanswered or busy numbers up to 3 times. Therefore, calls can be received at different times of the day.

The content and phasing of the messages for the mHealth intervention were developed collaboratively with former patients through focus group interviews, cognitive interviews, and discussions with health promotion experts at the Provincial Medical Office (research to be published separately) using classic behavior change theories. The messages were then developed into short audio clips of 30 to 120 seconds each (in English and Afrikaans). Based on the formative research, messages delivered over the 42 days are divided into four periods:

- Days 1-2: An intense 2 days of self-care messages (2 per day). The theme of these messages revolves around coping with pain and recuperation.
- Days 3-14: Mainly self-care messages (1 per day). The theme is around strategies and practical tips on pain and wound management.
- Days 15-28: Coping and inspirational messages (1 per day). The theme is around coping with the wound inspiring and encouraging them to include their partners into the recovery period.
- Days 29-42: Inspirational messages (triweekly). The theme is around offering alternatives to penetrative sex and inspiring them to complete the period penile penetration-free.

Outcomes

The primary outcome is occurrence of sexual intercourse (vaginal or anal) at any time in the 42 days after the procedure. Secondary outcomes include (1) adoption of nonpenetrative sexual behaviors in the first 42 days after the procedure, (2) self-reported sexually transmitted infection symptoms at baseline and 42 days after the procedure (as a marker of unprotected sex), (3) sexual risk behavior at baseline and 42 days after the procedure, and (4) sexual risk propensity at baseline (as a control for risk-taking personality) [9].

Sample Size

A total sample size of 1188 (inflated by 10% for loss to follow up, n=594 in each arm) is needed to detect a 10% reduction of penile sexual events in the intervention group with 90% power with an alpha of .05. The control event rate is estimated at 60% based on previous studies in similar populations.

Recruitment

Participants are recruited at the clinics where MMC services are offered in the greater Cape Town area. There are two roaming VMMC teams in the area offering services 4 days per week. The research assistants are divided between the teams and follow them depending on where they are on a set weekly schedule.

Allocation

The randomization sequence will be generated by a biostatistician using a computer-generated table of random numbers. Assignment sequences will be placed in consecutively numbered opaque sealed envelopes ensuring allocation concealment. The study numbers are allocated consecutively as the patients come into the waiting area and written in the top corner of the envelope, which is handed to the participant.

Blinding

This will be a single-blind RCT: data collectors, researchers, and analysts will all be blind to the patient's allocation to study arm. The envelopes are numbered consecutively by the fieldworkers, and at the end of each recruitment day, the team sends a list of the participants' study ID numbers, mobile numbers, and preferred language of messages to an office-based study administrator who has the group allocation master list. The study administrator then logs on to the HISP website and registers the mobile phone details of the intervention group, who start getting messages the next day. At no stage does the team in the field know the allocation of any study number, and at no stage does the study administrator come into contact with the participants or their personal information.

Data Collection

Data is collected through self-administered paper and pen questionnaires offered in either English or Afrikaans. The consenting participants fill out the questionnaire while they wait for their HIV testing and preoperative counseling. They are asked to come back to the clinic for a follow-up visit after 6 weeks. HIV status will be collected (coded) from files if consent is given by the participant. Completed questionnaires are processed and captured at the office by the data capturer and stored in a locked room. The completed questionnaires are linked to the participants through their study numbers only and not the electronic health platform.

Follow-Up Procedures

Participants return to the same clinic where they were recruited (or a nearby convenient public space) after 6 weeks for a follow-up visit consisting of a questionnaire. Based on many years of panel studies in the population, the team has developed the following mechanism for ensuring high retention: as part of the consent process, the participant will complete a contact form including his phone number and the names and phone numbers of two people close to him. He will also be given an appointment card that indicates the date of the 42-day follow-up visit. In the 6 weeks following surgery, participants are contacted with a brief phone call at 1, 3, and 5 weeks to remind them of their follow-up date and to reschedule if necessary. If a participant does not show up for the follow-up visit, contact is attempted up to 3 times in the following 2 weeks to reschedule. If the participant is reached but unable to reschedule, he is invited to complete a subsample of the follow-up questionnaire (10 questions) via the telephone. If he is not located, he is considered lost to follow-up.

Analysis

Descriptive Analysis

Data will be analyzed using Stata 13 statistical software (StataCorp LP) according to the intention-to-treat principle. Descriptive statistics will be used to summarize the data. Continuous outcome variables will be tested for normality using descriptive statistics (eg, histograms, qq plots, and box plots). If normally distributed, continuous variables will be presented as means and standard deviations; if not, they will be reported as medians and interquartile ranges. Categorical data will be presented as proportions. An alpha of .05 will be considered

statistically significant, and 95% confidence intervals will be reported where appropriate. Baseline prognostic variables and possible confounders will be compared between intervention and control groups using the appropriate univariate statistical methods. Clinical imbalances will be considered in further adjustment regression models.

Inferential Analysis

The primary outcome—occurrence of any homosexual or heterosexual penetrative intercourse at any time in the first 42 days after VMMC—will be compared between the intervention and control groups. The primary analysis will be to detect a difference in proportions using an unadjusted binomial test. Additionally, generalized linear regression models for the analysis of binary outcomes will be used to study the effects of the intervention as well as possible synergistic effects, taking potential confounders into account if necessary (eg, age, religion, marital status, education, employment, depression). The final covariate model will include all variables known to have a meaningful impact on bias in the estimate of the treatment effect. The covariate adjusted relative risk for treatment effect and 95% confidence interval will be reported. A covariate adjusted absolute risk difference for the effect of treatment and the 95% confidence interval will also be presented. In addition, we will report number needed to treat.

Secondary outcomes will be analyzed in the same manner as the primary outcome. A per-protocol compared to intention-to-treat sensitivity analysis will be performed on the primary outcome.

Missing primary outcomes will be assumed to be missing at random; however, if more than 15% of all primary outcomes that should be available for analysis are missing, a sensitivity analysis will be undertaken in addition to the primary missing at random analysis and results compared.

Other Substudies

There is a substudy embedded in the follow-up survey at 42 days which looks at how the study population reacts to the mobile system. The purpose is to evaluate the level of learnability and feasibility for the user in real life. This includes responsiveness to messages. Another study of nonresponse will be conducted comparing answers to a smaller number of questions (on exposure and outcome) of those lost to follow-up with those who remained in the cohort.

Ethics and Dissemination

Ethical Issues

The three fundamental principles of research ethics—respect, beneficence, and justice—will be upheld through the use of an approved informed consent form, a completely confidential enrollment procedure and documentation system, and thorough ethical training and certification of all research staff that come in contact with participants. HIV results will be linked to individuals through a coded system. No interviewer will have access to an individual's HIV test results. The phone messages will only be accessible by the intended recipient, who will be given a password. Thus, there is no potential for accidental revealing of the patient's VMMC or HIV status or participation in the study. The study was approved by the Health Research Ethics Committee of Stellenbosch University (ref N14/08/108) and is registered in the Pan-African Clinical Trial Registry [PACTR201506001182385].

Informed Consent

The informed consent will be administered either one-on-one with the participants or in a group format. The group format will be followed up by a one-on-one session before signing. This consent process will be administered by a trained study recruiter. The staff member will offer to read the informed consent word-for-word to the participant. If the participant declines the offer, the staff member will give the participant ample time to read the consent form. When the participant has read the consent form, the staff member will go over the essential elements contained within. If the participant declines to read, all aspects of the informed consent will be reviewed in a language understood by the participant (English or Afrikaans). As part of the consent processes, the staff member will ask a series of open-ended questions to assess the participant's understanding of the consent. If they fail to get more than 80% of the answers right, they will be asked to read the informed consent form once again; the recruiter can then focus on the issues that they answered incorrectly and try to clarify the information. Once the above procedure has been completed successfully, the study recruiter will read out the signature page to each participant before they sign the form. A copy of the signed form will be given to the participant.

Quality Control

Standard operating procedures were developed and key staff were trained formally in clinical research standards. A clinical monitoring visit was conducted by an external consultant and adaptations were made thereafter. All fieldworkers received training on good clinical practices.

Dissemination

Two publications from the development of the intervention are planned, and at least three publications on the effectiveness of the intervention and the substudies described above are planned. Results from the study will be published within three years of study completion in Creative Commons and open-access journals. The data will be owned by Stellenbosch University and protected under South African law. A description of the project and the variables will be provided to Swedish National Data Service, where the data will be stored.

Results

Enrollment was completed on June 29, 2016. Follow-up of enrolled participants is ongoing. Loss to follow-up is under 10%. No interim analyses have been conducted.

Discussion

Summary

This trial will test a novel intervention developed with a participative, theory-based approach. If it is found to be effective, the intervention should have application to other areas

of health care, particularly where human resource shortages are chronic.

Limitations

There could be some response bias due to social desirability, meaning that those who got the messages may be more likely to report they did not have sex than those who did not get the messages (because they have been reminded repeatedly, not necessarily because they did not have sex). Additionally, the participant could potentially have healed completely before the official 6-week postoperative period ended, which would mean that penetrative sex was theoretically clinically safe. A patient could also unintentionally report his allocation status to a nurse during a clinical follow-up visit, thus contaminating the blinding. Finally, there is a possibility that going through the male circumcision procedure may disinhibit men from practicing safe sex such as using condoms with casual partners. The original study protocol included a 6-month follow-up to study the effects of the intervention on such risk compensation. However, funding did not allow for this and this arm was removed. Future studies should include such aspects where possible.

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Authors' Contributions

ST and VD designed the study, YT and DS collected data and oversaw the day-to-day operations including all ethical applications, and TE, MMc, and MP did the sample size calculations, oversaw randomization process, and wrote the analysis plan.

Conflicts of Interest

None declared.

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Abbreviations

HISP: Health Information Systems Program
RCT: randomized controlled trial
UNAIDS: Joint United Nations Programme on HIV/AIDS
VMMC: voluntary medical male circumcision
WHO: World Health Organization

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Protocol

MHealth to Improve Measles Immunization in Guinea-Bissau: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Recent studies have revealed a low measles vaccination (MV) rate in the Republic of Guinea-Bissau (West Africa) that has not increased in accordance with the increasing coverage of other vaccinations. Measles is the deadliest of all childhood rash/fever illnesses and spreads easily, implying that if the vaccination coverage is declining there is a significant risk of new measles outbreaks [27]. Meanwhile, mobile health (mHealth; the use of mobile phones for health interventions) has generated much enthusiasm, and shown potential in improving health service delivery in other contexts.

Objective: The aim of this study is to evaluate the efficiency of mHealth as a tool for improving MV coverage while contributing to the mHealth evidence base.

Methods: This study will take place at three health centers in different regions of Guinea-Bissau. Participants, defined as mothers of the children receiving the MV, will be enrolled when they arrive with their children at the health center to receive the Bacillus Calmette-Guérin vaccination, usually within one month of the child's birth. Enrolment will continue until a study population of 990 children has been reached. The participants will be randomly assigned to a control arm or one of two intervention arms. Each of the three groups will have 330 participants, distributed equally between health centers. Participants in the first intervention arm will receive a scheduled short message service (SMS) text message reminding them of the MV. Participants in the second intervention arm will receive a voice call in addition to the SMS message, while the control arm will receive no interventions. The MV is scheduled to be administered at 9 months of age. Although the vaccine would still be effective after 12 months, local policy in Guinea-Bissau prevents children aged >12 months from receiving the vaccination, and thus the study will follow-up with participants after the children reach 12 months of age. Children who have not yet received the MV will be offered vaccination by the project group.

Results: The study will analyze the efficiency of the intervention by determining its overall effect on MV coverage and timeliness when children reach 12 months of age. The main analysis will be stratified by intervention group, health center, level of education, ethnic group, and role of the person receiving the text messages (eg, mother, father, other family member). Secondary outcomes include the average number of health center visits (with intention to obtain the MV) required before successful administration.

Conclusions: Despite the rapid proliferation of mHealth projects, only a small number have been evaluated in terms of direct links to health outcomes. This gap in knowledge requires solid evidence on which policy-makers can base decisions. This study aims to produce significant knowledge about mHealth implementation within a Sub-Saharan context while creating data-supported evidence.

Trial Registration: Clinicaltrials.gov: NCT02662595; https://clinicaltrials.gov/ct2/show/NCT02662595 (Archived by WebCite at http://www.webcitation.org/6jH8YiSjY)

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KEYWORDS

mHealth; eHealth; SMS reminders; voice reminders; Guinea-Bissau, ODK; Africa; RapidSMS; health systems strengthening; randomized controlled trial; measles; immunization

Introduction

Background

The use of mobile phones as a tool for health interventions (mHealth) has shown significant potential worldwide, and has been used in low income settings. The benefits of such interventions include low start-up costs [1] and the possibility of reaching a great number of people. According to recent reports [2,3], a number of mHealth initiatives have already been conducted around the world. Despite these advances, mHealth has untapped potential, especially in the African region, where the number of such initiatives is the lowest in the world [3]. Although the rapid proliferation of mHealth projects has generated enthusiasm [4], more evidence establishing their efficacy and effectiveness is needed [3,5,6].

Current studies from the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) and the Global Alliance for Vaccines and Immunization (GAVI) reveal a low measles vaccination (MV) rate in Guinea-Bissau that has not increased in accordance with the increasing coverage of other vaccinations. In 2014 the United Nations International Children's Emergency Fund (UNICEF) estimated that MV coverage among children 12-23 months of age in Guinea-Bissau was 64% [7], a number that has steadily decreased since 2004 [8].

Meanwhile, other studies have shown that mHealth interventions can be efficient in increasing awareness and demand for health services [9-14]. An important prerequisite for mHealth projects to be successful is access to mobile phones, which has grown rapidly in many developing countries. According to the World Development Indicators provided by The World Bank, it was estimated that in 2013 there were 74 cellular subscriptions per 100 people in Guinea-Bissau (compared to 45 in 2011 and 63 in 2012) [15].

Measles is the deadliest of all childhood rash/fever illnesses and spreads easily, implying that if the MV coverage is declining [16] there is a significant risk of new measles outbreaks [17]. Recent reports from World Health Organization conclude that increased activities are needed to resume progress towards the 2015 Millennium Development Goals of measles control and elimination [18,19]. In addition, recent studies have lead the Strategic Advisory Group of Experts on Immunization to suggest that MV is associated with possible beneficial effects on all-cause mortality [20]. Interventions that enhance the timeliness and coverage of MV are therefore likely to have a great beneficial impact on child health. Thus, we suggest an mHealth intervention to increase MV coverage by sending vaccination reminders by short message service (SMS) texts to mothers before their child's scheduled MV. While this intervention aims at increasing awareness amongst mothers, it also presents potential benefits regarding the supply of MVs. Current policies in Guinea-Bissau require a minimum number of children to be present before a vial of vaccine can be opened, and since the health centers typically only administer vaccinations one or two days per week, mothers will often the be sent home and told to return a different day. This intervention has the potential to coordinate the vaccination visits and help ensure that enough children are present for the health centers to open a vial of vaccines on a given day, and ensure that mothers arrive on the correct day at the health centers.

Studies from the INDEPTH Network and GAVI have demonstrated that rural regions have particularly low MV coverage, so this intervention will focus on the rural regions of Tombali, Gabu, and Cacheu in the Southern, Eastern, and Northern Guinea-Bissau, respectively.

Objectives

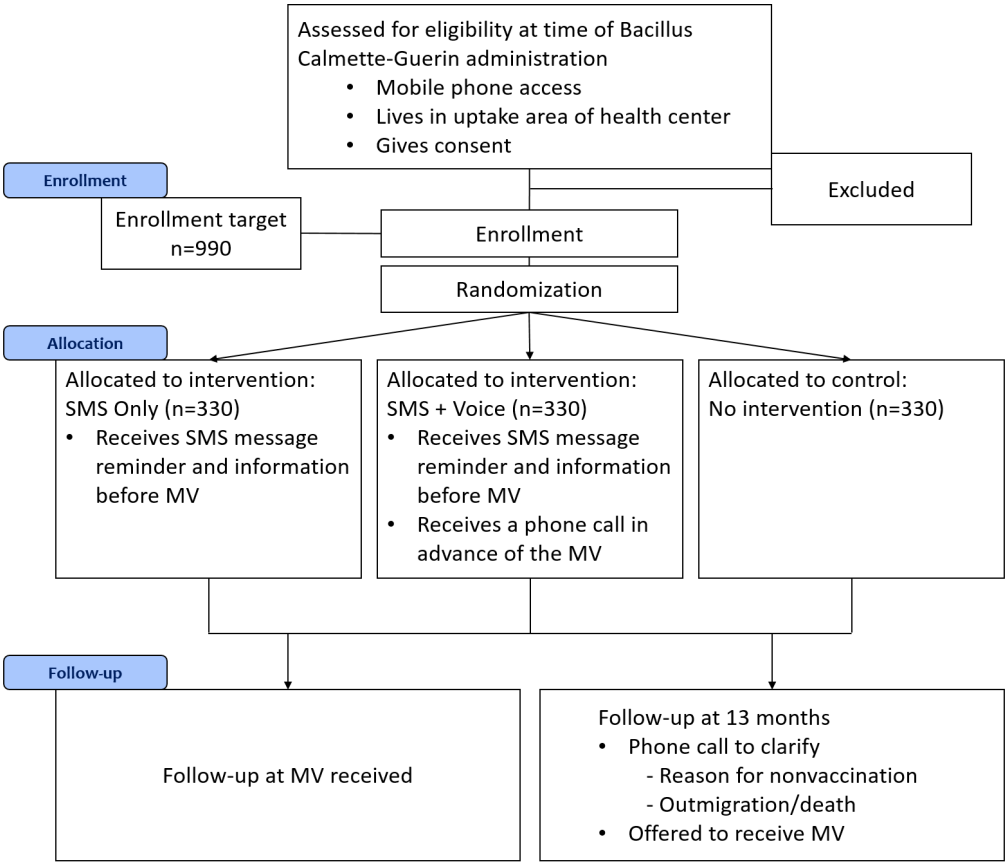
The primary objective of this intervention is to enable a beneficial impact on child health by improving timeliness and coverage of MVs using simple and cost-efficient methods. Specifically, the study aims to investigate whether a mobile phone targeted reminder system can be used in the context of rural Guinea-Bissau, and what effect this intervention can be expected to have, as well as potential obstacles and barriers to implementation.

Methods

Trial Design

This study is designed as a multi-site, three arm, parallel randomized controlled trial (RCT). Participants will be randomized to either one of two intervention arms (one receiving an SMS reminder, the other receiving the SMS reminder and an additional voice call) or a control arm (no intervention) with a 1:1:1 allocation ratio (Figure 1).

Figure 1. Study flow.



Informed Consent Forms

Informed consent will be obtained for all study participants before enrollment. The study will be described to the potential participants by trained study workers at the health centers. The project description will be explained in the preferred language of either Portuguese or Creole. After the project has been explained, the potential participant will be asked a number of questions related to the project to ensure adequate understanding, and informed consent forms will be signed.

Randomization and Blinding

Three randomization sequences (one per health center) were generated using a software algorithm. The randomization sequences are only accessible for the central project group, and will be used when the central project assistant is adding study participants to the scheduling system and delivering phone messages. Participant allocation is concealed to the study assistants at the health facilities, and will only be revealed during the follow-up interview when, and if, the participants come to the health facility to receive MVs.

Setting and Participants

Study participants, defined as mothers of the children receiving the MV, will be enrolled at one of three selected health facilities when their children receive their first vaccination, usually the Bacillus Calmette-Guérin vaccine, which is administered shortly after birth. The study will be explained to the mothers by the health workers in the local language (Portuguese Creole), and pending their informed consent, the mothers will be enrolled in the study. Enrollment is completed by the health worker, who will take note of the participant's phone number(s), date of birth, and the baby's name. A sticker with a unique study identification number will be placed on the child's vaccination card to indicate that this child is participating in the study.

The inclusion criteria for enrollment in the study are that the participant has access to a cell phone (either her own phone or the phone of a household member or community contact) and that she lives in the uptake area of the health center.

A study assistant will collect information regarding the participant, including age, ethnic group/primary language, and level of education. This information will be entered into a digital questionnaire using an Android device. The data will be successively transferred to a central information technology (IT) system, where a central study assistant will randomize participants and enter the data into the system responsible for scheduling and sending SMS messages, and creating call-lists for the participants scheduled to receive verbal messages.

The enrollment period for this study component will continue until a study population of 990 children (see sample size calculation below) has been reached (total enrollment time is estimated to be approximately 6 months). We will follow up after children reach 12 months of age, since MVs are scheduled to be administered at 9 months of age, and local policy in Guinea-Bissau prevents children aged >12 months from receiving the MV. Thus, this component of the intervention is estimated to last no longer than 18 months.

Intervention

The intervention being evaluated is a cell phone reminder and coordination system, which seeks to coordinate potential recipients of MV with MV opportunities (ie, days in which MV is administered either at their local health center, or at a relevant outreach day). Participants allocated to intervention groups will receive two SMS text reminders in the local language of Portuguese Creole. The first message will be delivered three days before the suitable MV opportunity, and the second will be sent one day before. If the participant is allocated to also receive a phone call, a project worker will call the supplied phone number two days before the MV opportunity.

SMS messages are *active* in the cell phone network for 24 hours, after which the delivery attempt will be considered failed. If the delivery attempt of a first message fails (ie, three days before MV opportunity), the message will be redelivered. If delivery of the second message fails (ie, one day before MV opportunity), it will not be redelivered due to time rendering it irrelevant. If a phone call fails it will be reattempted two times: once on the same day, and a final attempt on the day before MV opportunity. We will register all failed message delivery attempts and account for these in the subsequent analysis.

If several phone numbers are supplied, SMS texts will be sent to all phone numbers. Voice calls will made to one number, and if the call to the first number is not successful, the second number will be attempted, and so on. Voice calls, like the SMS texts, will be made in the Creole language.

If a study participant does not arrive at the MV opportunity, or if the MV opportunity is cancelled or unavailable for any reason, the study participant will receive a new set of messages/voice calls at the next relevant MV opportunity, assuming the child is still eligible (ie, child is 9-12 months of age). The new set of messages will be delivered regardless of whether earlier delivery attempts for the participant failed.

Follow-Up

When MVs are given in one of the selected health centers, the participants will be registered in the system as having received the vaccination at the given date. The study assistant will also take note of a set of follow-up questions concerning the participants' motivation for receiving the vaccination as well as a final question as to whether the participant received and understood the text reminder/voice call. The answers to these questions will eliminate the blinding of within the study, since the participants' answers will reveal their allocation group. In addition, data regarding price of phone call and time spent per phone call will be collected after each call, and analyzed in terms of cost effectiveness.

A qualitative analysis will be done when children reach 13 months of age, for all participants not registered as having received MVs. The analysis will be based on phone interviews to determine the main reasons for not receiving the vaccine, and it will be registered whether the child has received MV at a different location, moved out of the area, or died. All of these participants will be offered MVs for their children.

A selection of participants from each intervention group (n=10-15), who registered their children as having received the MV, will be visited by a study assistant in order to conduct a face-to-face follow-up interview. These interview will focus on the participants' perception of the intervention message and the overall experience of the intervention. Data collection will rely on digital questionnaires filled out by project assistants during house visits. Difficulty with logistics (ie, locating and visiting the participants) explain the relatively small number of participants selected for this analysis.

Location and Duration of the Project

In coordination with the Ministry of Health in Guinea-Bissau, three participating health centers will be selected in the aforementioned regions of rural Guinea-Bissau. The centers will be selected based on the size of the health center (ie, the capacity for enrolling enough study participants during a period of six months), distance to neighboring health centers, mobile cell network coverage, and current level of outreach/other studies.

The first component was carried out in the period from October, 2015 to March, 2016. The second component is scheduled to begin in the first quarter of 2016 and end in the third quarter of 2017 (18 months).

Development of Reminder Content and Timing

In order to assess the intervention context, and determine the optimal timing and content of the messages to be used in the RCT, a qualitative analysis will be conducted. The analysis will be based on field visits in the rural areas to observe the context for the intervention, including the daily routines for mothers with children aged 6-12 months and their usage of mobile technology. In addition to these observations, a number of semistructured qualitative interviews will be conducted to acquire knowledge about what time of day a message would be preferred, and potential cultural barriers preventing the delivery of messages to household members or neighbors (if the mother does not own a phone).

During the interview, the interviewee will be presented with one of three different versions of the intervention message, and asked questions to evaluate their understanding:

1. A very brief description of measles infection and the reasons for vaccination, inspired by a post card MV reminder intervention that was implementing using the *health belief model* [21].

2. A shorter and more imperative message telling the participant to go to the health center to receive the MV.

3. A verbal message read to the interviewee by the interviewer. The messages will be personalized with the baby's name and the name of the relevant health center.

All of the messages will be presented in two formats, depending on whether the message is to be delivered directly to the participant's phone or via the phone of a household member/neighbor. The indirect message variants will be evaluated by presenting them to nearby household members

and assessing their understanding and willingness to relay the message.

Technical Implementation

Building on the efforts of UNICEF, the technical aspects of the project will be based on the open source IT system, RapidSMS. This system is well documented, and has previously been applied successfully in comparative interventions in Kenya and Rwanda [10,22]. The system is customizable and will be adapted to the context of this study. The RapidSMS system will generate reports on SMS texts that failed to be delivered to the recipient (eg, due to cell phone being off for longer periods of time, or a changed phone number). These texts will be delivered again. To enable digital data collection using tablets/phones, an adapted version of Open Data Kit will be used.

To enable capacity building, and thus increase the chances of the system being implemented if the intervention is deemed successful, the technical implementation will be done in close coordination with technical personnel from the national Ministry of Health.

Results

In order to evaluate mHealth as a viable means of increasing MV coverage and timeliness, an RCT will be conducted. The mHealth intervention will be evaluated using the outcomes in Textbox 1.

Textbox 1. Outcome measures of the randomized control trial.

- **Primary outcome A:**

  MV coverage at 12 months of age. Difference in MV coverage at 12 months of age between the intervention groups and the control group.

- **Secondary outcome B:**

  Timeliness. Difference in timeliness of MVs administered, measured as median age of vaccinated children.

- **Secondary outcome C:**

  Average number of visits to the health center (with the purpose of receiving MV) needed before MV is successfully administered.

- **Secondary outcome D:**

  Analysis of context and evaluation of the different intervention messages.

- **Secondary outcome E:**

  Cost/benefit analysis of verbal telephone messages versus SMS messages. The costs in terms of time spent (voice calls), SMS fees, and technical setup will be evaluated against the observed behavior change.

- **Secondary outcome F:**

  Reasons for nonvaccination. Qualitative study of the main reasons for noncompliance with the Expanded Program on Immunization, among participants whose children have not received the MV before 13 months of age.

- **Secondary outcome G:**

  Effect of collecting multiple phone numbers. Analysis of whether the number of phone numbers collected per participant influences the success rate of the intervention.

- **Secondary outcome H:**

  Qualitative evaluation of the participants' perception of the intervention message and overall experience of the intervention.

Safety & Ethics

Ethical Considerations

One of the key challenges in relation to mHealth is the issue of privacy and data security [23], especially when potentially stigmatizing diseases or substance abuse could be disclosed if family members or others see the text messages, or gain access to the phone used for the intervention [24]. This issue becomes all the more relevant since we have chosen to include mothers, some of whom do not have their own phones, but only have access to shared phones. However, it is our judgment that vaccination reminders do not represent any risk of unwanted disclosure. In addition, a recent study from Argentina concluded that 96% of the study participants (pregnant women attending antenatal care) responded that they would like to receive text messages and phone calls [25]. We have chosen to include participants who do not have their own private phones in an attempt to avoid adding further to the *digital divide* (ie, social inequality due to lack of access to and/or knowledge of information and communication technology).

Another ethical consideration is how to embrace illiteracy/multiple spoken languages without adding to cultural divides or discrimination against certain population segments or ethnic groups. Culture-specific wording of messages is also important, in order to avoid unintended negative effects [26]. At the time of enrollment, trained health workers will describe the study in detail to the potential participants, and assess their understanding in order to obtain their informed consent. All information will be available in Creole (the primary spoken language of Bissau).

To avoid sending SMS reminders to participants who have died or moved out of the study area, or those whose children have died or received the vaccine ahead of schedule, follow-up will

be done to the extent possible at the health facilities. It is likely that some of these events will go unnoticed, potentially resulting in inappropriate messages being sent. This problem does not differ from current practices of the Health and Demographic Surveillance System routines, in which families are occasionally asked about deceased members of the household. The possibility of receiving a message regarding a deceased child will furthermore be explained during the informed consent phase.

Registration and Ethical Approvals

This project has obtained the approval of the ethical committee of Guinea-Bissau as well as a guiding statement from the ethical body Udlandsudvalget in Denmark. The project has also registered with clinicaltrials.gov (reg.no. NCT02662595).

Data Management & Statistical Analysis

Data Management

The data will be collected using digital questionnaires and stored in a protected database. The data will not be shared with people or organizations outside of the Bandim Health Project, unless proper authorizations are obtained from the ethical committee in Guinea-Bissau. However, the collected data might be made available to an external project group as part of ongoing monitoring and evaluation efforts.

Sample Size Calculations

Current statistics indicate MV coverage of approximately 75% at 12 months of age in the rural areas of Guinea-Bissau. Drawing on experiences from other studies implementing SMS reminders [13], we aim for an increase in MV coverage of 10 percentage points. Using a significance level of 5% and 80% power, and a hypothesized increased MV coverage to at least 85% in each of the intervention arms (compared to the control arm), a total of 810 children are needed (270 in each arm). Adjusting for expected loss-to-follow-up between 15-20% (eg, outmigration, death, children being vaccinated elsewhere), which is comparable to other mHealth studies [27], we plan to enroll 990 study participants (330 in each arm).

The current median age of MVs given before 12 months of age in rural Guinea-Bissau is approximately 295 days of age [7]. The age distribution is fairly normal, and in the following power calculation we have used a normal approximation: with 270 children in each arm and an MV coverage of at least 75%, we are able to detect a change of 7 days in median age (using a significance level of 5% and 80% power).

Statistical Analysis

The main outcome of MV coverage at 12 months of age (366 days of age) will be calculated as percent who received MV at the health centers, among all children enrolled. Furthermore, coverage will also be calculated based on follow-up interviews when children reach 13 months of age, among study participants whose children did not receive the MV at the health centers. The coverage (percentages) will be compared using Mantel-Haenszel statistics stratified for health center for each of the intervention groups (SMS and voice calls) compared with the control group. The secondary outcome B (Textbox 1) of timeliness of MVs will compare age distributions between vaccinated children, among all children having received MVs before 12 months of age (366 days), using linear regression adjusted for health center. A statistical significance level of 5% will be used. A subanalysis will stratify for study participants having their own private mobile phone versus those using the phone number of another community member. Due to the groups being randomized, we do not expect baseline imbalances. In the case that such trends do occur, we will be unable to rule out other imbalances or unmeasured confounders. The main outcome will therefore be the crude estimate. However, we will investigate the impact of adjusting for unbalanced background factors in sensitivity analyses. The study will be conducted and reported in accordance with Consolidated Standards of Reporting Trials guidelines [28].

Discussion

Possible Constraints

External threats to the project, such as strikes in the health sector, shortages of measles vaccine, and other interventions in the same region, will prompt ad-hoc decisions. Problems with vaccine delivery to the vaccination sites will result in the rescheduling of intervention messages (eg, the reminder messages can be rescheduled until vaccine is restocked).

Dissemination of Results and Publication Policy

Articles are planned for each of the main study components. The main article, concerning the second study component, will contain a statistical analysis linking the effect the mHealth intervention to health outcomes in terms of MV coverage and timeliness. The primary author of the article will be Emil Rossing, with the remaining core members of the project team listed as contributing authors.

A second article will analyze the cost and effect of the mHealth intervention, linking the intervention to vaccination coverage, and add to the evidence base for mHealth interventions. In addition to these articles, the findings of this study will be presented to the National Ministry of Health in Guinea-Bissau, which will also be included as much as possible during the project implementation.

Limitations and Anticipated Problems

Several problems are anticipated in this study, including technical obstacles such as an unstable cellphone network, and low or no signal in some areas. In order to mitigate these issues, extra attention will be given to *delivery reports* to ensure that the text messages are delivered correctly. In addition, the impact of network-related problems will be covered by the follow-up questionnaire.

The project is also vulnerable to other interventions related to the MVs that are being carried out within the study area, since this could distort the findings of this study. To minimize this risk, the study team will coordinate closely with the National Ministry of Health in Guinea-Bissau.

By only enrolling participants who have access to mobile telephones, there is a risk of potentially adding to social injustice by focusing on a selected demographic with comparably better access to resources, sometimes referred to as *digital divide*. However, we have tried to mitigate this problem by defining

access to a mobile telephone in the broadest sense possible, by also including participants who will receive the reminder message on the phone of their community's *health communication agent*. Such agents will be community residents employed by the Ministry of Health as contact points to disseminate information about health events, such as vaccination campaigns. These agents will also help to mitigate the limitation of study participants that do not speak Creole. However, the fact that there are multiple spoken languages in the study area still poses a limitation to the project.

Acknowledgments

This project has been guaranteed funding by Bandim Health Project and Research Center for Vitamins and Vaccines. The project is also committed to applying for funding from other sources, and a one-year PhD faculty scholarship has kindly been granted by the University of Southern Denmark.

Conflicts of Interest

None declared.

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Abbreviations

GAVI: Global Alliance for Vaccines and Immunization
INDEPTH: International Network for the Demographic Evaluation of Populations and Their Health
IT: information technology
mHealth: mobile health
MV: measles vaccination
RCT: randomized controlled trial
SMS: short message service
UNICEF: United Nations International Children's Emergency Fund

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Protocol

Telemedicine for Gestational Diabetes Mellitus (TeleGDM): A Mixed-Method Study Protocol of Effects of a Web-Based GDM Support System on Health Service Utilization, Maternal and Fetal Outcomes, Costs, and User Experience

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Abstract

Background: Women with insulin-treated gestational diabetes mellitus (GDM) require close monitoring and support to manage their diabetes. Recent changes to the diagnostic criteria have implications for service provision stemming from increased prevalence, suggesting an increased burden on health services in the future. Telemedicine may augment usual care and mitigate service burdens without compromising clinical outcomes but evidence in GDM is limited.

Objective: The Telemedicine for Gestational Diabetes Mellitus (TeleGDM) trial aims to explore the use of telemedicine in supporting care and management of women with GDM treated with insulin.

Methods: The TeleGDM is a mixed-methods study comprising an exploratory randomized controlled trial (RCT) and a qualitative evaluation using semistructured interviews. It involves women with insulin-treated GDM who are up to 35 weeks gestation. Participating patients (n=100) are recruited face-to-face in outpatient GDM clinics at an outer metropolitan tertiary hospital with a culturally diverse catchment and a regional tertiary hospital. The second group of participants (n=8) comprises Credentialed Diabetes Educator Registered Nurses involved in routine care of the women with GDM at the participating clinics. The RCT involves use of a Web-based patient-controlled personal health record for GDM data sharing between patients and clinicians compared to usual care. Outcomes include service utilization, maternal and fetal outcomes (eg, glycemic control, 2nd and 3rd trimester fetal size, type of delivery, baby birth weight), diabetes self-efficacy, satisfaction, and costs. Semistructured interviews will be used to examine user experiences and acceptability of telemedicine.

Results: The trial recruitment is currently underway. Results are expected by the end of 2016 and will be reported in a follow-up paper.

Conclusions: Innovative use of technology in supporting usual care delivery in women with GDM may facilitate timely access to GDM monitoring data and mitigate care burdens without compromising maternal and fetal outcomes. The intervention may potentially reduce health service utilization.

Trial Registration: Australian and New Zealand Clinical Trials Registry (ANZCTR): ACTRN12614000934640; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=366740 (Archived by WebCite® at http://www.webcitation.org/6jRiqzjSv).

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KEYWORDS

gestational diabetes; telemedicine; Internet; electronic personal health record

Introduction

Recent changes to tighten the diagnostic criteria for gestational diabetes mellitus (GDM) [1] mean many more women will be diagnosed with this condition, placing increased demand on clinical services to provide diabetes care. Women with insulin-treated GDM, in particular, often require more intensive follow-up and support for titration of insulin and overall management of GDM [2,3].

The prevalence of GDM is estimated to be 6% to 15% of pregnancies [1,4] dependent on whether the diagnostic criteria set by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) or the Australasian Diabetes in Pregnancy Society (ADIPS) is used. The IADPSG's revisions in recent years give higher prevalence estimates [1].

Good control of blood glucose level (BGL) in GDM is important to minimize the risk of pregnancy and birth complications associated with the condition. Such complications can include large for gestational age (LGA) babies, macrosomia, increased likelihood of cesarean delivery, preeclampsia, and fetal shoulder dystocia [3-5]. First-line therapy to control hyperglycemia involves dietary modification and physical activity [1,3,6] or oral hypoglycemic agents (OHA) [3]. An insulin regimen is initiated if the OHA therapies are inadequate in optimizing BGL or there is evidence of increased risk of macrosomia [6]. Approximately 50% of women with GDM go on insulin regimen, which requires close monitoring and intensive follow-up for regular insulin titrations to control persisting hyperglycemia [2].

The increasing prevalence of GDM [7-10] and the intensive clinical care needed have implications for the capacity of health care services to provide timely care and the clinical outcomes of such care. There is a need to explore innovative ways to deliver care and support for women with GDM to ease the service burden while not compromising quality of care. This may also potentially deliver cost efficiencies and savings.

In our systematic review [11], telemedicine has emerged as a potentially effective intervention to address service utilization while producing maternal and fetal outcomes similar to or better than usual care.

Telemedicine is defined as "the use of telecommunications technology to provide medical information and service" [12]. Telemedicine (also known as telehealth) has been implemented as a monitoring intervention in diabetes, heart failure, and chronic obstructive pulmonary disease [9,10,13] with promising results. For instance, a small study that trialled the use of cellular phones to transmit self-monitoring blood glucose data in type 2 diabetes found the approach was feasible, easy to use, and resulted in patients having fewer hospital visits [8]. Recent studies exploring a smartphone application or text messaging in type 1 and/or 2 diabetes reported improvements in glycemic control in favor of the telehealth approaches [14,15], while self-efficacy and quality of life were unchanged [14]. A study of telemedicine in heart failure patients reported better quality of life and heart failure self-care while hospital utilization remained unchanged [13]. While there may be some cautious optimism about the benefits of telehealth-based interventions, usage by patients appears modest, approximately 34% to 39% [16]. It remains to be seen how all this translates to GDM, especially in a real-world clinical setting.

Specifically in GDM, telemedicine interventions compared to control/usual care may reduce service utilization such as face-to-face clinic visits (4.25 [standard deviation or SD 0.93] vs 6.22 [SD 1.48], respectively; P=.002) and unscheduled visits (0.50 [SD 0.73] vs 2.89 [SD 1.05], respectively; P<.001) [12], while achieving similar outcomes (with trends in favor of telemedicine) for glycemic control, birth weight, incidence of macrosomia [11,12,17,18] and diabetes self-efficacy [12,17-19]. The main limitations of studies of telemedicine in GDM that we identified in our systematic review of the literature [11] are that there are very few randomized controlled trials (RCT) and sample sizes tend to be small. None of the trials included in our review evaluated costs, perhaps due to the lack of an agreed standardized evaluation framework for telehealth interventions. We also identified other methodological limitations such as shorter interventions and the heterogeneous nature of the outcomes and telehealth interventions used [10,20-22]. Interventions were perhaps too short to have significant measurable impacts; outcome measures varied across studies, posing challenges to conducting effects through pooled data analysis, and the interventions varied considerably, ranging from telephone support and videoconferencing to text messaging [10,20-22], making comparison of studies and generalizability difficult.

Our innovative study, the Telemedicine for Gestational Diabetes Mellitus (TeleGDM) trial, uses a Web-based approach to augment the management of women with insulin-treated GDM. Our aim is to explore the effects of telemedicine on health system performances including patient utilization of outpatient clinical care, maternal and fetal clinical health outcomes, and patient and clinician satisfaction and acceptance with respect to the intervention technology. In addition, a cost comparison between the two arms of the trial will be performed to determine if there are any provider cost savings that might be associated with changes in outpatient clinic attendance.

We hypothesize that with timely access to patient GDM self-monitoring data, health service utilization would be decreased without compromising maternal and fetal outcomes with an associated provider cost saving, greater satisfaction with the telemedicine, and a positive user experience.

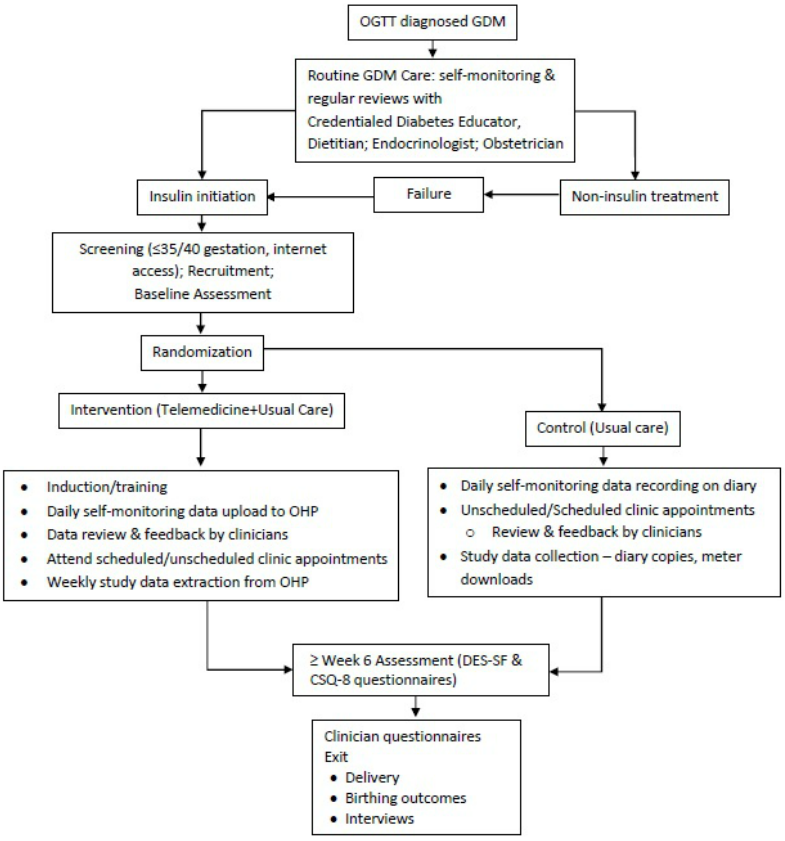
The project is registered with the Australian and New Zealand Clinical Trial Registry [ACTRN12614000934640], and ethics approval was granted by Northern Health Human Research Ethics Committee (HREC P/11/14) and Bendigo Health Human Research Ethics Committee (HREC/15/BHCG/44).

Methods

Study Design

The TeleGDM trial is a mixed-methods study comprising an exploratory RCT and a qualitative evaluation using semistructured interviews (Figure 1). RCTs are the gold standard for providing evidence for practice [23,24] but have a major limitation of ". . . not tell(ing) the whole story . . . " [25]. Qualitative methods such as interviews can provide more in-depth information about participant experiences [26] than would otherwise be captured by quantitative methods alone.

Figure 1. Study design flowchart.



Population, Setting, and Inclusion Criteria

The first group of participants comprises pregnant women diagnosed with GDM who have commenced insulin therapy to control hyperglycemia. These women attended outpatient GDM clinics at two tertiary hospitals between August 30, 2014, and October 30, 2016, inclusive of follow-up. One hospital is in an outer metropolitan region with a catchment population of significant cultural and linguistic diversity. The other is regionally located and serves a population with a rural background. Combined, the two hospitals have approximately 5000 live singleton births annually, and approximately 800 of the pregnancies are affected by GDM.

Women with GDM (patient participant group) are eligible for inclusion if they have a clinical diagnosis of GDM based on the IADPSG criteria following an oral glucose tolerance test [1]. Other eligibility criteria include gestation up to 35 weeks and access to the Internet via a personal computer, smartphone, or tablet. Prepregnancy glucose intolerance, twin pregnancies, GDM not treated with insulin, and other types of diabetes are exclusion factors.

The second group of participants are Credentialed Diabetes Educator Registered Nurses (CDE-RNs) who provide GDM care at the two centers. The CDE-RNs are directly involved in the RCT component of the study and provide care to women with GDM in the course of their usual practice. The number of these clinicians across the two sites is 8; all are requested to complete the clinician assessments for the study.

Recruitment and Randomization

The women with GDM regularly attend outpatient GDM clinics at the hospitals. It is at these weekly clinics that prospective participants are recruited face-to-face. Clinicians identify potentially eligible patients, give them a study brochure and/or seek permission for referral to the lead researcher or study research assistants. Following referral, participants are

approached for face-to-face screening, detailed briefing, consent, randomization, and completion of baseline questionnaires. A 1:1 randomization schedule was generated in STATA 11.0 (StataCorp LP) by an independent statistician. The lead researcher and RAs have no involvement in routine care of the patients.

Some ethnic groups (Indian, Asian, Arabic/Middle Eastern, Pacific Islander, Aboriginal, and African) are considered high risk for GDM [27]. Previous GDM and use of insulin in past pregnancies are also considered high risk factors for GDM. Therefore randomization was stratified according the level of risk (high or low). Stratification avoids group allocation imbalances on factors that have significant influence on prognosis, avoids type 1 error, and improves study power for small trials [28]. Group assignments are concealed in two sets of opaque envelopes; the first set is the randomization schedule for the low risk subgroup and the second for the high risk GDM subgroup. Following consent, the envelopes are consecutively opened for assignment by the recruiter. Clinicians are not blinded to group allocations because they need data from the intervention for clinical care.

Usual Care (Control)

Usual care refers to clinical GDM care processes currently in practice at the participating hospitals, and this will be the control group. In line with recommended best practice [29,30] diagnostic screening for GDM occurs at 24 to 28 weeks gestation for women with no known history of diabetes or earlier for those considered high risk for GDM. Following diagnosis through to end of pregnancy, ongoing care is provided via a multidisciplinary team of endocrinologists, dietitians, and CDE-RNs. The role of the team is in addition to obstetric care.

From an endocrinology perspective, care involves an initial group counseling and education with a CDE-RN and dietitian covering aspects of GDM self-management. The CDE-RNs provide the pregnant women with free BGL meters from an approved supplier. The meters are individual use and the women purchase their own consumables (ie, test strips and lancing devices). Treatment targets are ≤5.0 mmol/L for preprandial BGL and ≤6.7 mmol/L for 2-hour postprandial BGLs. Insulin is initiated or titrated if BGLs are above target over three successive days. Ongoing face-to-face appointments are scheduled with members of the team as needed until delivery. Appointments generally occur every one to two weeks as determined by the clinicians. Patients on insulin have more frequent reviews especially in the early stages of insulin initiation. Self-management involves keeping a daily paper diary record of GDM self-monitoring data (1 preprandial and 3 postprandial BGLs, insulin dosing, symptoms, and dietary information). The diaries are reviewed by the clinicians at each outpatient clinic. The women also have the option to call the CDE-RNs out of scheduled appointments if BGLs are outside target.

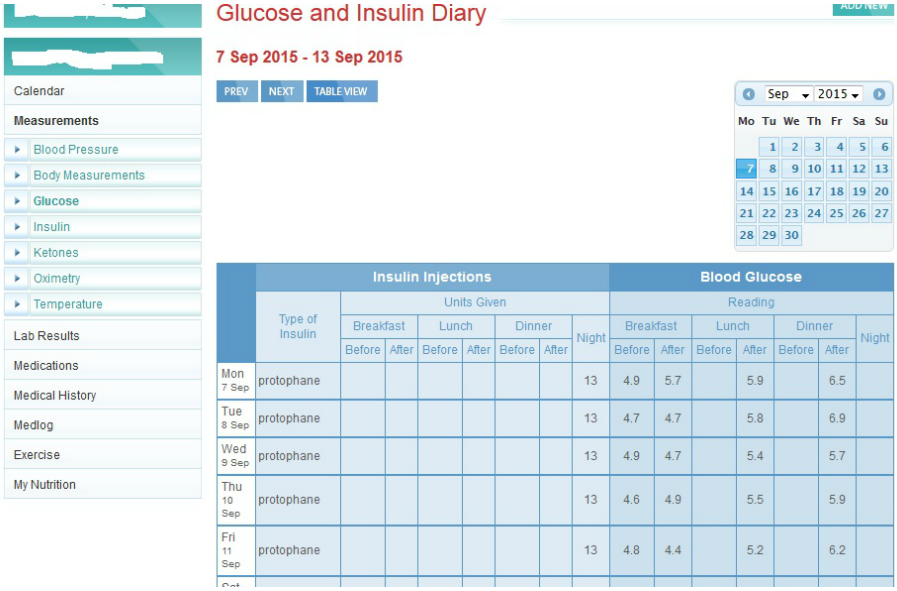
Telemedicine (Intervention)

The intervention is telemedicine as an adjunct to usual care. The main distinction to usual care is GDM self-monitoring data is shared via a telemedicine system in lieu of paper diaries. The intervention uses a Web-based portal, Online Health Portfolio (OHP) [31], for data sharing and communication between patients and clinicians and is premised upon (1) women with GDM undertaking regular GDM self-monitoring and entering data; (2) timely availability of data to clinicians via the Web-based OHP, hence timely response to the women's GDM care needs informed by the available data; and (3) upon carrying out advice and feedback the women will better manage GDM and require less frequent appointments. Currently there is no empirical evidence for OHP, and it was chosen for this study on pragmatic reasons and anecdotal accounts of independent endocrinologists who used it in their practice.

Online Health Portfolio is a secure Web-based patient-controlled personal health record that is accessed securely through an Internet browser on a personal computer, smartphone or tablet. It is a proprietary system developed and owned by a vendor who is independent of the study. It uses 256-bit data encryption and 5-minutes inactivity time logout. Besides data entry and preview, the users can have graphical visualization of summary data and trends filtered by pre- or postprandial meal type or time, set up automatic reminders on the internal calendar, and set trigger levels for BGL alerts. Reminders may be forwarded to the patient's smartphone as a short message service (SMS) text. There is an internal messaging feature within OHP to enable 2-way messaging of free text between clinicians and patients. Clinicians also have the option to send an SMS text to the patient's smartphone from OHP. Participating patients use their own Internet-connected devices while clinicians use their usual hospital-provided Internet-connected computers. Username and password access to OHP is independent of all other hospital applications and systems. While patients are at liberty to access OHP at any time, clinicians interact with OHP during the course of normal work hours (8:00 AM to 4:30 PM), Monday through Friday. Multimedia Appendix 1 and Multimedia Appendix 2 show of some screenshots of the OHP.

The research team have no financial interest in the OHP. The lead researcher (TR) has had some input into modifications and refinements to the Web portal in order to enhance usability by the patients and clinicians. An example is the introduction of the diary view format in Figure 2. The vendor usually charges an annual subscription fee (AUD $85) to patients to use OHP while clinicians' subscriptions are free. For this study, patient subscriptions are covered in the study budget. OHP consumes negligible amounts Internet data, thus adding no perceptible costs to patients' own home or mobile Internet service.

Figure 2. Diary view format introduced after modifications to enhance usability of OHP.



Upon enrollment, patient participants undergo individual semistructured 30 to 45 minutes induction by the lead researcher or research assistants.

The induction is hands-on and covers the initial set-up with participants practicing all the tasks they are expected to perform independently from then on. Induction covers signing up, logging on, navigating through the OHP Web portal, data entry, messaging, and reviewing data trend/summary graphs. All data entry is practiced using the previous day's data. Performing BGL self-monitoring, administering insulin, and following dietary advice are part of routine diabetes education and counseling provided by a multidisciplinary endocrinology care team as described under usual care. Participants are also instructed on how to share this health information with the GDM clinicians for the purpose of providing clinical care and with the project lead investigator for research data collection and data management purposes. When required and in order to improve study data collection, the lead researcher may set up automatic reminders on OHP to send reminders every second day to prompt the noncomplying patient to enter data. Activating or setting up automated reminders is not routine but it is targeted for those who fail to perform data entry according to expectations. This avoids inundating those who are compliant with unnecessary reminders.

Participants are asked to enter their GDM self-monitoring data onto OHP daily or every other day in order to minimize backlogs and associated data entry errors. Maintaining a paper diary is optional. Automated alerts about new data entries are sent to the clinicians via email prompting the clinicians to log in under their credentials to review the patient data. When required and depending on the reviewed data or patient queries, clinicians provide feedback to the patient via the messaging service about any necessary alterations to treatment (eg, insulin titrations, changes to diet). The CDE-RNs act as the gatekeepers to interact with the telemedicine system and to consult or liaise with other GDM service team members. Patients can also email or print reports for other interested parties who do not have direct access to the Web-based shared data.

Induction for clinicians involved in providing care was conducted by the lead researcher. It consisted of setting up log-on credentials, using and navigating through the OHP webpage, setting up alerts, reviewing patient data, and messaging. The induction included both demonstration and hands-on practice in group setting.

Tasks expected of clinicians are to review patient data at their convenience, fitting in with their other routine clinical commitments through the day during weekdays. At the minimum, data are reviewed every 1 to 2 days during the week. Clinical decision making and advice in relation to ongoing management of GDM is at the discretion of the clinicians in accordance with existing clinical protocols without interference from the researchers. The same applies to scheduling of clinic appointments. Clinicians may also remind a patient when no data have been entered.

For research data collection, participant engagement, and/or troubleshooting purposes, the lead researcher periodically contacts participants via the OHP messaging feature or telephone and extracts all data from OHP to collate in a secure MS Access study database. The lead researcher is the primary contact for basic technical support queries, escalating any queries that cannot be resolved to the OHP vendor.

Sample Size

As an exploratory RCT, a stringent sample size calculation was deemed to be less critical for the TeleGDM trial. Therefore sample size has been set at 100 participants. This determination was largely pragmatic, based on resources, time constraints, the balance of probability for detecting a statistically significant difference in the primary outcome and a reasonable power for secondary outcomes. Estimations based on a finding of 44% fewer clinic visits among those receiving telemedicine versus controls [32] indicated a required sample size of 42 with a power of 0.9 for a similar outcome. Thus if the primary outcome in our study were to be less than the latter cited study, or there was 30% attrition, our set target sample offers good prospects for detecting a difference in the primary outcome.

Data and Outcomes

Data for research is collected by the lead researcher. This includes weekly extraction of data from OHP for those in the intervention arm in addition to questionnaire outlined below. For controls, photocopies of patients' paper diaries are obtained when these patients attend their clinic appointments. In addition to these photocopies, where possible, BGL data are directly extracted from the BGL meter via USB cable connection. Finally, once patients have reached the study end point, they also asked to send outstanding self-monitoring data copies of their diaries via email or as photos via smartphone-based multimedia messaging service.

Demographic data together with diabetes self-efficacy and client satisfaction are collected at baseline with follow-up at least 6 weeks after enrollment in the trial. Self-efficacy and satisfaction are measured using the Diabetes Empowerment Scale–Short Form (DES-SF) [33] (Multimedia Appendix 3) and Client Satisfaction Questionnaire–8 Item (CSQ-8) [34,35] (Multimedia Appendix 4). The DES-SF is a shorter version of the original 28-item questionnaire for measuring self-efficacy in people with insulin- or noninsulin-treated diabetes [36]. The original questionnaire has three subscales: managing the psychosocial aspects of diabetes, assessing dissatisfaction and readiness to change, and setting and achieving goals. The longer version has high construct validity and good reliability [18,36]. The shorter version has 8 items, has high reliability (alpha of 0.85), and the scores were found to change positively with improvement in HbA_{1c} [33]. To minimize the burden on participating women we selected the DES-SF to assess diabetes self-efficacy. The CSQ-8 has been used in diabetes research [37] and was assessed for reliability and validity in a childbirth service evaluation [38]. It is reported to have strong reliability, excellent face validity [34,35], good psychometric properties, high client and staff acceptability, and sensitivity to programs of varying quality [37]. The CSQ-8 is available under paid license while the DES-SF is free with appropriate attribution. Both the DES-SF and SCQ-8 questionnaires are self-completed face-to-face or administered over the phone at baseline and at least six weeks from enrollment. Further information on outcomes and data collection time points is provided in Table 1.

The primary outcome of the quantitative exploratory RCT component of the study is service utilization. Maternal and fetal outcomes, satisfaction, and costs are secondary outcomes. In particular, one of the limitations of studies in our systematic review [11] was the lack of cost evaluation, however basic. Considering that studies appear to show virtually similar clinical outcomes between telemedicine and usual care/control [12,17-19], a form of cost comparison becomes important. There are several methods for undertaking health economic evaluation, one of which is cost minimization. This type of health economic evaluation is defined as ". . . evaluation method to use when the case for an intervention has been established and the programmes or procedures under consideration are expected to have the same, or similar, outcomes. In these circumstances, attention may focus on the cost side of the equation to identify the least costly option" [39]. At the time of this protocol study, patients not covered by the Australian Medicare paid AUD $280 for each face-to-face consultation with a clinician for GDM care at the centers in this study. Because diabetes education, endocrinology, and dietetics are the key outpatient specialties involved directly in GDM management and therefore targeted for influence by the TeleGDM intervention, the AUD $280 cost rate will be assigned to these for service provided to patients between study entry and study exit. Study participant outpatient consultations data covering service access between commencement of recruitment and end of data collection for computation of provider costs will be sourced from the hospital data management unit. While clinicians provide service over the phone, which is a cost to the hospital, patients are not billed and hence this cost will not be included. Furthermore, implementing the intervention required existing equipment and infrastructure for the brief induction. Costs for these were considered negligible and therefore were not taken into consideration. Also Australian public hospitals by their nature are nonprofitmaking entities. Where fees are charged these are normally break-even and include overheads. Besides the AUD $85 per patient subscription there is no separate license fee for OHP.

Technology is central to the telemedicine support service for GDM and an important feature for evaluation. As such, technology capability will be assessed through the volume of data uploads by patients and qualitatively through sections 2 and 3 (system and information quality) of the Health Infoway System and Use Assessment Survey [40] (Multimedia Appendix 5).

Outcomes of interest are outlined in Table 1. These are aligned with the dimensions of the telehealth evaluation framework proposed by the Institute for a Broadband-Enabled Society [41-43].

Table 1. Outcomes and indicators matched to the telehealth evaluation framework dimensions.

Outcome	Telehealth evaluation framework dimension	Measures/ indicators	Assessment instrument/ data source	Time point
Primary				
Patient service utilization	Patient control	Number of scheduled face-to-face consultations	Attendances and nonattendances from outpatient activity dataset; patient medical records	Study exit
		Number of unscheduled face-to-face consultations		
		Number of telephone consultations		
Secondary				
Clinical measures and satisfaction	Clinician quality of care	Glycemic control	BGL[a] extraction from OHP[b]; glucometer downloads; patient paper diaries	Enrollment; delivery
		Glycemic stability	Time (days) to BGL stabilization	Between enrollment and delivery
		Insulin adjustments	Time (days) between insulin adjustment	Between enrollment and delivery
		Macrosomia	Fetal ultrasound biometry	2nd (17-22 weeks) and 3rd (>22 wks) trimester
		Diabetes self-efficacy	DES-SF[c]	Baseline; ≥6 weeks
		LGA[d]	Birth weight > 90th percentile	Delivery
		Neonate admission to SCN[e]	Patient medical record	Delivery
		Type of delivery (NVD[f], LUSCS[g], other)	Patient medical records	Delivery
		Mother/patient satisfaction with clinical care	CSQ-8[h]	Baseline; ≥6 weeks
				Enrollment; delivery
Costs	Organization sustainability	Service provider costs	Routine billing administrative data for face-to-face/staff costs; OHP subscriptions	Study exit
Tertiary				
Usage (patients and clinicians)	Technology capability	Clinician system, information and service quality, usage	Modified Canada Health Infoway System And Use Assessment Survey	6 months from beginning of study
		OHP access; volume of data uploaded	Extraction from OHP logs	Study completion

[a]BGL: blood glucose level

[b]OHP: Online Health Portfolio

[c]DES-SF: Diabetes Empowerment Scale–Short Form

[d]LGA: large for gestational age

[e]SCN: special care nursery

[f]NVD: normal vaginal delivery

[g]LUSC: lower uterine segment cesarean section

[h]CSQ-8: Client Satisfaction Questionnaire–8 Item (CSQ-8)

Qualitative Evaluation

The aim of the qualitative evaluation is to supplement the RCT by exploring patient and clinician acceptance, adoption, and experiences of telemedicine to support care in the management of GDM. A semistructured interview approach is used for both patient and clinician participants. The interview schedule is outlined in Multmedia Appendix 6. Subjects include those who are assigned to the intervention arm of the TeleGDM RCT and the CDE-RNs. A purposive sample of patients will be selected with the aim for up to 15 patients. Since there are only a few clinicians, all CDE-RNs who actively interact with OHP during the RCT will be included. Interviews are conducted by the lead researcher and the questions are open-ended, focusing on gathering interviewee experiences with telehealth-supported GDM management and the technology under use. Clinician interviews are face-to-face while patient interviews are carried out over the phone for the convenience of new mothers. All interviews are audiorecorded digitally for later verbatim transcription.

The interviews will be supplemented with field notes/observations. Notes or written diaries throughout the trial allow for an analysis that provides a narrative account of practice [44]. The narrative adds to the evaluation by highlighting factors in the local setting which may influence the success or failure of the intervention [44,45].

Data Preparation and Analysis

Quantitative data analysis will be performed using Stata/IC 13.1 (StataCorp LP) with an intention to treat analysis. Missing data for the primary outcome is expected to be minimal as all patient appointments and outcomes are recorded. For the DES and CSQ-8 losses to follow-up will employ last observation carried forward for missing values. Since case BGL data is serial and expected to be nonlinear, case mean of nearby data points imputation will be used for missing data.

Summary univariate statistics will be used to describe the study populations and compare study groups at baseline. Categorical variables will be summarized as raw numbers and percentages and between groups comparisons will utilize chi-square statistics. Multivariate statistical analysis will be performed to compare the groups on primary and secondary outcomes. In addition, survival analysis will be performed to explore time to reach glycemic stability. Statistics will be reported with standard deviations or 95% confidence intervals as appropriate. Statistical significance will be indicated by $P<.05$.

Patient and clinician interviews will undergo thematic analysis supported by NVivo 11 (QSR International). The interview transcripts will be analyzed separately for each participant group using an inductive approach to identify and/or infer themes and codes from the transcripts. Further themes will be classified according to the dimensions of telehealth evaluation framework [41].

Results

At the time of submission of this paper, recruitment and data collection were underway. Data analysis was pending and results expected at the end of 2016.

Discussion

Summary

Use of telemedicine to support care, specifically in the management of GDM, through a multiplatform Web-based personal health record is an innovative use of current technologies. It is envisaged the study will show reductions in health care utilization (eg, face-to-face clinic appointments) with an associated service provider cost saving. Other expected effects are GDM clinical outcomes similar to if not better than usual care. In addition, it is anticipated that both clinicians and patients will express greater satisfaction, usability, and positive views for telemedicine-supported GDM management.

The increasing prevalence of GDM and associated burdens [1-3] calls for innovative ways of service provision. The TeleGDM study explores a Web-based telemedicine approach to providing care and support to pregnant women with insulin-treated GDM. The intervention in the TeleGDM study relies on reliable and acceptable technology for efficient data sharing between patients and clinicians. Underpinning the intervention is the idea that telemedicine provides an engagement and interaction platform between the patient and clinician independent of face-to-face visits. The intervention incorporates some of the elements which are common for Web-based interventions (eg, self-management, communication, individualized feedback) [46].

Comparison With Previous Work

A few previous studies [12,17-19] have specifically explored telemedicine for GDM. These studies found better service utilization in terms of fewer face-to-face appointments and better diabetes psychological self-efficacy. There are some marked differences between the TeleGDM study and previous studies; TeleGDM uses technologies (broadband Internet and the ubiquitous mobile telephony Internet) which were not previously available. While in theory the approach in the TeleGDM study appears similar to those in the previous studies, the intervention has been implemented as adjunct to usual care for ethical reasons. That is, usual care is the current standard of care at the study sites, and therefore it would be unethical to deny patients what is current practice in lieu of a test intervention. However, the adjunct nature of the intervention means concurrent elements of usual care could become confounders.

Strengths and Limitations

The strength of the TeleGDM is the innovative use of current technologies in GDM, particularly in the Australian context. Second, the study uses a mixed-method approach to enhance the rigor of the evaluation and incorporates elements of a framework proposed for evaluating telehealth interventions in Australia [41]. The study includes cost evaluation, an important consideration which telehealth studies are often criticized for excluding [10]. Costs are only considered from a provider perspective and limited to billable consultations for pragmatic reasons, a potential methodological limitation. As such, a full economic evaluation that takes into account other costs could be a future consideration.

Internet security is one of the barriers to uptake of Web-based interventions [46]. Hence OHP uses 256-bit data encryption,

individual username and password access, and an inactivity timeout. Despite these security measures, data breaches cannot be completely ruled out. Any interactions over the Web carry the risk that user privacy and confidentiality may be breached, however minimal. This may happen as a result of unauthorized access during the course of transmission, hacking into system servers, or users not exercising due diligence in securing their log-on information.

Conclusion

TeleGDM is an innovative use of technology to support care and management of insulin-treated GDM. It may mitigate burdens on the health care service and the women with GDM without compromising clinical outcomes. Results of this study are expected by the end of 2016.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Online Health Portfolio data entry screenshots.

[JPG File, 105KB - resprot_v5i3e163_app1.jpg]

Multimedia Appendix 2

Online Health Portfolio data view screenshots.

[JPG File, 189KB - resprot_v5i3e163_app2.jpg]

Multimedia Appendix 3

Diabetes Empowerment Scale--Short Form (DES-SF).

[PDF File (Adobe PDF File), 21KB - resprot_v5i3e163_app3.pdf]

Multimedia Appendix 4

Client Satisfaction Questionnaire-8 Item (CSQ-8).

[JPG File, 363KB - resprot_v5i3e163_app4.jpg]

Multimedia Appendix 5

Canada Health Infoway System and Use Assessment Survey.

[PDF File (Adobe PDF File), 51KB - resprot_v5i3e163_app5.pdf]

Multimedia Appendix 6

Clinician and patient interview schedule.

[PDF File (Adobe PDF File), 63KB - resprot_v5i3e163_app6.pdf]

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Abbreviations

ADIPS: Australasian Diabetes in Pregnancy Society

CDE-RN: Credentialed Diabetes Education–Registered Nurse
CSQ-8: Client Satisfaction Questionnaire–8 Item (CSQ-8)
DES-SF: Diabetes Empowerment Scale–Short Form
GDM: gestational diabetes mellitus
IADPSG: International Association of Diabetes and Pregnancy Study Groups
LGA: large for gestational age
OHP: Online Health Portfolio
RCT: randomized controlled trial

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Protocol

Protocol for a Randomized Controlled Trial Evaluating Mobile Text Messaging to Promote Retention and Adherence to Antiretroviral Therapy for People Living With HIV in Burkina Faso

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Abstract

Background: Retention in care and adherence to antiretroviral therapy (ART) among people living with human immunodeficiency virus (PLHIV) is a critical challenge in many African countries including Burkina Faso. Delivering text messaging (short message service, SMS) interventions through mobile phones may help facilitate health service delivery and improve patient health. Despite this potential, no evaluations have been delivered for national scale settings to demonstrate the impact of mobile health (mHealth) for PLHIV.

Objectives: This study aims to test the impact of SMS text messaging reminders for PLHIV in Burkina Faso, who are under ART. The evaluation identifies whether patients who receive SMS text messages are more likely to (1) retain in care (measured as a dichotomous variable), (2) adhere to antiretroviral regimens (measured as the number of doses missed in the past 7 days), and (3) experience slower disease progression (measured with T-lymphocytes cells). The second objective is to assess its effects on the frequency of health center visits, physical and psychosocial health, nutrition and whether the type of message (text vs image) and frequency (weekly vs semiweekly) have differential impacts including the possibility of message fatigue over time.

Methods: This 24-month, wide-scale intervention implements a randomized controlled trial (RCT) to evaluate the impact of four variants of a mHealth intervention versus a control group. Our sample comprises adult patients (>15 years of age) undergoing antiretroviral therapy with access to mobile phone services. Multivariate regression analysis will be used to analyze the effect of the intervention on the study population. Data collection is done at baseline and three follow-up waves 6, 12, and 24 months after the intervention starts.

Results: The targeted 3800 patients were recruited between February 2015 and May 2015. But political uncertainty delayed the launch of the intervention until October 2015. Data analysis has not yet started. The first follow-up data collection started in April 2016. To the best of our knowledge, this is the first research that explores the effects of mobile message reminders using a wide-spread sample across an entire nation over a 2-year horizon, especially in a Francophone African country.

Conclusions: We hypothesize that the interventions have a positive impact on retention in care and adherence to ART schemes and that a more sluggish disease progression will be observed in the short run. However, these benefits may fade out in the long run. The study expects to advance the research on how long mHealth interventions remain effective and when fatigue sets in the context of wide-scale interventions. This information will be useful in designing future wide-scale mHealth interventions in developing countries.

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KEYWORDS

HIV; PLHIV; mHealth; SMS; RCT; developing countries

Introduction

Background

Several factors inhibit retention in care and adherence to antiretroviral therapy (ART) among people living with human immunodeficiency virus (PLHIV). Typical reasons include individual and social obstacles, such as lack of information on treatment procedures, social stigma, discrimination, and competing priorities that prevent patients from considering antiretroviral treatment as a worthwhile investment of time, energy, or resources [1,2]. In developing countries, economic and contextual barriers may further amplify these challenges because patients are resource-constrained and health facilities may not be easily accessible leading to substantial costs in terms of wage losses and travel expenses [3].

Discontinuation of ART regimens is particularly prevalent in Sub-Saharan Africa. Systematic reviews have found that approximately 22.5% of patients discontinue ART within 10 months and 56% are lost to follow-up or death during the first 2 years of the treatment [4,5]. HIV patients are perhaps not fully aware of the long-term consequences of dropping out from ART treatment. Lack of retention in care and adherence to antiretroviral therapy increases HIV viral loads and the probability of transmission, reduces the number of T-lymphocytes cells in the blood (CD4 count)-an indicator of how well the immune system is working and a strong predictor of HIV progression-leads to deterioration in the quality of life and can be responsible for creating virus strains that are resistant to current HIV medication [6-9]. Favorable health outcomes for PLHIV require lifelong compliance with ART programs. At the macro-level the negative side effects of poor compliance with ART can deteriorate the efficiency and efficacy of public health care systems by increasing the burden of the disease and the potential costs of care in the future [10-12].

The World Health Organization (WHO) promotes the use of innovative mobile technologies to overcome barriers that undermine access to health care and the quality of care delivery in resource-poor countries [13]. mHealth is an important element of this approach as it can help alleviate some of the existing obstacles in the delivery of quality care [14-16]. Mobile technologies may help patients undergoing ART to maintain the treatment routine as they provide instant communication unrestricted to location [17,18]. Specifically, the use of text messaging (short message service, SMS) reminders may support PLHIV to take their pills every day, schedule refills of their prescriptions, and assist them through common side-effects. Such reminders are considered to be a low-cost, low-barrier intervention [19]. Especially in resource-constrained developing countries where some patients live far from the health centers and a system of regular home visits by health care providers is not in place [1-3], regular text messages may help patients to remain in care and adhere to their antiretroviral regimens [20-22]. These advantages have promoted the rapid expansion of mHealth projects that aim to improve health outcomes in patients living with HIV and other diseases across the developing world [23].

Despite the possibility of cost-efficient, easy outreach through SMS, recent studies have shown contrasting evidence. While several studies have demonstrated that mobile text message reminders are effective in enhancing adherence to ART programs [24-28] others do not find any effects [29,30]. Research in Kenya demonstrates that 53% of the participants who received weekly SMS reminders achieved adherence of at least 90% during the 12 months of the study [24]. In the control group, only 40% of the participants achieved similar adherence levels. Evidence from a small study in Brazil also suggests that adherence to ART increased due to text message reminders at least during the 4-month study period [28]. In contrast, a 6-month study in Yaoundé, Cameroon, found that standardized motivational mobile text messages did not increase adherence [29]. Likewise, research conducted in some states in India did not find a statistically significant impact of mobile phone reminders on time to virological failure or ART adherence at the end of a 2-year study period [30]. Moreover, we are not aware of any long-term study that has been conducted in a Francophone African country where perceptions, preferences, and health systems are considerably different as compared with Anglophone African countries [31].

Justification

The background provided above motivates continued research on the impact of mHealth interventions in developing countries. The majority of the existing studies are limited to geographically circumscribed areas such as capital centers, and are based on small sample sizes or on short-time horizons [24-30]. For instance, the Brazilian study carried out a 4-month study with as few as 21 Brazilian female PLHIV [28]. Similarly, the 2 studies in Kenya followed less than 550 participants and included no more than 3 health facilities for a period of 12 months [24,27]. The intervention in Cameroon included 1 hospital and 198 participants for a period of 6 months [29]. While the intervention in India had the longest time horizon of 2 years and a relatively large sample of 631 participants it was based on data from 3 health centers located in only 2 states [30]. Thus, research based on a sample across an entire nation with a longer-term horizon is warranted. The present study is timely as it is based on a wide-spread intervention across Burkina Faso with a 2-year horizon. These design features improve the study's external validity. Furthermore, the study will enhance our understanding of the extent to which mHealth interventions promote healthy behaviors and support psychosocial wellbeing. Therefore, the study will contribute to an improved understanding of when, why, and for whom mHealth interventions work [32,33].

Objectives

The main objective of this trial is to determine the impact of four different packages of SMS message reminders to promote HIV patients' retention and adherence to ART as well as their health outcomes in a large-scale randomized controlled trial

(RCT) in a Francophone country, namely Burkina Faso. We hypothesize that patients who receive text messages are encouraged to take their pills and reminded of the importance of ART for their health so that they remain in care longer than those who do not receive text messages. We also anticipate that enhanced retention and adherence will lead to positive health outcomes. Our objectives are (1) to inform best practices for enrolling PLHIV into ART programs and supporting them throughout care, (2) to provide insights on the key obstacles confronting patient retention and adherence to ART, (3) to advise on the most effective application of mobile technology for health interventions, including the short-, medium-, and long-term benefits that can be anticipated, and (4) to encourage long-term patient success with ART by promoting feasible and efficient strategies that may be adopted in resource-constrained settings. Concerning the effectiveness of SMS text messaging reminders, our intervention includes two complementary objectives. First, the study evaluates whether patients may experience fatigue from the SMS text messaging reminders. By carrying out 3 surveys at 6, 12, and 24 months after the launch of the intervention, we aim at determining the optimal period for such a type of mHealth intervention to be efficient. Second, the trial will evaluate the effects of message type (text vs ASCII image) and frequency (weekly versus semi- *weekly)*, i.e., the differences in the four treatment arms, on patient outcomes.

Methods

Trial Setting

The study is implemented in the Francophone African country of Burkina Faso. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reports that this country suffered a HIV prevalence of 0.9 in 2014 and the total number of PLHIV is estimated to be around 110,000 of which 94,000 are adults and 18,000 are children younger than 15 years [34]. The feminization of HIV is also observed in Burkina Faso since 59 percent of the adult PLHIV are women according to the National Council for the Fight against AIDS and Sexually Transmitted Infections (CNLS-IST) -the national committee in charge of the surveillance and fight against HIV/AIDS. The country provides free anti-retroviral treatment and its provision of HIV care follows WHO's international guidelines and strategies [35,36]. Burkina Faso's National Plan to combat HIV includes decentralization policies and multisector participation with the aim to increase the number of PLHIV who enroll at health centers that provide ART therapy and care [37]. Despite these efforts the fight against HIV and for ART adherence and retention remain a concern. Although the actual number of PLHIV enrolled in official files increased from 70,230 in 2013 to 76,342 in 2014, the actual number of patients undergoing active antiretroviral treatment was only 60% (42,145) in 2013 and 61% (46,623) in 2014. Similarly, despite the fact that the number of patients that becomes lost to follow up decreased almost by half from 2013 to 2014 (833 to 443), they are all attributed to fatalities [34]. These figures provide a first indication that adherence and retention to ART cannot be assured in Burkina Faso. And indeed, a survey carried out by UNAIDS in 2012 among 2,800 Burkinabe PLHIV revealed that adherence is perceived as a challenge due to negative side effects from treatment, the time and resources needed to regularly refill the stock of drugs and stigma [38]. The study we aim to implement allows us to assess whether and how retention and adherence may be improved.

Study Design

The study design rests on a five-arm, randomized, controlled trial with four treatment arms and one control group. With the support of the Burkinabe Ministry of Health and local health centers, HIV patients have been screened and recruited at 80 health care facilities that provide antiretroviral therapy across the 13 regions of Burkina Faso. Using a 7:7:7:7:10 allocation ratio, patients are randomized to one of the five-arms with the control group being slightly oversampled as we introduce two types of control groups; a control group of patients drawn from health centers which do not receive any of the interventions and a spillover-prone control group drawn from health centers which are visited by both treated and untreated patients. A member of the international survey team carried out the randomization in Stata. The team member did not have any interactions with patients. Once patients were randomly allocated, the intervention was launched and the SMS messages are sent. Patients in each of the five groups receive the public standard care but only four groups receive an SMS reminder that varies by the type of message (text versus American standard code for information interchange (ASCII) image) and its frequency (weekly vs semiweekly). The study collaborates with the health care personnel attending to the patients as well as the associations and self-help groups that provide psychosocial support to PLHIV. The former provide medical information and the latter carry out the survey interviews. The health personnel and the enumerators are not informed about the outcome of the random allocation of the participants. Because they do not know which patient is in which group, we do not expect bias. The study will keep track of the patients 6, 12, and 24 months after the intervention is launched.

Facilities Selection

The investigation will be implemented in health facilities across the 13 regions of Burkina Faso. The health centers are selected from a total of 100 registered facilities that are recorded in the documents of the CNLS-IST as providers of antiretroviral therapy across the 13 health care regions of Burkina Faso [34]. To be eligible to participate in this study, health centers need to fulfill two conditions. First, they need to exist and they need to be functioning. While this sounds like a straightforward requirement it is possible that despite being registered, facilities might have never become operational or have shut down. Second, the health centers need to be willing to collaborate. Specifically, we enrolled a total of 80 health centers with an intended average of 40 patients being recruited per center depending on the eligible population of PLHIV who frequent the health center. To avoid under or overrepresentation of a particular health center, eligible facilities must meet a minimum number of 15 HIV patients and are allowed to enroll a maximum number of 150.

Participants

Eligibility and Informed Consent

The participants need to fulfill five conditions. As an initial step for eligibility, participants must be enrolled in an ART program in 1 of the health care centers collaborating in the study. Second, each patient must provide written informed consent confirming their participation in the study. The informed consent includes signed permission to consult their medical records over the duration of the study. Third, participants must be older than 15 years because the focus of the study is on adult PLHIV. Fourth, participants who have been under ART for less than 4 years are preferred, although, experienced patients are also included. We aim at assessing differential effects for individuals initiating ART versus individuals who have been under treatment for a long time. Because the existing literature suggests that drop-out is highest among those initiating treatment, we place more emphasis on individuals who have recently started ART. Therefore, we aim that at least two-thirds of the sample consists of patients that have been under ART for less than 4 years. We trained and informed the health centers and enumerators about this sampling feature. We requested to be informed (by phone) in the case that patients were included, that have been longer on ART. Thus, from the central level we closely monitored the oversampling of patients, who have been under ART for less than 4 years. Fifth, patients must have reliable access to a mobile phone including a stable network connection. Access to a mobile phone is not a major bottleneck: according to the World Factbook there were 12.5 million subscribers in Burkina Faso in 2014, 68 of 100 inhabitants have a mobile phone, and there are 3 major mobile networks that reach out to the entire country [39,40].

Recruitment

The recruitment period lasted for 4 months because patients return to the health centers to refill their stock of antiretroviral medication at different intervals. This time period has been sufficient to reach the target sample size of 3800 individuals.

Randomization

Randomization was undertaken after the collection of the baseline data. As a first step we randomly identified 8 pure control health centers using the random number generator in Excel. These pure control centers allow us to assess whether there are within health center spillovers from those who receive reminders and those who do not. Across the 72 remaining health centers, we randomly assign individuals to 1 of 5 groups (ie, 1 of 4 treatment packages or the control group of patients who do not receive any text message). Due to the potentially large heterogeneity of patient socioeconomic profiles and variations across health centers, the study applies covariate balancing across multiple baseline covariates to minimize imbalance between treatment groups. To increase statistical power and the precision of the results, participants are ordered along key characteristics and randomized within these ordered blocks. The following characteristics are included in the ordering: gender, age and weight of the participant, duration under antiretroviral treatment, health center identifiers, the reported distance to the health center, CD4 counts, and subjective health rating. Following this 2-step procedure, participants are randomly assigned to 1 of 5 groups (4 of which receive various packages of SMS reminders and a control group, which does not). Thus, there are 2 control groups. One control group consists of individuals who do not receive messages but are affiliated to health centers where others receive messages and a pure control group, which consists of individuals who do not receive messages and are affiliated to the 8 pure control health centers where no one receives a message. The introduction of 2 types of control groups is motivated by a desire to address potential spillovers/contamination between treated persons (those who receive a SMS text message) and patients in the control group (those who don't receive the SMS text message) but frequent the same health center. We know that medical interventions such as deworming and cancer screenings have spillovers [41,42], similarly voter awareness and cash transfer programs have spillovers to untreated but close populations [43,44]. Having 2 control groups allows us to address whether both treated and untreated patients in the treatment health centers are covered by the intervention [43]. In the analysis, we will introduce a dichotomous variable for control patients from mixed-treatment control sites to assess whether their outcomes differ compared with patients from pure control sites who are unlikely to experience spillovers.

Intervention

The intervention comprises 4 treatment groups and 1 control group to investigate the impact of different types of SMS text message reminders sent out at different frequencies on patient outcomes. For groups 1 to 4, messages will be sent on a weekly basis. Patients of each of the 4 treatment groups will receive at least 1 text or image message per week. Image messages are used to ensure that the intervention reaches out to people with limited literacy skills and they will be sent as ASCII pictures. Because we do not expect the participants to have smartphones, we use ASCII images that can be displayed on basic mobile phones. The content and frequency of the messages will vary for each of the 4 treatment groups. While the first treatment group will receive only 1 text message per week (low frequency), the second treatment group receives a total of 2 text messages per week (high frequency). Meanwhile, the third group will get 1 text and 1 image message per week and, the fourth group will receive 2 image messages per week. All messages will be sent at 8 am and patients will not be prompted to respond. The impact of the treatments will be assessed in follow-up surveys at 6, 12, and 24 months after the start of the intervention. A detailed identification of the 5 groups, type of interventions, and timings are presented in Table 1.

Table 1. Identification of the five intervention groups.

Treatment arms		Intervention (per week)	Timing
Control group			
	Eight pure control health centers	No text nor image messages	
	Individuals from the remaining 72 centers randomly allocated to the control group.		
Treatment 1: text-only, low frequency		One text message	Every Monday at 8 am
Treatment 2: text-only, high frequency		Two text messages	Every Monday and Friday at 8 am
Treatment 3: text and image		One text message; one image message	Text: every Monday at 8 am; image: every Friday at 8 am
Treatment 4: image only		One message	Every Monday at 8 am

Furthermore, text messages are sent in French or 1 of the local languages (Moore, Jula, Gulmancema, Fulfulde, or Dagara). The baseline survey determined the main language of each participant to be used in the text messages. The content of the text messages will vary to ensure that the participants remain curious about the messages over the study period. We are concerned that individuals stop looking at an identical message after some time as they already know the content of the standardized message. Furthermore, we opted for a mix of messages instead of standardized messages due to concerns about exclusively "negative" framing (Textbox 1). However, we acknowledge that this approach does not allow us to systematically compare the implications of standardized messages across different treatment arms. Figure 1 shows two examples of the ASCII images that are sent.

Textbox 1. Examples of the text messages that are sent.

Hello. Do not forget to take your pills.

Your health is important. Take your pills.

You are very important. Do not play with your health. Take your pills.

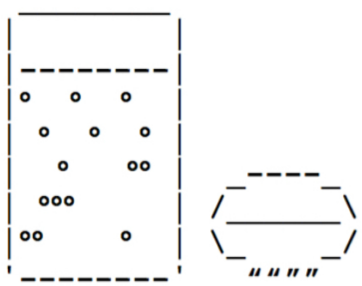
Are you very busy? This is why I remind you to take your pills.

Don't forget that you are strong, unique, funny and blessed. You are needed. This is why I would like to remind you to regularly take your pills.

Patients in the control group do not receive any text messages but only the standard care. Along with periodic clinical check-ups and treatment counseling, this includes routine monitoring of patient CD4 cells as measure of disease progression. Adherence support and/or additional treatment counseling may also be provided at the community level. This will be assessed during follow-up surveys.

Figure 1. Examples of ASCII images used in the intervention.

Example # 1: Glass of water and pill



Example # 2: Pill and thumb up

Sample Size

Power calculations need to account for the stratified nature of the sample. There are 80 treatment centers. We randomly preserve 8 pure control centers to assess spillovers. Within each of the remaining 72 centers, treated and untreated participants are sampled. Thus, for the majority of the centers treatment allocation is not at the level of the center but at the level of the individual. The sample size is calculated with the clustersampsi command of Stata, Version 13 assuming a power of 80% and

a significance level of 5%. Furthermore, we impose an intraclass correlation coefficient of 0.015 to quantify the degree to which patients within the same health center are related [45]. We allow for cluster sizes to vary because we know that the size of the eligible population varies across clusters. Thus, we impose a coefficient of variation of cluster sizes of 0.5 (ratio of the standard deviation of cluster sizes to the mean cluster size). Because we collect baseline information we can control for observable characteristics and their correlation with the outcome. We impose a correlation of 0.85. Lastly, because we expect that 35% of the patients will forget to take antiretroviral (ARV) medication from time to time, a target sample size of 3800 PLHIV is needed to obtain a "minimum detectable effect" of an increase in adherence from 65% to 70%. These adherence figures are based on a reported 67% adherence among female PLHIV in Burkina and the government target to bring adherence up to at least 80% [37,38]. As we are conservative about the possibilities of mHealth to raise adherence by 15% the sample was set up in such a way to also identify small gains.

Duration and Follow-Up Surveys

The intervention will run for a period of 2 years. We will conduct four outcome assessments during baseline as well as 6, 12, and 24 months into the intervention.

Ethical Concerns

The study faces two ethical concerns. First, we need to access patient medical records to monitor health indicators. We need to gain participant consent and have to ensure that confidentiality is protected during the period of the study. Only the health personnel and the local enumerators will know the individuals. In the dataset, all patient information will be anonymous and only linked to the participant's identification number that is given in the context of the study. No identity information will be disclosed. Second, as evident in the examples provided above, in order to prevent negative social stigma, the reminders do not disclose a participant's seropositive status. Participants will be informed of the possibility that texts could be read by other individuals who have access to their phone and they will have to consent to this risk in order to participate in the study.

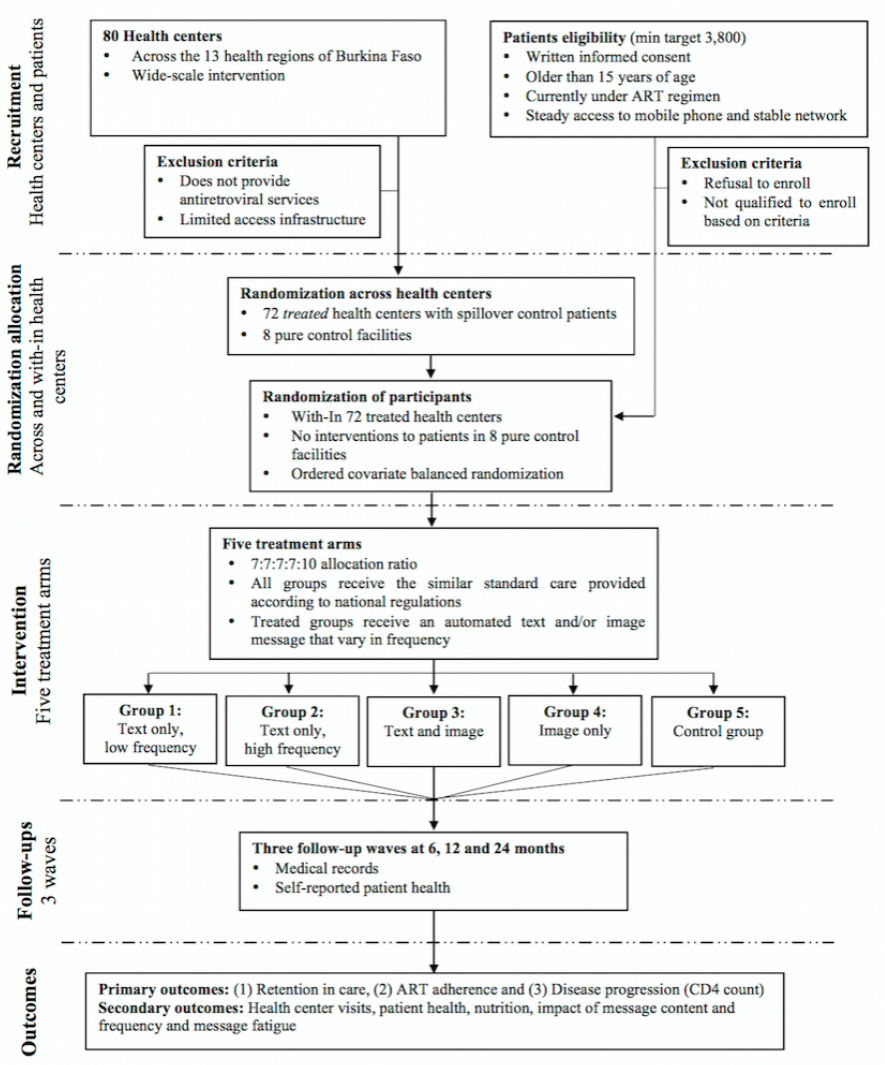
All relevant ethical clearance from the national ethics committee has been obtained (N° 2014-12-144).

Implementation of the Text Message Reminder System

The local telecommunication company EVOLE provides a computerized platform for sending the SMS text message reminders, re-launching text messages if delivery fails, and monitoring message receipt. The messages are sent in bulk and a record is kept of all communication. The computerized platform allows us to verify whether the text and image messages have been sent and that the intervention has been properly implemented. We will also use the monitoring data to analyze the quality of the SMS text message communication.

Details about the study design, facility selection, and patient eligibility including the random allocation mechanism, the intervention and the outcome variables are graphically presented in Figure 2.

Figure 2. Study flow.



Study Measures

Primary Outcomes

The study focuses on the measurement of three primary outcomes: retention in care, adherence to ART, and disease progression. Retention is measured by a dichotomous variable-whether a patient remains on ART 6, 12, and 24 months after the intervention has started as compared with baseline [46,47]. Retention could have been conceptualized also as the incidence or number of missed visits during a given reference period [48]. However, remaining in care is in itself an important challenge in Burkina Faso. This is in stark contrast to the situation of PLHIV in developed countries. Therefore, we decided to choose remaining on an ART regimen as our retention measure. Adherence or rather lack of adherence to ART is evaluated as the number of doses missed in the past 7 days, which is a self-reported measure [49-51]. It may have been better to use actual pharmacy dispensing data to calculate a medication possession ratio. However, our field experience suggested that it was not always feasible to obtain detailed and correct information about pharmacy dispensing. Contrary to developed countries where standards across hospitals may be similar, in Burkina Faso we observed considerable differences in the standards and routines across health centers both between regions and within them. Because we assess a wide-scale intervention our study also includes rural and remote areas, which are perhaps even less capable of providing this information. Therefore, we opted for inclusiveness knowing that this implies adjustments in the type of comparable indicators that can be collected and analyzed across health centers [51]. Lastly, disease progression is analyzed using patients' CD4 counts.

Information on these primary outcomes will be collected using individual questionnaires and patient medical records. Table 2 presents details about the indicators with information about the date of data collection.

Table 2. Primary and secondary outcome variables.

Classification		Indicators/measures	Baseline	Follow-ups (months after)		
				6	12	24
Primary outcomes						
	Retention in care	Dichotomous measure whether a patient remains on ART	X	X	X	X
	ART adherence	Number of doses missed in the past 7 days	X	X	X	X
	Disease progression	CD4 count	X	X	X	X
Secondary outcomes						
	Health center visits	Incidence and number of missed visits		X	X	X
	Patient health	Biomarker: body mass index	X	X	X	X
		Incidence of coinfection	X	X	X	X
		Mortality	X	X	X	X
		Subjective health rating	X	X	X	X
		Measures of mental health		X		X
	Preferences	Risk preference		X		X
		Subjective discount factor		X		X
	Nutrition		X		X	
	Message type and frequency	Comparison of the four interventions		X	X	X
	Message fatigue	Patients' perceptions of the intervention		X	X	X

Secondary Outcomes

Information on 5 groups of secondary outcomes will be collected. First, we will obtain information about the incidence and number of missed health center visits. Second, because we are also interested in more general physical and psychosocial health aspects we will gather information about the body mass index, the incidence of coinfections, mortality, as well as subjective and mental health ratings. In addition, we will collect information on the patients' levels of risk preference and their subjective discount factors. Third, we will also measure nutritional outcomes. Fourth, to assess design effects and the duration of effectiveness of the mHealth intervention, we will gather data on the message type and frequency. The sensitivity to message type (text vs ASCII image) and the frequency (weekly vs semiweekly) of receiving the messages will be measured by comparing the effects of the 4 different interventions on the primary outcomes [24-30]. Finally, message fatigue will be measured using patients' perceptions and possible changes in the impact on the primary outcome indicators across follow-up survey rounds. The secondary outcomes will be measured 6, 12, and 24 months after commencement of the intervention.

Analysis Plan

Our analysis will exploit the randomized nature of the intervention to attribute treatment effects. In addition to a simple comparison between the pooled treatments and the control group we will also assess the differential impact of the 4 treatment arms. We will employ multivariate regression models to assess the impact of the interventions on each of the primary outcome variables. For the continuous outcome measure (CD4 count) we plan to employ an Ordinary Least Squares model. For the count data (pill doses missed) and if the continuous outcome measure is skewed, we propose to make use of a Poisson model; for the dichotomous outcome (remaining on ARV regimen), we propose to employ a Logit model. In all models we will control for the clustering of participants within health centers.

We will make use of the coefficient estimates from the 4 treatment arms to establish a preference ordering of the effectiveness of the different types (text vs ASCII image) and frequencies (weekly vs semiweekly) of the SMS text message reminders. We will also estimate quantile regressions to identify which group(s) of participants are most (least) likely to have gained from the interventions. Comprehensive data on patient characteristics collected at baseline will allow us to control for confounding factors and patient heterogeneity. These patient characteristics include age, gender, ethnicity, education, whether the patient is the head of the household, income, and whether the patient works. The simple comparison of outcome variables across groups will be complemented by a difference-in-difference identification strategy where we jointly employ the data from the three follow-up surveys. This analysis will permit us to tease out the differences in health outcomes attributable to each of the 4 interventions while controlling for time-fixed effects.

The data will be collected and coded by trained enumerators and analyzed using the statistical and data analysis program STATA. We will use conventional levels of significance at 1%,

5%, and 10%. Because we identified three primary outcome variables we will make use of an inflated alpha when determining significance levels for each and every outcome separately. We apply this correction because the more significance tests we conduct at α=0.05, the more likely we are to claim that we have a statistically significant result. For a significance level of 5% the Bonferroni inflated alpha is 0.05/3 = 0.015.

We expect missing data to be below 5% and plan to address it using imputation techniques. However, the technique that we do use will depend on the characteristics of the missing information. Our goal is to avoid reducing the sample size without compromising statistical validity.

Results

Our project finished the recruitment of patients in May 2015. We have recruited the targeted 3800 patients across the 80 health centers and even oversampled by 38 patients. We kept 8 pure control health centers and randomized participants in the remaining 72 treated health centers across the treatment arms and the control group. The intervention started in October 2015 and follow-up data collection has started in April 2016. Analysis of the intervention has not yet started. The project was challenged by the sociopolitical instability in Burkina Faso during 2014, 2015, and early 2016. The initial launch of the study coincided with a coup d'état in Burkina Faso in November 2014. Despite the political turmoil in the country, the study received ethical clearance from the Burkinabe Ethics Committee for Research in Health in December 2014. A second coup d'état in September 2015 further challenged the project. But we could continue with the project and launch the intervention in October 2015. In January 2016, the terrorist attacks in Burkina Faso's capital Ouagadougou added another layer of uncertainty to the project. Throughout the sociopolitical instabilities in the country the local and the international team managed to keep the project running. We therefore expect that we can successfully complete the project and conduct the intended analysis as outlined in this protocol.

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Discussion

Summary

To date, very few rigorous evaluations have examined the impact of SMS text messaging reminders on retention and adherence of PLHIV. Existing studies are based on small samples not delivered widely at a national scale and tend to focus on short time horizons [24-30]. To the best of our knowledge, this study will be the first long-term RCT to assess the effects of a mHealth intervention using an intervention that is delivered at national scale. The study will also assess the effects of message type (text vs ASCII image) and frequency (weekly vs semiweekly), as well as, whether patients experience message fatigue over the course of the 2-year period of the intervention. To assess the impact of this intervention in a multivariate fashion, we will collect information on sociodemographic traits and several diseases-related outcome indicators. The findings of this study will enhance understanding of how interventions using mobile technology can influence HIV care and treatment. The conclusions from this study will contribute to more informed recommendations for mHealth in health care provision and the development of national and international guidelines for mHealth usage. We expect to define when, why, and for whom mHealth interventions may work. The findings may also be applicable to other African countries, which have similar epidemiological HIV profiles and social conditions as in Burkina Faso.

Limitations

We are not able to control for all possible external factors that may influence the results. These factors include, among others, appropriate supply of medication, political or civil struggles that may influence the functioning of the health system, and other community-level changes during the 2-year intervention period. All these contextual confounders will be documented and considered while interpreting the findings.

Conclusions

This study aims to contribute to the evidence on mHeath usage to support HIV care delivery in resource-poor settings. We will evaluate the impact of mHealth interventions for care and treatment of PLHIV, and thereby expect to inform strategies to improve health-related outcomes among specific populations. The study expects to advance the research on how long mHealth interventions remain effective in the context of wide-scale interventions in developing countries. We will determine the impact of mHealth in the short-, medium-, and long-term, and thus advance understanding of how mHealth interventions may complement other social and behavioral health interventions in developing countries.

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Authors' Contributions

NW, LA, and AB wrote the study protocol. NW and BT designed the study. NW, AB, and DO, supervise the study, DO and BT are responsible for the implementation. NW, BT, LA, and AB will conduct the statistical analysis. All authors approved the final protocol.

Conflicts of Interest

None declared.

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Abbreviations

ASCII: American standard code for information interchange
ART: antiretroviral therapy
ARV: antiretroviral
CNLS-IST: Conseil national de lutte contre le SIDA et les infections sexuellement transmissibles
CD4: T-lymphocytes cells
HIV: human immunodeficiency virus
UNAIDS: United Nations Programme on HIV/AIDS
PLHIV: people living with HIV
RCT: randomized controlled trials
SMS: short message service
WHO: World Health Organization

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Protocol

Development of a Mobile Phone-Based Weight Loss Lifestyle Intervention for Filipino Americans with Type 2 Diabetes: Protocol and Early Results From the PilAm Go4Health Randomized Controlled Trial

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Abstract

Background: Filipino Americans are the second largest Asian subgroup in the United States, and were found to have the highest prevalence of obesity and type 2 diabetes (T2D) compared to all Asian subgroups and non-Hispanic whites. In addition to genetic factors, risk factors for Filipinos that contribute to this health disparity include high sedentary rates and high fat diets. However, Filipinos are seriously underrepresented in preventive health research. Research is needed to identify effective interventions to reduce Filipino diabetes risks, subsequent comorbidities, and premature death.

Objective: The overall goal of this project is to assess the feasibility and potential efficacy of the Filipino Americans Go4Health Weight Loss Program (PilAm Go4Health). This program is a culturally adapted weight loss lifestyle intervention, using digital technology for Filipinos with T2D, to reduce their risk for metabolic syndrome.

Methods: This study was a 3-month mobile phone-based pilot randomized controlled trial (RCT) weight loss intervention with a wait list active control, followed by a 3-month maintenance phase design for 45 overweight Filipinos with T2D. Participants were randomized to an intervention group (n=22) or active control group (n=23), and analyses of the results are underway. The primary outcome will be percent weight change of the participants, and secondary outcomes will include changes in waist circumference, fasting plasma glucose, glycated hemoglobin A1c, physical activity, fat intake, and sugar-sweetened beverage intake. Data analyses will include descriptive statistics to describe sample characteristics and a feasibility assessment based on recruitment, adherence, and retention. Chi-square, Fisher's exact tests, t-tests, and nonparametric rank tests will be used to assess characteristics of randomized groups. Primary analyses will use analysis of covariance and linear mixed models to compare primary and secondary outcomes at 3 months, compared by arm and controlled for baseline levels.

Results: Recruitment was completed in January, 2016, and participant follow-up continued through June, 2016. At baseline, mean age was 57 years, 100% (45/45) of participants self-identified as Filipinos, and the cohort was comprised of 17 males and 28 females. Overall, participants were obese with a baseline mean body mass index of 30.2 kg/m2 (standard deviation 4.9). The majority of participants were immigrants (84%, 38/45), with 47% (21/45) living in the United States for more than 10 years. One third of all participants (33%, 15/45) had previously used a pedometer.

Conclusions: This study will provide preliminary evidence to determine if the PilAm Go4Health weight loss lifestyle intervention is feasible, and if the program demonstrates potential efficacy to reduce risks for metabolic syndrome in Filipinos with T2D. Positive results will lend support for a larger RCT to evaluate the effectiveness of the PilAm Go4Health intervention for Filipinos.

ClinicalTrial: ClinicalTrials.gov: NCT02290184; https://clinicaltrials.gov/ct2/show/NCT02290184 (Archived at http://www.webcitation.org/6k1kUqKSP)

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KEYWORDS

randomized controlled trial; lifestyle intervention; weight loss; Filipinos; type 2 diabetes; culturally adapted; Asian Americans

Introduction

Objectives

The Filipino Americans Go4Health Weight Loss Program (PilAm Go4Health) study is a 3-month pilot randomized controlled trial (RCT), evaluating a weight loss lifestyle intervention, with a 3-month maintenance phase and active waitlist control. This program is a mobile phone-based intervention that includes virtual social support, promotes physical activity (PA) and healthy eating, and was culturally adapted specifically for Filipino Americans. The overall objective of this trial is to assess the feasibility and potential efficacy of the PilAm Go4Health intervention to reduce risks for metabolic syndrome in overweight Filipinos with non-insulin dependent type 2 diabetes (T2D). Metabolic syndrome is a cluster of physical conditions (eg, obesity, hypertension, diabetes) that together increase the incidence of chronic diseases such as stroke and cardiovascular disease [1].

The purpose of this paper is to describe the design, cultural adaptation, and procedures of the PilAm Go4Health intervention. In addition, participant baseline characteristics, lessons learned from community stakeholder input, and recruitment strategies will be provided. This information will inform the development of future culturally relevant lifestyle interventions, and improve participant engagement and retention among hard to reach populations (particularly Filipinos).

Background

Filipinos are the second largest US Asian subgroup, totaling 3.4 million people [2]. This population suffers from some of the highest prevalences of obesity, T2D, and cardiovascular disease compared to most Asian American subgroups and non-Hispanic Whites [3,4]. Major contributors to the high prevalence of Filipino obesity-related chronic diseases include a genetic predisposition to abdominal fat distribution, cultural preferences for a high fat diet, and sedentary behavior [5,6]. Furthermore, as a community-oriented society, Filipinos harbor cultural beliefs with insular tendencies that limit their willingness to readily engage in Western health care practices [7,8]. Although Filipinos are one of the fastest growing US immigrant racial/ethnic populations, they are seriously underrepresented in preventive health research [9]. Given the high prevalence of chronic disease in this high-risk population and the escalating costs of health care, it is imperative to identify effective intervention strategies to reduce these preventable health disparities.

Risk-reduction interventions such as the Diabetes Prevention Program (DPP) have been effective in delaying and reducing diabetes risks, even with modest amounts of weight loss and PA [10]. Recent systematic reviews have revealed that digital technologies using mobile phone-based interventions have the potential to promote both PA and weight loss [11,12]. Furthermore, a recent Cochrane review reported that mobile phone-based interventions had a beneficial effect on blood glucose control in self-management of T2D [13]. Currently there are over 97,000 commercial electronic mobile health (mHealth) apps available to the public [14]. To date, only a limited number of studies have evaluated the effectiveness of these commercial mHealth apps with regards to the promotion of healthy lifestyle behaviors.

Despite the success of the DPP in reducing diabetes risks, DPP guidelines require frequent face-to-face visits (16 or more) that are labor-intensive and burdensome to health care staff and patients alike [15]. Leveraging digital technology with lifestyle interventions is an ideal strategy to address the issue of frequent labor-intensive face-to-face visits, particularly among Filipinos, given their propensity to use smartphones and virtual social media (eg, Facebook) [16]. Remote education and coaching, along with virtual social support, would require fewer in-person meetings. A recent comparison of digital technology usage among Filipinos, Hispanics, Koreans, and Whites found that Filipinos were consistently ranked first or second as the most prolific users of smartphones, iPads/tablets, email, mobile apps, and social media platforms (eg, Facebook) [17]. In light of the existing health disparities and dearth of effective preventive health strategies for Filipinos, the prolific use of digital technology among Filipinos makes them ideal candidates for mHealth-supported lifestyle interventions to help mitigate their diabetes prevalence and cardio-metabolic risks [16]. Therefore, we adapted the original DPP (while retaining its core fundamentals) and created a culturally relevant mobile phone-based weight loss lifestyle intervention that includes virtual social networking for Filipinos. By leveraging advances in mobile technology, along with the rapid penetration of smartphone use among Filipinos and their propensity for Facebook social networking, we reduced the required number of DPP in-person meetings, resulting in a less labor-intensive intervention with the potential to improve cost-effectiveness.

Research Benefits and Impact

The PilAm Go4Helath study offers three important benefits to science. First, to our knowledge the PilAm Go4Health weight loss trial is the first culturally adapted mobile phone-based lifestyle intervention using digital technology that focusses on

Filipinos' virtual and in-person social networks to support target health behaviors. This multi-pronged social support intervention integrates in-person meetings, family participation, and a private Facebook group designed exclusively for study participants. The private Facebook group coalesces the following support elements: text and photos for education and coaching; real-time monitoring to promote target health behaviors; and weekly positive feedback and motivational messages to improve participant adherence and retention.

Second, trial findings will report on the efficacy of the PilAm Go4Health lifestyle intervention, which incorporates the commercially available Fitbit Zip (and corresponding mHealth app) to promote weight loss through PA and healthy eating. The Fitbit Zip is a state-of-the-art lightweight accelerometer/altimeter that is paired with an associated mHealth app to record and wirelessly transmit real-time step-count data. Use of the commercial Fitbit Zip will facilitate dissemination of our findings to a broader consumer population of Fitbit users.

Third, a community engagement approach was used to assist in the development of a culturally relevant intervention to enhance acceptability and improve participant recruitment, engagement, and retention [18,19]. Findings from the process that was used to culturally adapt the PilAm Go4Health intervention for Filipinos, and other strategies that were used for recruitment, engagement, and retention, may be useful for other research investigators and health workers when planning and developing health-related interventions for other racial/ethnic and diverse populations.

Methods

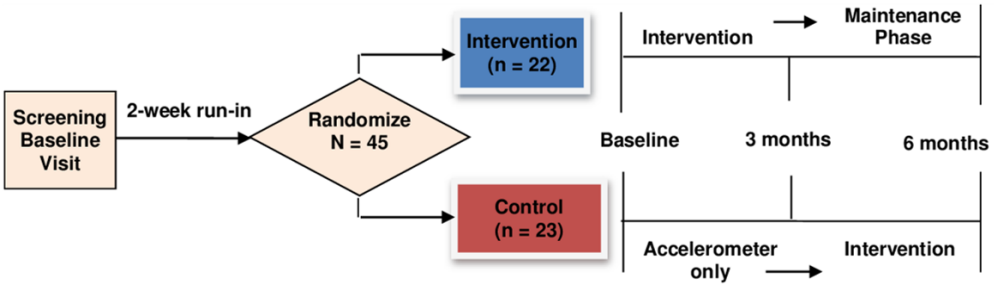
Study Design

This study was a 3-month pilot RCT with an active waitlist control and a 3-month maintenance design (Figure 1) . The objective of this trial is to assess the feasibility and potential efficacy of the PilAm Go4Health intervention to reduce risks for metabolic syndrome in Filipinos with T2D. The primary aims are to: (1) assess the feasibility of a mobile phone-based lifestyle intervention using digital technology (accelerometer, mHealth app, and private Facebook group) as measured by participant recruitment, engagement, adherence, and retention; (2) determine preliminary estimates of the effect of primary outcomes (percent weight) and secondary outcomes (waist circumference, fasting plasma glucose, glycated hemoglobin A1c [HbA1c] levels, PA, and diet [reduced fat and sugar-sweetened beverage intake]); and (3) conduct post-program process evaluations to obtain participant feedback regarding cultural relevancy, barriers to adherence, perceived efficacy for healthy behaviors, and suggestions for intervention improvements.

Cultural adaptations to the PilAm Go4Health study design were based on stakeholder feedback. During discussions with community leaders and members prior to study implementation, we learned that Filipinos are less likely to participate in research studies if they are randomized to a control group that does not receive the intervention. Therefore, to incentivize participant recruitment, engagement, and retention, the control group was waitlisted to receive the PilAm Go4Health intervention immediately after completing the 3-month control period.

Prior to implementation, the study protocol was reviewed and approved as a minimal risk study by the University of California San Francisco Institutional Review Board/Committee on Human Subjects Research.

Figure 1. PilAm Go4Health Study design.



Conceptual Framework

Social cognitive theory was a guide for the PilAm Go4Health study design [20]. This theory posits that behavior change is influenced by one's environment (eg, socio-cultural and community). Individual demographics, acculturation, and health literacy factors may also influence behaviors, while environmental feedback (social support, whether positive or negative) can reinforce or discourage behaviors. Social support may also affect self-efficacy for a given behavior; self-efficacy is the confidence to successfully reproduce target behaviors (eg, increase PA and reduce high fat/calorie intake for weight loss). PilAm Go4Heatlh uses social networking (virtual and in-person meetings with family and peers) to promote self-efficacy for healthy behaviors and weight loss.

Sample

The proposed sample size of 45 is conventional for pilot studies, with attrition estimated at 10%, for a final sample of 40 participants. Inclusion and exclusion criteria were based on American Heart Association metabolic syndrome risks, diagnosis, and management, as well as the DPP trial [1,10]. Key inclusion criteria included: (1) self-identified as Filipino; (2) age >18 years; (3) World Health Organization body mass index (BMI) cut-point for Asians >23 kg/m^{2}for public health action

[21]; (4) physician diagnosed T2D confirmed by clinical data (eg, documentation of fasting blood glucose >100 mg/dL, a positive oral glucose tolerance test >200 mg/dL, or HbA1c >6.5%); (5) noninsulin dependent T2D; and (6) own a smartphone, tablet, or laptop computer. Key exclusion criteria included: (1) uncontrolled T2D (fasting blood glucose >200 mg/dL); (2) disabilities precluding ability to walk for 20 minutes; (3) glucose metabolism-associated disease (Cushing's syndrome, Acromegaly, or Pheochromocytoma currently under treatment, or chronic pancreatitis). A detailed list of inclusion/exclusion criteria are presented in Multimedia Appendix 1.

Recruitment

Study recruitment began in December, 2014, and all baseline assessments were completed in January, 2016. Participants were recruited from San Francisco and Daly City's Filipino communities. Filipinos represent 4.6% of San Francisco's population (32,268/806,696) and 34.5% of Daly City's population (34,998/101,443), the latter being the largest concentration of Filipinos in the United States [22,23].

Primary Recruitment Plan

Key aspects of the primary recruitment plan included: (1) contacting pre-identified potential Filipino participants (over 250 respondents) from the San Francisco Bay Area who expressed interest while participating in a prior study [17]; (2) offering diabetes education classes at Filipino community centers (eg, Lions clubs and faith-based organizations); (3) distributing study fliers at Filipino community events; (4) posting study flyers on public websites (eg, Craigslist, Filipino organization websites); and (5) advertising at Filipino community centers, faith-based organizations, ethnic markets, libraries, laundromats, community colleges and universities, and at local health care facilities (clinics and hospitals).

Alternate Recruitment Plan

The alternate recruitment plan included: (1) sending study invitations to potential participants receiving services at medical centers, primary care clinics, and diabetes clinics; (2) using a commercial mailing service to send study invitations to Filipino residents living in select zip codes listed in the publicly available US census database; and (3) distributing flyers at Daly City Chamber of Commerce events.

Intervention Strategies

This intervention incorporated the following four diabetes prevention strategies: (1) weight loss through PA and diet; (2) cultural tailoring of the intervention; (3) leveraging digital technology; and (4) integrating social support.

Weight Loss Through Physical Activity and Diet

This study was a 6-month intervention (3-month weight loss program with a 3-month maintenance period) to reduce weight and thereby diabetes risks via increasing PA (weekly step-count goals) and diet (lowering fat and sugary-beverage intake). Participants' goals were individually tailored from their baseline weight, weekly step-counts, weekly sugary beverage intake, and daily fat intake. Individual goals were to lose 5% body weight from baseline, increase and maintain steps up to 12,000 steps/day (increase weekly step-count goal by 20% based on total step-counts from the previous week), reduce sugary beverage intake (to once/week or less), and reduce total daily fat intake (to 25% of total calories from fat/day). The 3-month maintenance stage aimed to ensure long-term adherence to target health behaviors and maintain weight loss.

Cultural Tailoring of the Intervention

Cultural relevance of an intervention enhances effectiveness and acceptability for the target population by improving participant recruitment, engagement, and retention [18]. Cultural adaptations to the intervention were made, based on previously published data: Bender et al published guidelines in 2011 [19] and a recent 2015 study profiling digital technology use among diverse populations [17]; the National Heart, Lung, and Blood Institute (NHLBI) recommendations for culturally adapting Filipino American interventions [24]; and the NHLBI Filipino education materials for reducing risks of cardiovascular disease [25].

Additional tailoring, based on stakeholder (community members, leaders, and health care providers) feedback, incorporated relevant Filipino language, food, PA options, and social support. These factors included: social support in the form of in-person meetings that incorporated family members and virtual social support (private Facebook group); common Filipino PAs (ie, walking, dancing, and/or basketball); and healthy Filipino food alternatives such as roasted chicken, grilled fish, and brown rice (to replace fried pork, sausage, and white rice, respectively). To improve awareness and assist in tracking total daily calories consumed, a photo booklet was developed that included pictures of common Filipino foods, dishes, and beverages, along with the total calories and fat content for each item.

Materials were provided in English, the second official national language of the Philippines. English is taught in all Philippine schools and over 90% of Filipinos are proficient in English [7,26]. To deliver the intervention, the research team included members of Filipino descent who were trusted members of the community and were familiar with cultural values, community norms, and Tagalog language.

Leveraging Digital Technology: Fitbit Zip Accelerometer and mHealth App/Diary

Direct-to-consumer mHealth wearable devices pose multiple benefits for behavioral research. Self-monitoring and tracking of lifestyle behaviors (eg, PA and weight) have been shown to improve weight loss and health outcomes [12,27]. Therefore, the Fitbit Zip mHealth self-monitoring lifestyle behavior tracker with an associated mHealth app was chosen, based on recommendations from previous studies [28-31]. These studies demonstrated that the Fitbit encouraged high levels of adherence to self-monitoring of PA, exhibited high inter-device reliability for tracking PA step-counts, and was acceptable among participants. Furthermore, the Fitbit Zip is commercially available, affordable, and scalable.

The Fitbit Zip is a state-of-the-art lightweight accelerometer/altimeter sensor that wirelessly transmits real-time data for PA (step-counts, distance, duration, and energy expenditure in Metabolic Equivalent of Task [1 kcal/kg/hour])

and sleep (not measured in this study). An associated mHealth Fitbit app/diary is available for participants to input and self-report their daily food/drink type and calorie intake, and weekly weight. Real time feedback is provided by the Fitbit app in the form of chart and graph displays of lifestyle behaviors (eg, step-counts and calories consumed). These capabilities and features may help enhance participant self-report quality, prevent recall bias, and promote adherence and retention.

Integrating Social Support - Two Modalities

Filipinos place a premium on community, family, and social support [7]. Moreover, family and peer support are known to improve healthy behavior motivation, adherence, and maintenance [32,33]. Thus, to enhance social support, PilAm Go4Health included two social modalities: (1) in-person intervention sessions welcoming family participation, and (2) a virtual Facebook social networking group.

Mode 1: In-Person Intervention

This modality consisted of four individual office visits. The first visit (individual baseline randomization) focused on tailored short-term and long-term goals for the subject. To enhance social support for target behaviors, study subjects were asked to attend additional office meetings once per month for three months (Table 1). To lend support and encouragement, the intervention group's family members were welcomed to attend the in-person office visits. Family attendance at meetings was recorded.

Table 1. Intervention modalities.

Social Support Modality	Time Frame	Parameters
Mode 1: In-Person Intervention Sessions		
	Baseline Randomization (Individual)	Lifestyle balance and social networking
		Initiating physical activity and healthy diet
		Setting short-term and long-term goals
	1 Month (Group)	Benefits and ways to be physically active
		Social support for physical activity
		Culturally relevant physical activities
	2 Month (Group)	Benefits and ways to eat healthy
		Limiting fat intake and healthy eating out
		Healthy Filipino food alternatives
	3 Month (Group)	Relapse prevention
		Problem solving and staying motivated
		Social support for healthy behaviors
Mode 2: Virtual Social Networking Group		
	Ongoing Facebook chat room, baseline to 3-month (Group)	Administered and monitored by staff
		Only intervention participants invited
		12 weekly posted discussion topics
		Post educational materials
		Participants can share messages and photos

Mode 2: Virtual Private Facebook Group

Facebook is an online social network service with multiple interactive capabilities. To ensure privacy and maintain Health Insurance Portability and Accountability Act compliance, a PilAm Go4Health private Facebook group was created. This private Facebook group could be accessed through smartphones, tablets, or laptops, and was available only to PilAm Go4Health intervention subjects. The Facebook group was designed to encourage group interactions, bonding, and social support to help subjects achieve their short-term and long-term program goals, overcome barriers, and prevent relapse. Research staff administered, monitored, and moderated the PilAm Go4Health Facebook group. Each member's usage (number and frequency of logins, likes, and posts) was monitored and research staff posted weekly topics along with photos that promoted target health behaviors, and facilitated and oversaw ongoing discussions. Facebook subjects received a Facebook notification whenever a message was posted on the site. *Weekly topics* were adapted from the DPP core curriculum and the NHLBI Health Heart Education for Filipino Communities related to PA and diet [15,25]. Subjects were encouraged to post healthy Filipino recipes and photos. Topics included reducing fat with healthy Filipino food alternatives, and benefits of tracking step-counts, calories, food/drinks, and weight on the Fitbit app/diary. See Figure 2 for a PilAm Go4Health Facebook screenshot.

Figure 2. PilAm Go4Health Facebook Page.

Intervention Protocol

Intervention and control group subjects received a total of seven in-person office visits (Figure 1). After the screening baseline visit (SBV) and randomization visit, the intervention group received three intervention follow-up visits, and two maintenance follow-up visits. The control group received one control follow-up visit and three follow-up visits after the 3-month transition, in order to receive the intervention program.

Screening Baseline Visit

Potential subjects were screened by phone interview after providing verbal consent. Those who met all inclusion criteria were scheduled for an SBV. After administering informed consent, subjects attending the SBV were asked to answer questionnaires and provide sociodemographic data , consent to a brief physical exam and a fasting blood draw for study measures, receive a Fitbit Zip accelerometer, and attend a mobile phone and Fitbit Zip training session.

Run-In Period

After the SBV, eligible subjects immediately started a two-week run-in period, during which they were asked to wear a Fitbit Zip every day for at least 10 hours/day, and send photos of all food and drinks consumed for three consecutive days. Study eligibility required a 70% adherence rate, at minimum.

Fitbit Zip and App/Diary Training

Prior to starting the run-in period, eligible subjects received training on how to use the Fitbit Zip and download the app. Subjects who did not own a smartphone used their own tablets or personal laptops. At the randomization visit, only intervention group subjects were trained on how to download and use the Fitbit app/diary, and asked to input their daily food/drinks and calorie intake, and weekly weight. Active control group subjects were only trained to use the Fitbit Zip and download the app until the 3-month time point. After the 3-month control period, control subjects were trained to use the Fitbit app/diary when they received the intervention program.

All participants were asked to provide an overnight plan to store their Fitbit Zip. This information was used to initiate a recovery protocol if equipment was lost, and included a comprehensive interview to help subjects reconstruct step-by-step events of the previous 24 hours. Based on previous studies, this recovery protocol was 98% successful [29,30].

Facebook Training

Subjects receiving the intervention program received training to access and use the private Facebook group, with education on appropriate Facebook etiquette. Prior to joining the private Facebook group, each subject was assigned a secure email account (excluding personal information) for the PilAm Go4Health private Facebook group.

Randomization and Blinding

At the end of the two-week run-in period, subjects able to adhere to the run-in requirements 70% of the time were randomized to either the intervention group or active control group in a 1:1 ratio. A permuted block randomization method stratified by gender was used with randomly selected block sizes of 2 and 4. Prior to the trial, the study statistician created a computer-generated random allocation sequence. Investigators, research staff (who conducted anthropometric measures, entered data, and undertook data management), and study participants were unblinded during the study, but personnel performing the lab sample evaluations were blinded to treatment groups.

Intervention Group

Only subjects randomized to the intervention group immediately received the PilAm Go4Health intervention. Participants were asked to wear their Fitbit Zip at least 10 hours/day and use the Fitbit app/diary to input and track their daily food/drink and calorie intake, and to record their weight twice per week (Monday and Friday). Subjects received individually tailored goals, in-person intervention meetings, Fitbit Zip and Fitbit app/dairy training, and private Facebook group training (and an invitation to join the study Facebook group). Each subject's baseline weight, PA, and diet information were used to tailor their intervention for short-term and long-term goals. Based on each subject's progress during the study, they received tailored feedback and coaching, including barrier and support assessments, and information regarding the benefits of tracking health behaviors on the Fitbit Zip and Fitbit app/diary. Research staff monitored each subject's Fitbit Zip and Fitbit app/diary data (step-counts, food/drink and calorie intake, and weight), and Facebook logins, likes, and posts. All automatically recorded Fitbit Zip data were wirelessly uploaded to each subject's individual study Fitbit and Facebook account for storage on study data servers. Table 1 displays an overview of topics covered at each in-person office visit, and during private Facebook group participation.

Active Control Group

Subjects randomized to the active control group were asked to continue to only use the Fitbit Zip every day. During the randomization visit, each active control participant received Hepatitis B education, including the National Digestive Diseases Information - Hepatitis B handout for Asians and Pacific Islanders [34].

Office Visits - 1 Month Through 6 Months

After the randomization visit, intervention group subjects were asked to return once per month for three months, for intervention education, coaching, and support. At the 3-month visit, subjects transitioned to the 3-month maintenance, and were asked to return for a 4-month progress evaluation and 6-month office visit. Active control group subjects were asked to return at the 1-month visit for a progress evaluation, and received Hepatitis C education. After completing the 3-month control period, active control subjects transitioned to receive the PilAm Go4Health intervention, and were asked to return for intervention follow-up visits at four, five, and six months. At the final 6-month office visit, all subjects completed the PilAm Go4Health study (see Figure 1).

At the 3-month office visit, all intervention and control subjects were asked to answer questionnaires and consent to a physical exam and fasting blood draw. Intervention subjects were asked to participate in a post-program process evaluation (semi-structured interview) before transitioning to the 3-month maintenance program.

At the 6-month office visit, all intervention and control group subjects were asked to complete questionnaires, consent to a physical exam and a final fasting blood draw, and participate in a post-program process evaluation (semi-structured interview). All subjects completed the study at this visit, and were removed from the Fitbit study account and private Facebook group account. Subjects who completed the 6-month study were allowed to keep their Fitbit Zip, and research staff assisted subjects in setting up their own personal Fitbit accounts.

Outcome Measures

Primary and secondary outcomes were measured at baseline, 3 months, and 6 months. Process evaluations were collected only at 3 and 6 months. During the analysis phase of this project, the primary outcome will be percent change in body weight, while secondary outcomes include changes in waist circumference, fasting plasma glucose, HbA1c levels, step counts, and dietary fat and sugar-sweetened beverage intake. Participants also provided feedback on the intervention program regarding cultural relevancy, compliance to the mobile phone-based intervention, compliance to the virtual social networking, barriers to use, perceived efficacy, and suggestions for intervention improvements.

In addition to the primary and secondary outcomes, self-reported information regarding self-efficacy for PA and social support were collected at baseline, 3 months, and 6 months. Sociodemographics, health literacy, and acculturation data were collected only at baseline. Table 2 presents all study questionnaires, planned administration, evidence of validity and reliability, and references.

Table 2. PilAm Go4Health outcome measures and surveys/questionnaires.

Outcomes	Time of collection	Scale / Collection Method
Primary Outcomes		
BMI, weight, height, and waist circumference	Baseline, 3 months, and 6 months	(1) Weight measured with Professional Digital Floor Scale
		(2) Height measured with Healthometer PORTROD Height Rod
		(3) Waist circumference (standing) measured with a tape measure midway between lower rib margin and iliac crest [35]
		(4) BMI = kg/m2
Fasting plasma glucose & HbA1c	Baseline, 3 months, and 6 months	Venipuncture blood specimen collected at the Clinical and Translational Science Institute Clinical Research Service Center
Secondary Outcomes		
Physical activity	Baseline, 3 months, and 6 months	(1) Objectively measured total daily step-counts collected by the Fitbit Zip and mHealth app
		(2) Self-reported International Physical Activity Questionnaire [36] - 27 items (Cronbach alpha median 0.80)
Diet	Baseline, 3 months, and 6 months	(1) Fat-Related Diet Habits Questionnaire [35,37] - 22 items (Cronbach's alpha = 0.77)
		(2) Beverage Intake Questionnaire [38] - 15 items (Cronbach's alpha range 0.97 to 0.99)
Other Outcomes		
Self-efficacy for physical activity	Baseline, 3 months, and 6 months	Self-efficacy for Physical Activity Questionnaire [39] - 12 items (Cronbach alpha range 0.78 to 0.82)
Self-efficacy for diet	Baseline, 3 months, and 6 months	Eating Confidence survey [39,40] -16 items (Cronbach alpha range 0.83 to 0.84)
Social support for diet and exercise	Baseline, 3 months, and 6 months	Social Support for Diet and Exercise Survey [41] – 23 items (Cronbach alpha range 0.80 to 0.93)
Self-reported health	Baseline, 3 months, and 6 months	Patient-Reported Outcomes Measurement Information System Survey Global Health [42] - 10 items (internal consistency=0.81, validity=0.86)
Process evaluations	3 months and 6 months	Comprehensive, semi-structured interviews to solicit participant feedback on cultural relevancy, compliance to the mobile intervention, barriers to use, and suggestions for intervention improvements (at 3 and 6 months)
Baseline Outcomes		
Sociodemographics and medical history	Baseline only	Gender, ethnicity, birth date, primary language, years lived in United States, marital status, number of children, education level, employment and health insurance status, income, hyperlipidemia, smoking, hypertension or other chronic illnesses, and/or family history of diabetes
Acculturation	Baseline only	Marin Short-Acculturation Scale for Filipino Americans [43] - 12 items (Cronbach alpha range 0.79 to 0.85)
Health literacy	Baseline only	Short-Health Literacy Survey [44,45] - 3 items (Reliability range 0.74 to 0.84)

Data Collection

Data were collected during in-person office visits, via self-reported PA and diet, and through the Fitbit Zip and Fitbit mHealth app/diary. In-person data included questionnaires and anthropometric data that were collected during research office visits. Self-reported PA and diet included questionnaires on PA (days per week, type, and duration of exercise), and diet (sugar-sweetened beverage intake, fat related diet intake) that will be collected along with self-efficacy and social support for phsycial activity. See Table 2 for questionnaire details. All study data were entered via encrypted computers and transferred to the research study's secure database servers. Likewise, participants' oral responses obtained from semi-structured interviews will be coded and stored on the same secure encrypted research study database servers. Fitbit Zip and app/diary data were wirelessly uploaded and transmitted in real-time directly to secure Fitbit database servers that identify participants only by their assigned Gmail account (no personal information was transferred). In turn, the study Fitbit account was tied to a secondary Fitabase database server that included all participants in our secure study Fitbit account. Fitabase is a secure confidential research platform that collects data from Internet-connected consumer devices, such as Fitbit

accelerometers and mHealth apps. Fitabase aggregates data, allowing researchers to easily organize, analyze, and export data gathered from study participants. Research staff have access to all participants' Fitbit data (step-counts, weights, and food/calorie intake) through the study Fitabase account.

Data Analyses

Regarding aim 1 of the study, feasibility will be assessed based on recruitment (eligible participants who were screened, completed the run-in, enrolled, and randomized), adherence (during the 3-month intervention, at least 70% compliance with the Fitbit Zip, mHealth app, and weight and calorie diary), and retention (6-month program retention and attrition rate). All results will be tabulated by study arm, and reported with descriptive statistics and effect sizes or 95% confidence intervals.

Descriptive statistics will be used to analyze the sample characteristics pertaining to aim 2 of the study. Prior to the analyses, validity of the randomization will be checked by assessing the randomized groups for characteristics measured before randomization using chi-square, Fisher's exact tests, t-tests, and nonparametric rank tests, as appropriate. If potentially confounding imbalances are found, we will adjust the between-group analyses for potential confounders of treatment assignment. The primary analysis will use analysis of covariance to compare primary and secondary outcomes at 3 months by arm, controlling for baseline levels. Outcomes will be transformed as necessary to meet assumptions of normality and equal variance. In a supplementary analysis (for more efficient data use), we will include on-treatment outcomes analysis for the control group at 6 months, using a linear mixed model to account for the repeated measures on waitlist controls, and include a smooth function of time to reduce potential bias from secular effects. In addition, we will assess within-group changes in the immediate intervention group between 3 and 6 months, as a preliminary measure of the durability of the intervention effect in the maintenance phase. We will also use these models to estimate residual variances and within-person correlation, which will be crucial to future trial planning. Exploratory mediation analysis will be conducted to test the association between step-counts and diet on change in outcomes.

Aim 3 will be assessed using semi-structured interview methods. At the 3-month post-intervention time point, participants' qualitative perspectives on their experience during the intervention (advantages, barriers, and support) and use of mobile technology (perceived usefulness, ease of use) were obtained. Qualitative data will be coded and analyzed. Transcripts will be independently coded for initial themes and then checked for inter-rater agreement by at least two research investigators. Content analysis will be conducted by marking and categorizing key words and phrases to identify emerging themes [46,47]. Data analysis will identify links across themes. Themes will be reviewed, discussed, and resolved through consensus. The research team will meet to review and discuss transcript-coding, achievement of data saturation, consensus regarding identification and definition of themes, and selection of illustrative excerpts from transcripts. Dependability of the data interpretation will be supported by investigator triangulation, a process whereby more than one investigator analyzes the data [48]. Themes derived from the data will be used to refine and further culturally tailor the intervention, in preparation of a larger full-scale RCT proposal.

Results

Baseline Data

Study participants were recruited, enrolled, and randomized between December, 2014 and January, 2016. Of the 57 potentially eligible participants who completed the SBV and two-week run-in period, 45 were eligible for study enrollment, and were randomized into one of two groups: the PilAm Go4Health intervention group (n=22) or the active control group (n=23). See Figure 3 for details.

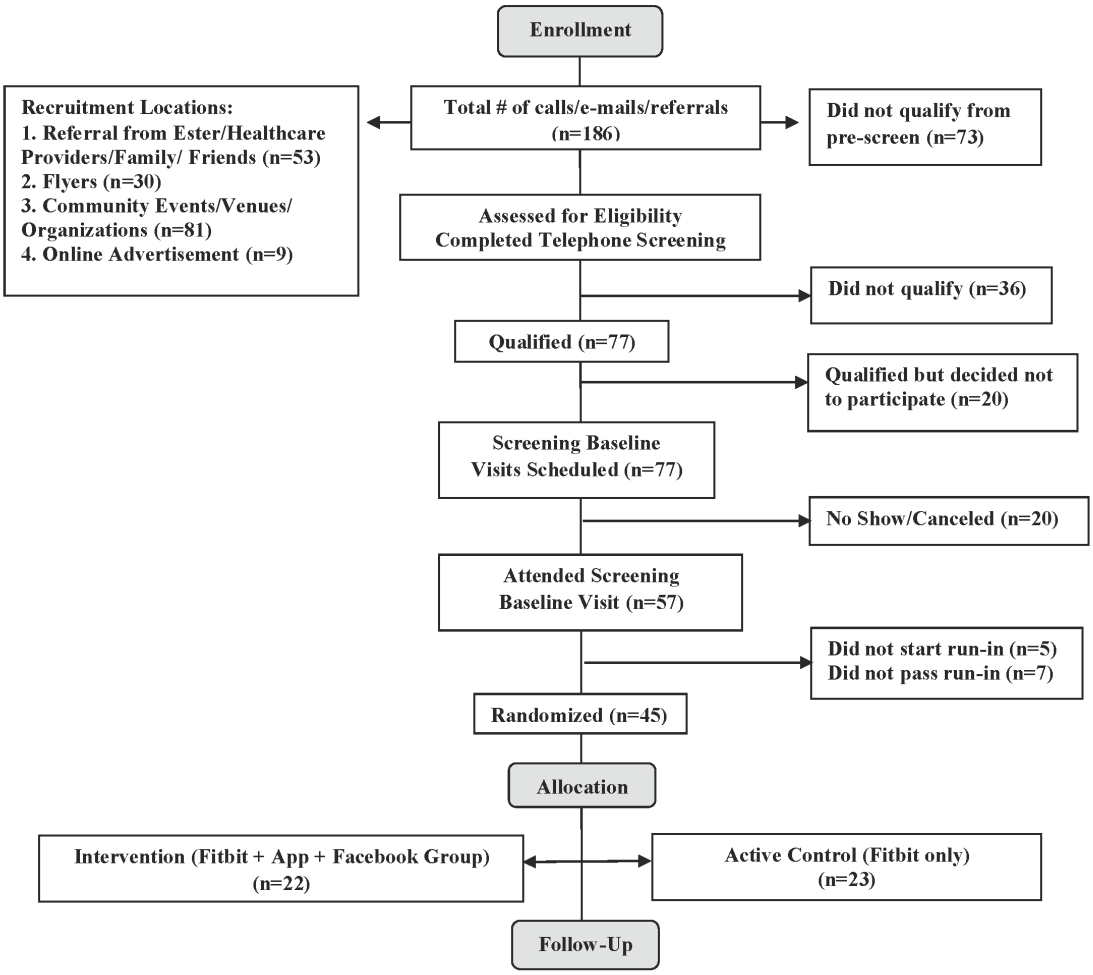
Table 3 presents the baseline characteristics of study participants. Overall, the mean age of participants was 57.6 (standard deviation [SD] 9.8) years with approximately one-third of the cohort being male (38%, 17/45) and two-thirds female (62%, 28/45). More than half of all participants had completed college (56%, 25/45), were married/cohabitating (67%, 30/45), and employed full or part time (69%, 31/45). The majority of participants were Filipino immigrants (84%, 38/45) who had lived in the United States for more than 10 years, and close to half (47%, 21/45) had 3-to-5 people living in their household. Overall, participants were in the obese BMI category, with a mean BMI of 30.2 kg/m^2(SD 4.9) and were in the high disease-risk category with a mean waist circumference of 100.0 cm (SD 11.5) [49]. The mean fasting blood sugar level was 140.4 mg/dL (SD 27.5) and mean HbA1c was 7.4 (SD 0.99) within blood test levels for diabetes [50]. Participants in the intervention group were all Filipino immigrants (100%, 22/22), whereas 30% (7/23) of the active control group participants were born in the United States. Comparisons of baseline characteristics demonstrated two statistically significant differences (P<.05) between the intervention and control groups: years lived in the United States, and BMI.

Table 3. Baseline sociodemographics, anthropometrics, and serum lab results.

Variable		N=45 Mean (SD) or % (n)	Intervention N=22 Mean (SD) or % (n)	Control N=23 Mean (SD) or % (n)	*P*-value
Age in years		57.6 (9.8)	57.4 (9.8)	57.7 (10.0)	0.90
Race (Filipino)		100 (45)	100 (22)	100 (23)	1
Gender					0.85
	Male	37.8 (17)	36.4 (8)	39.1 (9)	
	Female	62.2 (28)	63.6 (14)	60.9 (14)	
Marital status					0.063
	Never married	11.1 (5)	4.5 (1)	17.4 (4)	
	Divorced/widowed	22.2 (10)	31.8 (7)	13.0 (3)	
	Married/cohabitating	66.7 (30)	63.6 (14)	69.6 (16)	
Education					0.67
	Some college	24.4 (11)	18.2 (4)	30.4 (7)	
	Completed college	55.6 (25)	63.6 (14)	47.8 (11)	
	Graduate school	20.0 (9)	18.2 (4)	21.7 (5)	
Employed					0.21
	Full or part time	68.9 (31)	77.3 (17)	60.9 (14)	
	Unemployed	4.4 (2)	4.5 (1)	4.3 (1)	
	Retired	26.7 (12)	18.2 (4)	34.8 (8)	
Years lived in the United States					0.003*
	Native born	15.6 (7)	0 (0)	30.4 (7)	
	5 to 9 years	2.2 (1)	0 (0)	4.3 (1)	
	10 years or more	82.2 (37)	100 (22)	65.2 (15)	
Number living at home					0.82
	<3	42.3 (19)	40.9 (9)	43.5 (10)	
	3 to 5	46.7 (21)	50.0 (11)	43.5 (10)	
	>5	11.1 (5)	9.1 (2)	13.0 (3)	
Previous pedometer use					0.41
	Yes	33.3 (15)	27.3 (6)	39.1 (9)	
	No	66.7 (30)	72.7 (16)	60.9 (14)	
Outcome measures					
	Weight (kg)	75.8 (17.0)	71.6 (9.1)	80.3 (22.3)	0.21
	Waist circumference (cm)	100.0 (11.5)	97.4 (8.2)	102.8 (14.1)	0.24
	BMI (kg/m^2)	30.2 (4.9)	28.4 (3.3)	32.2 (5.7)	0.048*
	Fasting glucose (mg/dl)	140.4 (27.5)	135.8 (23.1)	145.3 (31.7)	0.39
	HbA1c (%)	7.40 (0.99)	7.26 (0.89)	7.55 (1.09)	0.45
	Steps (steps/day)	7431 (1789)	7142 (1475)	7743 (2091)	0.40

* $P<0.05$ between group difference in baseline characteristics.

Figure 3. Consort Flow Diagram.



Discussion

The objective of this 3-month pilot RCT, with a wait-list control and 3-month maintenance phase, was to assess the feasibility and potential efficacy of the PilAm Go4Health program to reduce risks for metabolic syndrome in Filipinos with T2D. To our knowledge, this is the first such culturally adapted intervention program incorporating digital technology specifically targeting Filipinos with T2D that are at high risk for metabolic syndrome. Data collected thus far demonstrates

feasibility for recruiting this specific, hard to reach population to participate in a weight loss program that promotes PA and healthy eating. Participant referral, primarily through word of mouth from family and community members, and face-to-face recruitment through community cultural events, were the most effective approaches, indicating a high level of interpersonal contact that promotes trust may have been needed to motivate study participation.

Lessons Learned with Recruitment Strategies

Overall, recruitment was challenging, requiring approximately one year for this hard to reach Filipino population with T2D. One problematic barrier was due to the study's rigorous inclusion/exclusion criteria (see Multimedia Appendix 1) that precluded those with frequently occurring T2D comorbidities such as gout, hypertension, and heart disease. Of the 186 prescreened potential participants, 67 were excluded due to related comorbidities. For example, many were excluded due to factors preventing weight-loss (eg, polycystic ovary disease and thyroid disease), heart disease complications, bone and joint problems, and uncontrolled T2D. Of the 77 potential participants who qualified to move on to the in-person SBV, 12 decided not to participate and 8 cancelled or were lost to follow-up. Among those who declined, several cited the barrier of a long commute to the research office. Of all planned recruitment strategies that were implemented, the most time efficient recruitment venues were Filipino community health fairs and cultural events, yielding 32 potential participants. This result may have been due to a combination of factors, including the ease of access to a high density of qualified potential participants in a confined area over a short period of time. In contrast, general public events such as the Daly City Chamber of Commerce events and public dance events that yielded only 6 potential participants, and shopping malls that yielded 17 potential participants, required much more solicitation time on the part of the recruiters compared to other venues and strategies.

Overall, the most effective recruitment strategies were referrals from family, friends, community leaders, and health care providers/clinics, resulting in 53 potential recruits. Filipinos place family and community, along with social support, as a priority in their lives [7]. Thus, the endorsements received from personal and trusted sources may have motivated potential participants to contact our research office.

Flyers posted in hospitals and the health institution’s shuttle buses resulted in 20 potential recruits, whereas posting flyers at community centers and public areas (gyms, coffee shops, and laundromats) were not as effective, yielding only 10 potential recruits. Filipinos with T2D may be more likely to frequent health-related venues compared to more general public areas, thereby explaining the relative differences in the effectiveness between these two recruitment strategies.

Online advertisements through websites, Craigslist, Facebook, and a select mailing service were not as effective as anticipated, compared to in-person recruitment efforts. The social aspect of the personal contact may have encouraged participation versus the relatively impersonal digital media contacts.

Potential Limitations

In addition to the limitations referenced above, including the study design (eg, unblinded research staff and participants), recruitment issues due to stringent inclusion/exclusion criteria, and adherence to protocol due to lost Fitbit Zips, there are several other potential study limitations. First, it may be difficult for older participants, and those without previous experience using mobile phones and mHealth apps, to comply with this study protocol, thus adversely impacting engagement and retention rates. However, evidence indicates that in a similar mHealth study, older participants and those without previous experience using digital technology were able to adhere to the intervention protocol requirements without influencing outcomes or retention [51]. To further mitigate potential problems using digital technology, family members with digital technology experience were encouraged to partner with participants exhibiting difficulties using the Fitbit Zip or the mHealth app/diary. Second, for those subjects who worked or were unable to attend regular Monday through Friday office hours, weekend and evening in-person office visits were available. Third, the potential subject’s primary care providers were mailed a *Study Provider Letter* to inform them of the subject’s intent to participate. This information offered the primary care provider an opportunity to screen out high risk or inappropriate participants from the study. Additionally, by alerting providers to the nature and overall details of the study, the potential of general practitioners implementing a treatment plan that would bias the study was reduced. Finally, the small sample size and targeted Filipino population living in northern California limits the generalizability of the findings to other populations. However, a major strength of this study is that it has been designed not only to be culturally appropriate for Filipinos, but translatable to other at-risk populations.

Conclusion

If the PilAm Go4Health Weight Loss Program demonstrates potential efficacy, it would aid in the identification of effective intervention strategies that could significantly reduce risks for metabolic syndrome in Filipinos with T2D. This program will also lay the foundation for a larger full-scale RCT to demonstrate intervention effectiveness, and operational- and cost-effectiveness. Furthermore, if the PilAm Go4Health intervention demonstrates feasibility and acceptability in this high-risk minority population, it could be developed into a sustainable and scalable healthy lifestyle intervention program that could be adapted and widely disseminated to other high-risk racial/ethnic and diverse populations.

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Authors' Contributions

MSB is the principal investigator who conceived the study idea and methodology, oversaw the intervention cultural adaptation, implementation, data collection, and analysis, and drafted the manuscript. GMS, the statistician for the study, prepared the data analysis section for the paper and critically reviewed the manuscript draft. CV contributed to the cultural adaptation of the intervention, coordinated intervention implementation, helped with data collection, prepared the data for analysis, and contributed to and reviewed the manuscript draft. SA provided guidance for the organization of the paper and critically reviewed the manuscript drafts.

Conflicts of Interest

None declared.

Multimedia Appendix 1

PilAm Go4Health Inclusion/Exclusion Criteria.

[PDF File (Adobe PDF File), 43KB - resprot_v5i3e178_app1.pdf]

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Abbreviations

DPP: Diabetes Prevention Program
HbA1c: glycated hemoglobin A1c
mHealth: mobile health
NHLBI: National Heart, Lung, and Blood Institute
PA: physical activity
PilAm Go4Health: Filipino Americans Go4Health Weight Loss Program
RCT: randomized controlled trial
SBV: screening baseline visit
T2D: type 2 diabetes

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Protocol

Optimizing Rehabilitation for Phantom Limb Pain Using Mirror Therapy and Transcranial Direct Current Stimulation: A Randomized, Double–Blind Clinical Trial Study Protocol

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Abstract

Background: Despite the multiple available pharmacological and behavioral therapies for the management of chronic phantom limb pain (PLP) in lower limb amputees, treatment for this condition is still a major challenge and the results are mixed. Given that PLP is associated with maladaptive brain plasticity, interventions that promote cortical reorganization such as non-invasive brain stimulation and behavioral methods including transcranial direct current stimulation (tDCS) and mirror therapy (MT), respectively, may prove to be beneficial to control pain in PLP. Due to its complementary effects, a combination of tDCS and MT may result in synergistic effects in PLP.

Objective: The objective of this study is to evaluate the efficacy of tDCS and MT as a rehabilitative tool for the management of PLP in unilateral lower limb amputees.

Methods: A prospective, randomized, placebo-controlled, double-blind, factorial, superiority clinical trial will be carried out. Participants will be eligible if they meet the following inclusion criteria: lower limb unilateral traumatic amputees that present PLP for at least 3 months after the amputated limb has completely healed. Participants (N=132) will be randomly allocated to the following groups: (1) active tDCS and active MT, (2) sham tDCS and active MT, (3) active tDCS and sham MT, and (4) sham tDCS and sham MT. tDCS will be applied with the anodal electrode placed over the primary motor cortex (M1) contralateral to the amputation side and the cathode over the contralateral supraorbital area. Stimulation will be applied at the same time of the MT protocol with the parameters 2 mA for 20 minutes. Pain outcome assessments will be performed at baseline, before and after each intervention session, at the end of MT, and in 2 follow-up visits. In order to assess cortical reorganization and correlate with clinical outcomes, participants will undergo functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) before and after the intervention.

Results: This clinical trial received institutional review board (IRB) approval in July of 2015 and enrollment started in December of 2015. To date 2 participants have been enrolled. The estimate enrollment rate is about 30 to 35 patients per year; thus we expect to complete enrollment in 4 years.

Conclusions: This factorial design will provide relevant data to evaluate whether tDCS combined with MT is more effective than each therapy alone, as well as with no intervention (sham/sham) in patients with chronic PLP after unilateral lower limb amputation. In addition, this randomized clinical trial will help to investigate the neurophysiological mechanisms underlying the disease, which could potentially provide relevant findings for further management of this chronic condition and also help to optimize the use of this novel intervention.

Trial Registration: Clinicaltrials.gov NCT02487966; https://clinicaltrials.gov/ct2/show/NCT02487966 (Archived by WebCite at http://www.webcitation.org/6i3GrKMyf)

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KEYWORDS

cerebral cortex; clinical trial; electrical stimulation; electric stimulation therapy; factorial design; mirror therapy; non-invasive brain stimulation; transcranial electrical stimulation

Introduction

Phantom limb pain (PLP) belongs to a group of neuropathic pain syndromes characterized by pain in the amputated limb [1-4]. In Western countries, the main reason for amputation is chronic vascular disease. In other parts of the world, civil wars and landmine explosions result in many cases of traumatic amputations in otherwise healthy people [5]. In the United States, 54% are due to vascular disease, 45% due to trauma, and less than 2% to cancer. According to the amputee coalition, there are approximately 2 million amputees in the United States and 185,000 amputations occur every year. From the individuals that had an amputation due to vascular disease, 50% will survive more than 5 years. Of the ones who had a lower extremity amputation due to diabetes, up to 55% will require the amputation of the second leg in 2 to 3 years.

PLP is experienced by 50% to 80% of the amputees. Although PLP may decrease or disappear over time, prospective studies indicate this is often not the case. Even 2 years after amputation, 59% of the patients reported PLP with only 5% to 10 % decrease in the intensity, exemplifying how it still remains a significant clinical problem that impairs quality of life [3,4].

Mechanisms of Phantom Limb Pain

The precise mechanisms underlying development of pain in patients with limb amputation are not well elucidated. It has been demonstrated that long standing limb amputation can cause structural reorganization of the brainstem, thalamic nuclei, or the somatosensory cortex leading to maladaptive plastic changes [6-11]. Given the high concordance between motor and somatosensory plasticity, it is reasonable to assume that reorganization of the somatosensory cortex can also be detected in the motor cortex [12].

After an upper limb amputation, either shrinkage of the upper-limb region or expansion of the surrounding areas (lip/facial) is found in the primary somatosensory (S1) and motor (M1) cortex [6,8,10,13] . Using functional magnetic resonance imaging (fMRI), Lotze et al showed that the shift in the lip representation into the primary motor and somatosensory cortex is correlated with the amount of PLP [14,15]. Cortical reorganization secondary to an amputation additionally involves a decrease of GABA activity and an increased excitability of the corticospinal neurons over M1 [16-18] . These findings led to the current view that this reorganizational change represents a main pathophysiological mechanism of PLP [8,15,19,20] . Current rehabilitative therapies to treat PLP do not take into account such maladaptative plastic changes. An ideal therapeutic approach to treat PLP should aim to modulate and reverse the maladaptive plastic changes involved in the development of chronic PLP [21].

Transcranial Direct Current Stimulation and Mirror Therapy

In this context, given that current options for pain treatment have insignificant or no effect on brain plasticity, the investigation of alternative approaches such as neuromodulation techniques can be used not only to alleviate pain but also to revert maladaptive plasticity. One candidate to promote plastic changes is transcranial direct current stimulation (tDCS). tDCS delivers a low intensity current that can modulate (facilitate or inhibit) spontaneous neuronal activity, its long term effects are likely to be mediated by mechanisms of synaptic long term potentiation and depression affecting neuroplasticity [22,23].

Recent studies have confirmed the therapeutic potential of tDCS in treating PLP. In 2013, Bolognini et al showed that a single session of anodal tDCS (2 mA, 15 min) targeting M1 induced a selective short-lasting decrease of PLP [24]. In addition, the same group showed the pain relief cumulative effects of tDCS with repeated sessions. After 5 consecutive days of anodal tDCS over M1 (1.5 mA, 15 min), participants experienced sustained decrease in PLP which lasted for 1 week after the end of the treatment, along with enhanced control of phantom limb movements [24,25]. These studies point out the preliminary yet promising role of tDCS in relieving PLP. The next step in this investigation would be to combine tDCS with a behavioral intervention. The learning of new skills (that is accompanied by behavioral changes) is linked to changes in neuronal activity and excitability [26]. They might reflect changes in synaptic strength, for example, N-methyl-D-aspartate (NMDA) receptor-dependent long term potentiation (LTP) [27].

Soler et al [28] conducted a factorial trial testing the combined effects of tDCS and visual illusion to treat patients with chronic neuropathic pain associated with spinal cord injury. The combination of tDCS and visual illusion was associated with the greatest pain reduction as compared to the either therapy alone. The results demonstrate and provide important preliminary data to support the rationale of this trial.

Therefore, combining tDCS with a behavioral intervention may optimize PLP rehabilitation. Mirror therapy (MT) seems to be the optimal behavioral intervention to activate sensorimotor cortex as shown by several studies [14,29-31]. Ramachandran et al (1996) were the first to describe the use of MT in order to evaluate its effects on phantom limb sensation in 10 upper limb amputees [32]. Foell et al [14] found a 27% decrease on a visual analogue scale (VAS) in 13 patients with unilateral upper limb amputation and chronic PLP after 4 weeks (15 min daily) of MT training (size effect=0.52). In addition, they found a relationship between the pain change after MT and a reversal of dysfunctional cortical reorganization in S1. In a pilot study involving 40 patients with PLP and unilateral amputation, Darnall et al [30] showed a significant reduction in average pain intensity at 1 and 2 months after home MT (25 min daily). There are also promising results from case reports and randomized clinical trials on the effectiveness of MT as a pain intervention in patients with PLP following amputation of upper or lower limbs [29,30]. However, the response to MT is usually heterogeneous, with treatment's gains variable across individuals. Considering this heterogeneity and the fact that the analgesic effects of MT are not yet elucidated, it would be reasonable to combine it with a top-down cortical intervention, such as tDCS, aiming to improve its analgesic effect. Therefore, combining these two interventions could optimize the effects of each therapy alone, resulting in cortical changes and an efficacious and long lasting relief from PLP.

In summary, there is a great unmet need for non-invasive treatments for chronic PLP. In this protocol, we will test a novel rehabilitation approach combining a behavioral therapy (MT) with a method of brain modulation (tDCS) to treat and investigate the mechanisms of PLP.

Aims and Hypotheses

Primary Aim

The primary aim of this clinical trial is to perform a comparative analysis of the efficacy of tDCS and MT as a rehabilitative tool for the management of chronic PLP in unilateral lower limb amputees.

Secondary Aim

The secondary aim of the study is to examine the mechanisms underlying PLP using two neurophysiological techniques. Single-pulse and paired-pulse transcranial magnetic stimulation (TMS) will be utilized to assess cortical mapping and cortical excitability changes associated with cortical reorganization. In addition, fMRI will be employed to assess brain changes, including the quantification of maladaptive cortical reorganization.

Hypotheses

We hypothesize that the combination of tDCS and MT will achieve greater effects when compared with the isolated use of either tDCS or MT, as well as with the sham tDCS combined with sham MT with regard to improvement (greater pain reduction) of chronic PLP, as indexed by the VAS scale in participants with unilateral lower limb amputation.

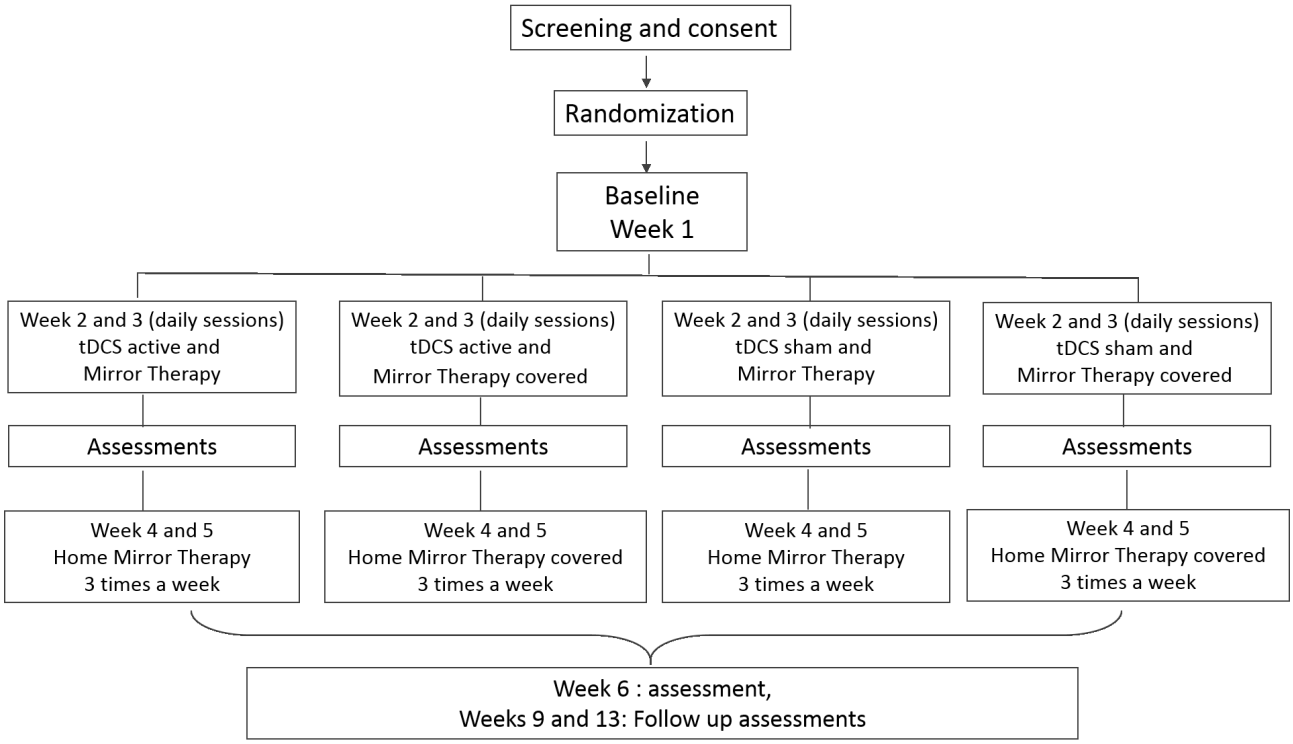
Our second hypothesis is that the combined group (tDCS and MT) will have a greater activation than any therapy alone and the no therapy group (sham tDCS and covered mirror) in the TMS and fMRI evaluations. In addition, neurophysiological and hemodynamic changes will be correlated with pain reduction.

Methods

Study Design

A prospective, randomized (allocation ratio 1:1:1:1), placebo-controlled, double-blind, factorial superiority study will be carried out (Figure 1).

Figure 1. Flow chart of the study based on CONSORT criteria.



Study Setting

Patients will be recruited from the Limb Loss Clinic of the Spaulding Rehabilitation Hospital/Network and additional recruitment around the Boston, MA area. All study procedures will be performed at the Spaulding Neuromodulation Center in the Spaulding Rehabilitation Hospital, Charlestown, MA, USA.

Eligibility Criteria

The eligibility criteria (inclusion and exclusion) for the study are shown in Textbox 1. Since the safety of tDCS in the pregnant population (and children) has not been assessed, pregnant women (and children) will be excluded. Women of child-bearing potential will be required to take a urine pregnancy test during the screening process.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Able to provide informed consent to participate in the study
- Subject is older than 18 years
- Unilateral lower limb amputation
- 3 months of PLP after the amputated limb has completely healed
- Average pain of at least 4 on a numeric rating scale (NRS), ranging from 0 to 10 in the previous week
- If the subject is taking any medications, dosages must be stable for at least 2 weeks prior to the enrollment of the study

Exclusion criteria

- Pregnancy or trying to become pregnant in the next 2 months
- History of alcohol or drug abuse within the past 6 months, as self-reported
- Presence of the following contraindication to tDCS and TMS
  - Ferromagnetic metal in the head (eg, plates or pins, bullets, shrapnel)
  - Implanted neck or head electronic medical devices (eg, cochlear implants, vagal nerve stimulator)
- History of chronic pain previous to the amputation
- Head injury with post-traumatic amnesia for greater than 24 hours, as self-reported
- Unstable medical conditions (eg. uncontrolled diabetes, uncompensated cardiac issues, heart failure or chronic obstructive pulmonary disease)
- Uncontrolled epilepsy or prior seizures within the last 1 year
- Suffering from severe depression (as defined by a score of >30 in the Beck Depression Inventory)
- History of unexplained fainting spells or loss of consciousness as self-reported during the last 2 years
- History of neurosurgery, as self-reported
- MT within 3 months prior to enrollment

Interventions

Transcranial Direct Current Stimulation

tDCS will be performed during the MT session, as this technique may facilitate behavioral changes by enhancing neuroplasticity and increasing functional connectivity. The Soterix Medical 1×1 tDCS stimulators device (Soterix Medical Inc.) will be utilized. This device sends a low-level current from the positive electrode (anode) to the negative electrode (cathode). During tDCS, low amplitude direct currents will be applied via scalp electrodes and penetrate the skull to enter the brain. Direct current will be transferred by a saline soaked pair of surface sponge electrodes (35 cm^2) and delivered by a specially developed, battery-driven, constant current stimulator with a maximum output of 10 mA.

The tDCS device can be used with codes that correspond to active or sham stimulation, allowing a truly double-blind procedure. Participants will receive daily stimulation sessions with active or sham anodal tDCS for 10 days (5 days each week). Participants will be allowed to reschedule up to 3 stimulation visits (maximum of 2 consecutives). During each active anodal tDCS session, an anodal electrode will be placed over M1, contralateral to the amputation side and the cathode over the contralateral supraorbital area and tDCS will be applied for 20 minutes at 2 mA [24]. For the sham tDCS, the same montage of electrodes used for the active stimulation will be applied; however, current will be applied only for the first 30 seconds of the 20 minutes session. This is a reliable method of sham stimulation as sensations arising from tDCS treatment occur only at the beginning of application [33].

Mirror Therapy

For the active MT sessions, participants will be asked to perform movements (15 minutes daily) using the unaffected limb while watching its mirrored reflection superimposed over the affected limb. During MT, participants will be asked to consciously relate the movement observed in the mirror to their phantom limb and to keep their attention focused on the task. Instructions will be explained verbally, demonstrated by a therapist, and performed by the subject in front of the therapist during the first 2 weeks (the MT sessions will be scheduled at the same time as the tDCS sessions). After the training, participants will continue MT everyday for 2 more weeks at home. Participants will be instructed to stop MT if it intensifies their pain, and to document if this happens. For the sham MT (covered MT), participants will be asked to perform movements in the same way as the active group but with a covered mirror.

Outcomes

Evaluation and Follow-Up

The participants in each group will be evaluated by an experienced researcher in the evaluation procedures and blinded to which group (active vs sham tDCS) each participant belongs.

The following 14 evaluations will be carried out: (1) evaluation 1 will be carried out one week prior to the intervention, (2) evaluations 2-11 will occur before and after the intervention, (3) evaluation 12 will take place right after the home-based MT is finished, (4) evaluation 13 will take place 4 weeks after the home-based MT is finished, and (5) evaluation 14 will take place 8 weeks after the home-based MT is finished.

Pain Assessment

Pain assessment will be indexed by the VAS for pain. This scale is commonly used to obtain self-reported ratings of pain level on a visual scale (ie, unbearable to none). Participants will rate the intensity of their PLP from 0 (indicating no pain at all) to 10 (indicating the worst pain felt). They will also report the frequency of PLP paroxysms, when PLP clearly increases above the background level from 0 (never during the day) to 10 (very frequently) [24,25,34]. This colored VAS will be used, from green (at 0) to red (at 10), as a visual indicator of pain. This assessment tool is frequently used in research studies evaluating pain levels [24,25,29,34-37]. VAS will be used to measure stump pain, non-painful phantom limb sensation, phantom movements, and phantom limb telescoping [25,34]. In addition, an adapted version of the Groningen Questionnaire after Arm Amputation will be administered. This questionnaire was originally meant to obtain information concerning complaints that may be developed after arm amputation and an adaptation of the current arm version was developed to assess participants with lower limb amputation. This questionnaire has been used in several clinical trials assessing PLP [38].

A pain and medication diary will be filled out daily by each participant during the total duration of the trial. This assessment tool will help to monitor daily changes in pain levels, medication dosage information, as well as safety. Participants will be asked to record the number of PLP paroxysms (ie, when PLP clearly increases above the background level) on a daily basis using a pain diary. In addition, the participants will record the intensity of the strongest episode as well as non-painful phantom limb sensation, phantom movements and stump pain on different colored VAS included in the diary. Moreover, participants will record their current medications and dosages daily in a pain medication diary, until completion of the study.

Neurocognitive and Psychological Assessments

Participants will undergo assessments of neurocognitive and psychological aspects such as depression or anxiety. In the case of depression the subjects will be assessed with the Beck depression inventory [39]. This self-reported inventory consists of 21 multiple choice questions and is a widely used method to classify depression severity. It assesses for the presence of several symptoms related to depression, such as irritability, hopelessness, and decreased cognitive performance. Physical symptoms such as weight loss and fatigue are also included. This instrument has been used previously to evaluate depression severity in patients with PLP [40], as well as in other chronic pain conditions [28,41,42]. With respect to anxiety, participants will be assessed with the Beck anxiety inventory [39]. This self-reported inventory consists of 21 multiple choice questions about the participant's overall “feelings” during the previous week. It is designed for an age range of 17 to 80 years old. Each question has the same set of 4 possible answer choices, arranged in columns and answered by marking the appropriate one with a cross [39].

In order to assess potential cognitive decline, participants will undergo evaluation with the Mini Mental State examination (MMSE). This is a sensitive, valid, and reliable 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive abilities. It will be used as a baseline evaluation [43].

Quality of Life, Safety and Adverse Effects Assessments

Each participant will undergo assessments to evaluate changes in quality of life and safety before and after the intervention. Quality of life will be assessed using the Short Form Health Survey (*SF-36*) [44]. SF-36 is used as a measurement of quality of life and provides a profile of functional health and well-being scores. It is also used as a psychometrical index of physical and mental health. This instrument is widely used as a quality of life assessment in patients after an amputation and those suffering from PLP [44-46]. In addition, the Stroop test will be performed. In this test, participants are presented with names of colors written in the same color or in a different color, thus on the one hand the word names a color (red) and is written in another color (blue). In this task, the automatized behavior (reading) is in conflict with the desired response (naming the color). The subject has to inhibit and/or suppress the automatic response of reading and naming the color the word is written in. The Stroop is one of the most commonly used tools for determining attentional problems and to assess executive function and working memory [47,48]. Here, the Stroop test will be used to assess cognitive changes from baseline to post-treatment and follow-up visits. Furthermore, the Patient’s Global Impression of Change scale will be applied in order to evaluate the participant's perception of change (if any) in the activity limitations, symptoms, emotions, and overall quality of life after their participation in the intervention visits of the trial [49].

Neuroimaging Study and Analysis

fMRI will be used to quantify patterns of activation associated with maladaptive cortical reorganization before and after treatment of each participant. Structural and functional imaging data will be acquired on a 3 Tesla Philips Achieva System (Best, the Netherlands) with a 32-channel phased array coil. Structural T1-weighted scans will be acquired using a turbo spin echo sequence (TE = 3.1 ms, TR = 6.8 ms, flip angle = 9°, voxel size 0.98 x 0.98 x 1.20 mm, no slice gap, acquisition matrix 256 x 254). Functional scans will be acquired with a single-shot EPI sequence (TE 28 ms, TR 2000 ms, flip angle 90 deg, and 3 mm isotropic resolution with no slice gap). Two functional runs will be collected each lasting 360 seconds in duration (see below for details regarding task design and contrasts of interest).

A repeated measures design (baseline and post-treatment) will be conducted for each participant. Additional baseline data will be obtained for secondary correlations. In addition, a sensitivity analysis testing the comparison of post-treatment will be conducted.

This design is based on previous work investigating the task-based activation of cortical motor networks associated with the observation and imagination of lower limb movements [50]. The task conditions will consist of the participant actively moving their non amputated limb (flexion and extension) at a predetermined frequency, followed by the same leg movement, but now the participant will be able to observe the image of his/her leg moving in a mirror (presented through an online video). These two conditions will be interleaved by a rest period of equal length in which the participant will be instructed to remain immobile. The following 3 conditions will therefore be investigated: (1) movement of the leg (MOV-LEG), (2) movement of the leg observing the mirror (MIR-LEG), and (3) rest condition. For the MOV-LEG, the participants will perform movements of the non amputated leg and each participant will be instructed about the type and pace of the movements. For the MIR-LEG, the participants will perform the same movements from the previous condition, looking at the mirror image of the intact leg in an online video. Again, each participant will be instructed about the type, pace, and video. During the rest period, the participants will rest and will be instructed to not perform any kind of movements. Each of the 3 conditions will have the same length (20 seconds). The fMRI session will have 4 runs each containing 6 blocks (6 repetitions of each condition).

For the analysis, the region of interest (ROI) will be selected. The ratio of activation between the MOV-LEG and MIR-LEG (in the respective ROI – contralateral to the respective leg) will be determined previously. Using this coefficient, a comparison across the 4 different conditions will be performed. For this sub study, a standard safety screening questionnaire will be administered prior to participation by the attending technician or study investigator (NINDS CDE) [51,52].

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) will be used to assess cortical excitability and cortical reorganization. For the TMS assessments, we will use Magstim Bistim2 stimulator and a figure 8 coil (Magstim Company LTDA, UK). The most distal muscle will be studied, in the case of the presence of the quadriceps we will place the electrodes over the rectus femoris, another pair of electrodes will be placed in the first dorsal interossei muscle (FDI), and a ground electrode will always be placed over the participant's distal prominence of the ulna bone. Electromyogram (EMG) recordings will be processed using Powerlab 4/30 (ADinstruments, Colorado Springs, CO, USA) with a band pass filter of 20-2000 kHz. Offline analyses will be performed using LabChart (ADinstruments, Colorado Springs, CO, USA). First, head measures will be taken to identify the approximate spot of the motor cortex (using the vertex as the reference) [53]. Then, the TMS coil will be held over the motor cortex at an angle of 90 degrees with respect to the sagittal line of the head. The hotspot will be determined by carefully eliciting the most stable and highest *motor-evoked potentia* l (MEP) amplitudes over the rectus femoris [54-56]. The best location will be marked with a pen on a swim cap, which will be worn by each of the participants. Resting motor threshold (rMTh) will be determined by eliciting 3 of 5 motor-evoked potentials (MEPs) with minimal peak-to-peak amplitude of 100 μV (according to Rossini et al) [57]. Changes in cortical excitability will be assessed by evaluating the MEP; to assess this aim 10 MEPs will be recovered for each hemisphere using 120% of the rMTh [53].

TMS measurements will include short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) using the paired-pulse technique [22]. For paired-pulse measurements, the first stimulus will be set to 80% of the individual rMTh, and the second stimulus to the individual 120% of the MEP intensity at inter-stimulus interval of 2, 3, 6, 9, 10, and 12 ms. Ten recordings of each inter stimulus interval protocol will be randomly elicited (total of 60 measures). Offline analyses will include measures of peak-to-peak amplitude, the area-under-the-curve of all MEPs, and the relative duration of cortical silent periods (CSPs) (time from last MEP until normal muscle activity was re-achieved). For the cortical mapping measures, 8 stimulations at 120 % of rMTh intensity (posterior to anterior current) will be delivered to each of 15 sites forming a 3x5 grid, with a constant 1.5 cm distance between sites, over M1 [22]. At each stimulation site, the peak-to-peak amplitudes of the recorded MEPs will be measured and averaged offline. The map center of gravity (CoG) will be computed for the medio-lateral (x) coordinates using the formula:

$$CoGx = (\Sigma xi * MEPi) / \Sigma MEPi \quad (1)$$

where MEPi represents the mean amplitude of the MEPs produced at one site. The sum of the average MEP amplitude will be calculated for each active site, where an active site was defined as a site at which the mean MEP amplitude was at least 0.05 mV.

Participant Timeline

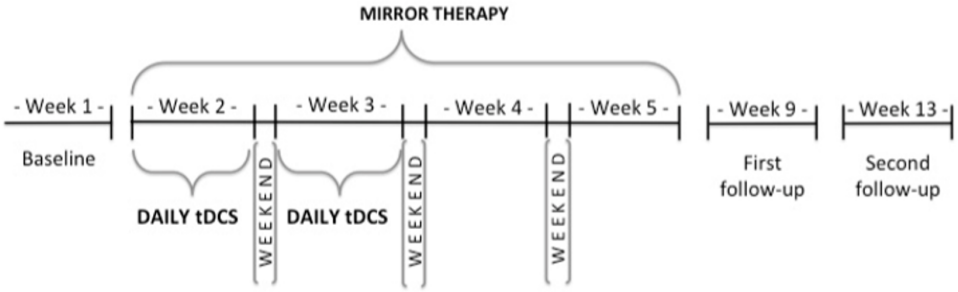
The study will take place for 13 weeks (Figure 2). All study procedures will be performed at the Spaulding Rehabilitation Hospital (Neuromodulation Center). Each participant will undergo 15 visits, described in Textbox 2.

Textbox 2. Study timeline.

Visits

- Visit 1: Consent and screening
- Visit 2: Baseline
- Visits 3-12: Intervention visit
  - After visit 12, the participants will continue MT (alone, without tDCS) at home for 2 more weeks
- Visit 13: End of home intervention (MT)
- Visit 14: Follow-up 1, 4 weeks after visit 13
- Visit 15: Follow-up 2, 8 weeks after visit 14

Figure 2. Schematic view of the experiment time points.



The participants randomized to receive sham tDCS will have the opportunity to enroll into an open label portion of the study at the conclusion of their participation in the randomized portion of the trial.

Study Sample

We will recruit 132 subjects with PLP of traumatic etiology; congenital or diabetic amputees will be excluded since these patients may have different neuroplastic profiles. Participants will need to meet all of the inclusion criteria and none of the exclusion criteria.

Sample Size Calculation

The sample size was calculated utilizing STATA 11 program. We based our calculation on a study carried out by Soler et al (2010) entitled “Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury” [28]. Using VAS as continuous outcome for the calculation and considering results from this study, a mean (SD) of 5.2 (1.5) in the experimental group (tDCS and visual illusion) and 6.4 (1.6) in the control group (visual illusion), and using a bidirectional alpha of .05 and power of 80%, we would need a total sample of 108 participants (27 in each group). In addition, estimating a conservative attrition rate of 20%, our sample size would be 132 participants. Although we calculated the sample for our primary aim, it is important to underscore that the power calculation will also be adequate for our secondary aim measuring neurophysiological outcomes. In fact, neurophysiological outcomes usually have less variability and thus needs smaller sample sizes to show significant differences. As shown in our preliminary data and data from other studies [55,58], effect sizes from TMS data will be larger and for the fMRI, we expect blood oxygen level dependent (BOLD) changes in sensory motor cortex around 3% to 5% (as shown by previous studies [50]), therefore a sample of 7 to 8 participants will be enough to detect significant changes.

Recruitment

Individuals with chronic PLP after a unilateral lower limb amputation will be primarily recruited through the Limb Loss Clinic at Spaulding Rehabilitation Hospital/Network in Charlestown, MA. The Amputee Program at Spaulding Rehabilitation Hospital has more than 120 in-patients with amputations per year, and its Limb Loss Clinic has more than 200 amputees with PLP. Spaulding Rehabilitation Hospital was the primary rehabilitation center that received patients with traumatic amputations from the Boston Marathon Bombings. In addition, we will approach colleagues at the other Harvard teaching hospitals, including Brigham and Women’s Hospital (BWH) and Massachusetts General Hospital (MGH), and outpatient clinics in the greater Boston area.

Randomization

Once eligibility and consent have been approved and completed, randomization will occur using the randomized list generated by an automatic Web-based randomization program. Participants will be randomly assigned to 1 of the following 4 groups: (1) Group 1 will receive active tDCS and MT, (2) Group 2 will receive sham tDCS and MT, (3) Group 3 will receive active tDCS and covered MT, and (4) Group 4 will receive both sham tDCS and covered MT.

The participants randomized to receive sham tDCS will have the opportunity to enroll into an open label portion of the study

at the conclusion of their participation in the randomized portion of the trial.

Participants will be randomly assigned to 1 of the 4 groups in a 1:1:1:1 allocation ratio. We will use stratified randomization methods with random block sizes of blocks of 4 and 8. Stratification will be based on the participant's baseline pain levels using 2 strata: less than or equal to an average 6 in VAS or greater than 6 in VAS). The randomization order will be kept in sealed envelopes; therefore participants will get their assignment according to the order of entrance in the study (for instance, participant 1 will be assigned the first envelope that will contain his/her assignment according to this block randomization list).This process will be carried out by a member of the research team who is not involved in the recruitment process or development of the study.

Sequence Generation

Eligible participants will be randomized based on an allocation sequence generated by an independent person not involved in the study through a true randomization process.

Allocation Concealment

A series of numbered, sealed, opaque envelopes will be used to ensure concealed allocation. The order of entrance to the study will determine the allocation of the participant.

Implementation

A researcher not involved in the study will be in charge of the allocation.

Blinding

Participants will be blinded by receiving sham tDCS stimulation with the same electrode montage as the active group. All trial researchers involved in the analysis and collection of data will be blinded to the treatment allocation group until after analyses are performed at the completion of the trial.

Blinding Assessment

The tDCS blinding questionnaire will be performed after the stimulation session. Each participant will complete a questionnaire to determine if the blinding methods were effective [59].

Data Collection Methods and Management

Data forms and questionnaires will be coded in a standardized manner, and double-entered into our database. Digital measures and recordings will be similarly tracked in our database and regularly backed up. Analyses will be conducted using standard statistical software such as SAS and Matlab.

Statistical Methods

The primary outcome is PLP indexed by VAS. PLP will be analyzed using intensity of pain over time. To analyze these data, we will initially adopt a mixed analysis of variance (ANOVA) model in which the dependent variable will be the outcome of PLP (such as VAS) and the independent variables will be group (active tDCS-MT; sham tDCS-MT; active tDCS-covered MT; sham tDCS- covered MT), time (baseline and after treatment and follow-up), and the interaction group time. In addition, we will add the random variable ID to account for within participant's variability and the repeated measures on time. Whenever necessary, post-hoc comparisons with Bonferroni correction for multiple comparisons will be carried out initially to explore significant main effects or interactions. *P* values for secondary and exploratory outcomes will be determined without corrections for multiple comparisons. Furthermore, Pearson's correlation analyses will be performed to assess the association between PLP relief and changes in non-painful phantom sensations, phantom movements, and telescoping, as measured with VAS. Finally, we will apply a path analysis [60] to the primary outcome data to determine if pain reduction associated with the combined intervention (tDCS plus MT) is due to direct effects versus indirect effects through improvement in secondary outcomes.

We propose that a direct effect of tDCS and MT on PLP can be assumed if the treatment effect cannot be explained by changes in psychological or functional outcomes.

Statistical models for pain will be developed using covariates that include baseline pain, psychological changes, functional changes, and the covariate treatment (main effect of treatment). To complete the path analysis, separate regression models will be run to model the effects of treatment on each outcome alone including all the secondary outcomes. Analyses of the secondary outcomes will be conducted in an exploratory manner (no correction for multiple comparisons). Secondary outcomes are other pain measurements, psychological, neuropsychological and quality of life measurements, and neurophysiological markers (as indexed by TMS and fMRI).

For the intention-to-treat analysis, we will use a conservative method and assume that participants will not improve from the last measured point. We will also perform a sensitive analysis for the missing data using other methods such as completers only.

Functional Magnetic Resonance Imaging Data Analysis

Image processing and analysis of functional data will be performed using standard analysis procedures in FSL version 5.0.5 (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain {FMRIB], Oxford University, Oxford, UK). Preprocessing includes head motion correction, B0 unwrapping, brain extraction, intensity normalization, high pass temporal filtering with a frequency cutoff of 120 seconds, and Gaussian spatial smoothing (6.0 mm full width at half maximum). Registration will be performed with FMRIB's Linear Image Registration Tool (FLIRT). Each functional image will be registered to the representative T1-weighted anatomical image (using a 6 degree of freedom boundary based linear registration) and to the MNI 152 template (using a 12-parameter nonlinear affine transformation with a warp resolution of 10 mm). Individual time series analysis will be carried out using a general linear model (GLM). Both active (leg moving and viewing) and passive (rest) conditions will be convolved with a Gaussian hemodynamic response function and their temporal derivatives will be used to model the data. The primary contrasts of interest will be conducted for leg moving versus leg viewing, as well as leg moving versus rest and leg viewing versus rest. The leg moving versus rest condition will be used to identify and define a ROI associated with movement of the contralateral

leg during the baseline condition. Activation within this ROI will be compared between pre and post conditions as well as within the same ROI transposed to the opposite hemisphere. As PLP is known to be associated with pathological ipsilateral activation [14,15,19], changes in the degree of lateralization of activation will also be analyzed pre-post in each individual as an index of maladaptive cortical plasticity.

Cortical Excitability

TMS data will be analyzed offline using LabChart (ADinstruments, Colorado Springs, CO, USA). Offline analyses will include measures of peak-to-peak amplitude, the area-under-the-curve of all MEPs, ICF, and SICI, and the relative duration of CSPs (time from last MEP until normal muscle activity was re-achieved). We will perform a mixed ANOVA model in which the dependent variable is the measurement of cortical excitability (rMThs, MEPs, SICIs, ICFs, CSPs) and the independent variables are the groups (tDCS active combined with MT active; tDCS active combined with MT sham; tDCS sham combined with MT active and tDCS sham combined with MT sham) and time (pre and post intervention). Furthermore, Pearson's correlation analyses will be performed to assess the association between PLP relief (VAS change) and cortical excitability changes, as derived from the TMS evaluations.

Harms

At the end of each stimulation session, participants will complete a side effects questionnaire for tDCS in order to evaluate potential adverse effects of tDCS (tingling, burning sensation, headache, neck pain, mood alterations) and MT (anxiety, grief, dizziness) on a 4-point scale (none, mild, moderate and severe). The participants will be asked whether they have experienced any side effects in an open-ended manner and they will then be specifically asked about headache, neck pain, scalp pain, scalp burns, tingling, skin redness, sleepiness, trouble concentrating, and acute mood change. If any side effects are reported, the degree of relatedness to the intervention will be assessed on a 5-point scale. This type of adverse events questionnaire has been used frequently in our previous tDCS studies [28], including in patients with PLP [61].

In addition, the Side Effects Questionnaire for TMS will be applied at each TMS assessment session. Participants will complete a questionnaire to evaluate potential adverse effects of rTMS (headache, neck pain, itching, and redness at the site of stimulation) on a 5-point scale [62].

Ethical Considerations

The present study complies with the principles of the Declaration of Helsinki and received approval from the ethics committee (institutional review board, IRB) of Spaulding Rehabilitation Network under the protocol number 2015P001065. Participants will agree to the participation by signing a statement of informed consent. The participants will be allowed to abandon the study at any time with no negative repercussions. All data will be collected in a de-identified manner. Each participant will be identified by an identification number referent to the enroll order. Data will be recorded in hardcopy and electronic form. Hardcopies will be stored in a secured filing cabinet at the administering institution. Electronic copies will be stored in encrypted files on a password-protected computer. All data will be kept for 7 years; following this time, hardcopies will be destroyed by shredding or burning and electronic copies will be deleted by formatting. Participant records will not contain any directly identifiable information.

Results

This clinical trial received IRB approval in July of 2015 and enrollment started in December of 2015. Currently, 6 participants have been screened and 2 of them successfully met the eligibility criteria. The first participant completed the entire protocol. The second participant is undergoing stimulation sessions. In addition to that, 2 participants are scheduled for screening in the next 2 months. The estimate enrollment rate is about 30 to 35 patients per year; thus we expect to complete enrollment in 4 years.

Discussion

To the best of our knowledge, this is the first study to combine tDCS and MT for the treatment of PLP. This paper offers a detailed description of a randomized, placebo-controlled, double blind, factorial trial aimed to evaluate the effects of tDCS combined with MT as a rehabilitative tool to decrease PLP, as well as to examine the neural mechanisms underlying PLP in unilateral lower amputees. The results will be published and will provide evidence regarding the use of tDCS combined with MT on this population.

Study Limitations and Potential Concerns

Some concerns regarding the study design should be discussed. One of them is the choice of using a factorial design; on one hand, this type of design was the best option given that there is no gold standard treatment for PLP. On the other hand, this design increases the number of groups and sample size. For the trial, a conservative approach was used to calculate the sample size in order to avoid a common limitation of clinical trials such as a difficult enrollment and recruitment. It is still possible that our sample size will not be adequate. We do consider that a sample of 132 participants will be appropriate to test our hypothesis, especially taking into account previous effects sizes and the addition of the mechanistic aims (TMS and fMRI).On the other hand, it should be noted that if we find an effect size that is smaller than the one proposed in the study it will not be considered clinically meaningful. This is a 4-year clinical trial; therefore, an expected recruitment rate of 33 subjects per year is appropriate, taking into account the amount of traumatic amputation in the New England area and that the Spaulding Rehabilitation Hospital is a major rehabilitation center for this population. In addition, the factorial design in this trial gives also the possibility of additional secondary analyses between groups. Finally, given the selection of a homogeneous sample (only lower limb and traumatic amputation), it is expected that the study will provide robust results regarding the effects of these treatments in isolation and in combination.

Anticipated Results

This is a promising clinical trial, given that the previous results reported by our research group showed a decrease in PLP levels indexed by VAS after anodal tDCS when compared with sham [24]. Additional findings showed that multiple sessions of anodal tDCS produced long lasting effects decreasing PLP for up to 2 months [25]. In this context, we anticipate that the combined group therapy (active tDCS and MT) will have a greater decrease on average scores of pain as compared with each therapy alone as well as with the sham/sham group. Furthermore, we expect that the decrease of pain will be correlated with the neurophysiological measurements that will be evaluated with neuroimaging and TMS. With this in mind, we hypothesize that the combined intervention will be able to modulate PLP, and this effect will be correlated with changes of maladaptive plasticity and the amount of cortical reorganization observed after the amputation.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Short presentation with images of intervention.

[PDF File (Adobe PDF File), 958KB - resprot_v5i3e138_app1.pdf]

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Abbreviations

ANOVA: analysis of variance
BOLD: blood oxygen level dependent
CoG: center of gravity
CSP: cortical silent period
fMRI: functional magnetic resonance imaging
IRB: institutional review board
MEP: motor-evoked potential
MIR-LEG: movement of the leg observing the mirror
MOV-LEG: movement of the leg
MT: mirror therapy
PLP: phantom limb pain
rMTh: resting motor threshold
ROI: region of interest
SICI: short-interval intracortical inhibition
tDCS: transcranial direct current stimulation
TMS: transcranial magnetic stimulation
VAS: visual analogue scale

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Protocol

Preventing Paradoxical Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome in High-Risk Patients: Protocol of a Randomized Placebo-Controlled Trial of Prednisone (PredART Trial)

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Abstract

Background: Early antiretroviral therapy (ART) initiation in patients diagnosed with HIV-associated tuberculosis (TB) reduces mortality among those with the lowest CD4 counts. At the same time, both early ART and a low CD4 count heighten the risk of paradoxical TB-associated immune reconstitution inflammatory syndrome (TB-IRIS). TB is common in patients starting ART in sub-Saharan Africa. Safe interventions that reduce the incidence or severity of TB-IRIS are needed. Prednisone has been shown to reduce symptoms and markers of inflammation when used to treat TB-IRIS.

Objective: To determine whether prophylactic prednisone in patients at high risk for paradoxical TB-IRIS initiating ART reduces the incidence of TB-IRIS.

Methods: We are conducting a randomized, double-blind, placebo-controlled trial of prophylactic prednisone (40 mg/day for 2 weeks, followed by 20 mg/day for 2 weeks) initiated at the same time as ART in patients at high risk for TB-IRIS (starting ART within 30 days of TB treatment and CD4 count ≤100/μL). The primary endpoint is development of TB-IRIS, defined using an international consensus case definition. Secondary endpoints include time to TB-IRIS event, severity of TB-IRIS, quality of life, mortality, hospitalization, other infections and malignancies, and adverse events including corticosteroid adverse effects.

Results: Enrollment for the trial began in August 2013. All 240 participants have been enrolled, and safety follow-up will be completed in March 2017.

Conclusion: No preventive strategies for TB-IRIS currently exist. If results of this trial demonstrate the efficacy and safety of prednisone, this will provide clinicians with an evidence-based preventive strategy in patients at high risk for paradoxical TB-IRIS when initiating ART.

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KEYWORDS

tuberculosis; HIV; paradoxical TB-associated immune reconstitution inflammatory syndrome (TB-IRIS); corticosteroids; prednisone; randomized controlled trial

Introduction

Overview

Tuberculosis (TB) is the most common opportunistic disease affecting HIV-1-infected patients in low- and middle-income countries; up to 42% of patients starting antiretroviral therapy (ART) in sub-Saharan Africa are on treatment for active TB [1]. When ART is commenced in patients on treatment for active TB, an immunopathological reaction known as paradoxical TB-associated immune reconstitution inflammatory syndrome (TB-IRIS) is reported in 18% of cases (95% CI 16%-21%), resulting in new or recurrent TB-related signs and symptoms. The most common clinical features are (1) pulmonary features such as recurrent cough, chest pain, and worsening radiographic pulmonary infiltrates and (2) inflammation and enlargment of lymph nodes. Although mortality attributed to TB-IRIS is relatively low (2%, 95% CI 1%-3%), TB-IRIS causes considerable morbidity, with 25% (95% CI 19%-30%) of cases requiring hospitalization [2]. Neurological involvement, less frequent than pulmonary and nodal involvement, is associated with substantial mortality [3].

Several clinical trials have evaluated the optimal timing of ART initiation in ART-naïve HIV-infected patients diagnosed with active TB. These were included in a recent meta-analysis which showed that early ART (around 2 weeks into TB treatment) in patients with CD4 counts ≤50/μL improved survival compared with starting at around 8 weeks [4]. However, low CD4 count and shorter interval between TB treatment and ART are two of the most important risk factors for TB-IRIS [2]. The same meta-analysis showed that early ART more than doubled the risk of TB-IRIS. In patients with a CD4 count <50/μL, the risk of TB-IRIS with early ART is particularly high [5,6]. Thus, while international guidelines now advise ART within 2 weeks in TB patients with CD4 <50/μL, it can be anticipated that this will increase the risk of TB-IRIS. Despite this, no evidence-based strategy for preventing TB-IRIS currently exists. TB-IRIS will continue to be a major complicating factor in ART programs in sub-Saharan Africa, even with the new World Health Organization guidelines recommending to start ART in all newly diagnosed HIV-infected patients regardless of CD4 count [7], because many HIV-infected individuals still enter care with low CD4 counts and active TB [8-10]. Therefore, interventions to reduce the incidence of TB-IRIS are urgently needed. TB-IRIS is thought to result from an exaggerated immune response in the context of rapidly recovering immunity in the presence of abundant *Mycobacterium tuberculosis* antigen at sites of disease. Attenuating this aberrant inflammatory response during early ART with corticosteroids may prevent TB-IRIS or at least reduce the severity of TB-IRIS clinical manifestations.

Corticosteroids in the Treatment of Tuberculosis

The host immune response contributes to pathology caused by TB [11], and corticosteroids have been used as adjunctive treatment in TB for several decades [12]. Corticosteroid treatment does not diminish the efficacy of TB treatment [12]. Evidence of significant clinical benefit from controlled clinical trials exists for treatment of TB meningitis, where it reduced short- to medium-term mortality [13,14], and pericardial TB, where it reduced the complication of constriction [15], as well as in the treatment of paradoxical TB-IRIS [16].

A Cochrane systematic review of corticosteroids as an adjunct to TB treatment in TB meningitis showed that corticosteroids reduced the risk of death (relative risk 0.78, 95% CI 0.67-0.91). The survival benefit occurred irrespective of the severity of TB meningitis [13]. One of the studies included in the review also demonstrated significantly fewer severe adverse events in patients who received dexamethasone [17]. In particular, eight cases of severe drug-induced hepatitis occurred in the placebo group and none in the dexamethasone group. Adverse drug reactions are another major complicating factor in the management of HIV-associated TB. By reducing the incidence of these hypersensitivity reactions, corticosteroids could potentially reduce morbidity, mortality, and the burden on limited health care resources.

The Investigation of the Management of Pericarditis (IMPI) trial was conducted in several African countries and evaluated prednisolone (and *M indicus pranii* in a factorial design) in 1400 patients with tuberculous pericarditis, of whom 67% were HIV-infected [15]. Participants were assigned to receive either prednisolone or placebo for a period of 6 weeks. The primary outcome was a composite of death, the first occurrence of cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis. There was no significant difference in the primary outcome between patients who received prednisolone and those who received placebo. Prednisolone therapy, however, was associated with significant reductions in the incidence of constrictive pericarditis and hospitalization, which were secondary endpoints.

In the IMPI trial, prednisolone was associated with an increase in cancers (1.8% vs 0.6%, *P*=.03). These were mainly HIV-related cancers, and most patients who developed HIV cancers were not taking ART at the time of enrollment to the trial (personal communication, IMPI investigators). These findings added to concerns regarding the use of adjuvant corticosteroids in HIV-infected patients present from two prior

trials conducted in Uganda evaluating prednisolone in HIV-associated TB, both conducted prior to ART availability. One showed that prednisolone was associated with more rapid clinical and radiological improvement but also with an excess of Kaposi sarcoma [18]; the other showed more rapid clearance of *M tuberculosis* from sputum with prednisolone treatment but also a transient increase in HIV viral load (as well as worsening of underlying hypertension, fluid retention, and hyperglycemia) [19]. A third trial in Zambia showed more reactivation of herpes zoster during prednisolone use in HIV-associated TB [20].

Corticosteroids in the Treatment of Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome

We previously conducted a randomized double-blind placebo-controlled trial of prednisone for the treatment of paradoxical TB-IRIS [16]. A 4-week course of prednisone (1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks) resulted in significantly reduced hospitalization and need for outpatient therapeutic procedures, and more rapid clinical improvement. There was no excess of corticosteroid metabolic adverse effects or severe infections in the prednisone arm. Significant decreases in the serum concentrations of interleukin 6, interleukin 10, interleukin 12p40, tumor necrosis factor α, interferon γ, and interferon γ-inducible protein 10 on prednisone suggest that the beneficial effect of corticosteroids in TB-IRIS was mediated at least in part through the attenuation of proinflammatory cytokine responses [21]. We have previously demonstrated that these same cytokines are differentially increased in the serum of HIV-associated TB patients who develop TB-IRIS compared to control subjects who start ART and do not [22].

In HIV-infected patients with pneumocystis pneumonia, early adjunctive treatment with corticosteroids reduces mortality and the risk of mechanical ventilation. It is presumed that as organisms are killed, inflammation increases in the lungs, leading to a worsening of the patient's clinical condition; corticosteroids possibly reduce or prevent this worsening by reducing inflammation [23].

We are currently conducting a randomized controlled trial (the PredART trial) in Khayelitsha, South Africa, with the primary objective to determine whether a 4-week course of prednisone in patients at high risk for TB-IRIS (starting ART within 30 days of starting treatment for TB and a CD4 count of ≤100/μL) reduces the incidence of TB-IRIS. This PredART trial is different to our prior treatment trial [16] in that prednisone is being evaluated as a preventive rather than treatment strategy and given at lower doses.

Among the secondary objectives, we aim to determine whether prednisone reduces the severity of TB-IRIS and the risk of hypersensitivity drug reactions and consequent drug interruptions in this group of patients as well as to assess its safety and potential changes in health-related quality of life (HR-QOL).

In summary, TB-IRIS is a common complication of ART in patients with HIV-associated TB. The risk of TB-IRIS is highest in patients with the lowest CD4 counts; rapid ART initiation in such patients (essential because of the proven survival benefit) increases this risk even further. Immunological studies have shown elevation of a range of proinflammatory cytokines at the time of TB-IRIS onset [22,24-26]. Corticosteroids have proven to be beneficial in the treatment of TB-IRIS. This effect is likely due at least partially to reductions in blood concentrations of key cytokines mediating the condition. We are therefore evaluating whether prednisone could also be beneficial in preventing TB-IRIS. Because in the majority of cases the onset of TB-IRIS is within the first 4 weeks of ART [27], prophylactic interventions may only be required for one month. Adjunctive corticosteroids in these profoundly immunosuppressed patients might not be without risk; they have been shown to increase the risk of Kaposi sarcoma and herpes reactivations [15,18-20], mainly in patients not on ART. All patients in our trial are receiving ART, which is likely to be at least partially protective against these adverse effects.

Methods

Study Design

This is a proof-of-concept, phase III, randomized, double-blind, placebo-controlled trial of prednisone to assess its efficacy and safety in preventing paradoxical TB-IRIS in high-risk patients starting ART. The intervention is oral prednisone 40 mg daily for 14 days started within 48 hours of initiating ART, followed by 20 mg daily for 14 days. Based on the average weight of participants, this is a lower dose than was used in our previous TB-IRIS prednisone treatment trial [16]. Our reasoning was that when using prednisone as prophylaxis (rather than as antiinflammatory treatment), a lower dose would be potentially effective with a lower risk for adverse events. In our decision regarding the prednisone dose for this trial, we factored in that rifampicin increases the clearance of prednisolone by 45% [28].

Sample Size Calculation

The incidence of paradoxical TB-IRIS in patients on TB treatment starting ART varies between 0% and 54% in the literature. In a recent meta-analysis, the pooled estimate was 18% (95% CI 16%-21%) [2]. However, the incidence is substantially higher in patients with a CD4 count ≤100/μL starting ART within 30 days of TB treatment because these are two major risk factors [2,29]. Assuming 35% cumulative incidence of TB-IRIS in the placebo arm and a 50% relative reduction in the prednisone arm and requiring 80% power to test for the difference in TB-IRIS at a 2-sided significance level of 5%, the sample size required was 110 in each arm. We therefore aimed to recruit 240 participants, assuming loss to follow-up of 10%.

Allocation

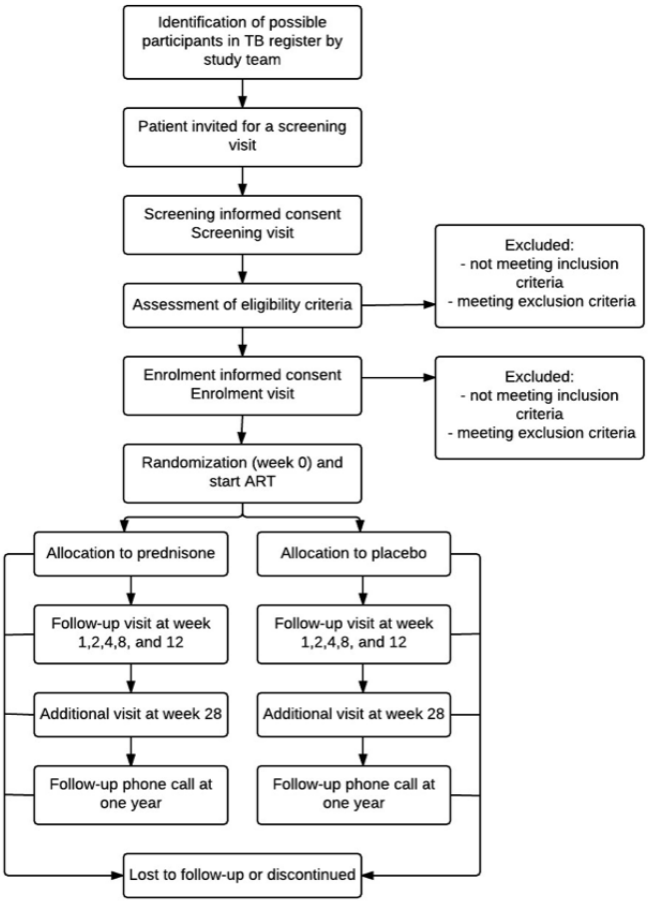
Blinded medication containers were packaged at an independent off-site pharmacy in a 1:1 randomization sequence with block sizes of 8. The sequence was prepared before the trial started by an independent statistician. The packages contain either prednisone 5 mg or identical placebo tablets. Each package has a number from 1 to 240. Participants are enrolled sequentially and receive the next study number from 1 to 240 with the corresponding medication package. Participants and all study

staff remain blinded to the treatment allocation throughout the course of the trial. When deemed essential for ongoing clinical management by the attending clinician, unblinding of the randomization allocation can occur.

Setting, Selection, and Enrollment of Participants

Participants are recruited from four different TB clinics in Khayelitsha, a township 20 kilometers from Cape Town's center with an estimated 500,000 inhabitants. An estimated 16% of the population is HIV infected [30]; TB case notification is 917/100,000 per year and HIV coinfection among TB cases is 60% (City of Cape Town, 2015). The study team identifies patients who could fulfill the enrollment criteria and invites them to attend a screening visit. Informed consent is obtained for the screening visit in the language of choice (mainly isiXhosa), an information leaflet about the trial is provided and discussed, and a screening visit is conducted. Patients who fulfill enrollment criteria are invited to enroll in the trial. Detailed information about the trial is provided by a member of the study team, who also answers all questions the patient has before enrollment. An enrollment informed consent form is signed if the patient agrees to participate in the trial. In patients who are unable to write, informed consent is taken in the presence of an independent witness, who signs the informed consent document next to the participant's thumb print. Participation is voluntary and patients can refuse participation or withdraw from the trial at any time without compromising their standard medical care (See Figure 1).

Figure 1. Flow of participants.



Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are shown in Textbox 1. Exclusion criteria include conditions where corticosteroid treatment is recommended and conditions in which corticosteroids are contraindicated or potentially harmful. Patients should be receiving standard intensive-phase treatment for drug-susceptible TB (rifampicin [RIF], isoniazid [INH], pyrazinamide [PZA], and ethambutol [EMB]) when enrolled in the trial.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Age 18 years or older
- HIV-infected
- CD4 count ≤100/μL (in the past 3 months)
- ART-naïve
- Confirmed diagnosis of TB or strong clinical and radiological evidence of TB with symptomatic response to TB treatment
- On TB treatment for less than 30 days prior to study entry
- Eligible for ART and patient consents to start ART within 30 days of starting TB treatment
- Written informed consent

Exclusion criteria:

- Kaposi sarcoma
- Pregnant
- TB meningitis or tuberculoma at TB diagnosis
- Clinical syndrome of pericardial TB at TB diagnosis
- Rifampicin-resistant TB
- On corticosteroids for another indication or on any other immunosuppressive medication within the past 7 days
- Uncontrolled diabetes mellitus
- Alanine aminotransferase >200 IU/L
- Absolute neutrophil count <500/μL
- Not on standard intensive-phase TB treatment
- Poor clinical response to TB treatment prior to ART as judged by the clinical investigators
- Hepatitis B surface antigen positive

Study Endpoints

The primary endpoint is the development of paradoxical TB-IRIS within 12 weeks of starting ART, defined using the International Network for the Study of HIV-associated IRIS (INSHI) consensus case definition [31]. Secondary endpoints are divided into efficacy and safety and tolerability endpoints (Textbox 2).

Textbox 2. Secondary endpoints.

Secondary efficacy endpoints:

- Time to TB-IRIS event from start of ART
- Severity of TB-IRIS events (defined by need for hospitalization, neurological involvement, and C-reactive protein)
- Duration of TB-IRIS events
- Mortality attributed to TB and TB-IRIS
- All-cause mortality
- Composite endpoint of death, hospitalization, or hepatotoxicity
- Other (non-TB) IRIS events
- Health-related quality of life assessments using the Patient-Reported Outcomes Quality of Life–HIV (PROQOL-HIV) [32], an adaptation of the HIV symptom index [33], and the EuroQol Five Dimensions Questionnaire (EQ-5D-3L) [34]
- Adverse events and severe adverse events ascribed to TB treatment, ART, or co-trimoxazole
- Discontinuation of ART or TB treatment for more than 5 days due to adverse events
- Number of hospitalizations and total days hospitalized

Secondary safety and tolerability endpoints:

- Corticosteroid-associated adverse events (predefined as hypertension, hyperglycemia, hypomania/mania, depression, acne, epigastric pain, upper gastrointestinal bleeding, Cushingoid features, new edema, and avascular bone necrosis)
- Laboratory safety data: glucose, full blood count, and electrolytes
- Other infections and malignancies
- All grade 1, 2, 3, and 4 adverse events using the Division Of AIDS Table For Grading the Severity of Adult and Pediatric Adverse Events [35]

Medication

Study medication is prednisone tablets (5 mg) or identical placebo. The study medication was manufactured by the Gulf Drug Company in Durban, South Africa; this company supplies prednisone (Trolic) to the South African government hospital pharmacies, and the product is registered with the Medicines Control Council of South Africa. Participants receive 8 tablets daily (40 mg prednisone or placebo) for 14 days followed by 4 tablets daily (20 mg prednisone or placebo) for 14 days. Study medication is dispensed at week 0 (for the first 14 days) and at week 2 (for the next 14 days). During these first four weeks of the trial, concomitant treatment with nonsteroidal anti inflammatory drugs, any systemic corticosteroid medication, or any other immunosuppressive medication or chemotherapy is prohibited. The protocol requires that the study drug be stopped in the following situations: Kaposi sarcoma or new World Health Organization stage 4 opportunistic condition diagnosed, diagnosis of rifampicin-resistant TB, development of TB-IRIS requiring open label prednisone, requirement for prohibited concomitant medication, diagnosis of pregnancy, request by the participant, clinical reasons believed to be life threatening by the trial doctor, or interruption of ART or study drug for more than five days by the participant or by clinician (eg, in the event of ART toxicity).

ART is provided according to the South African Department of Health guidelines [36]. First-line ART consists of tenofovir (TDF) 300 mg daily, emtricitabine (FTC) 200 mg daily, and efavirenz (EFV) 600 mg daily. In case of contraindications or toxicity, TDF is substituted with abacavir (ABC) and EFV with nevirapine or lopinavir boosted with ritonavir (LPV/r). LPV/r is double-dosed in patients taking rifampicin [37]. ABC only became available for use in the public sector during the course of our trial. Before its availability, TDF was replaced with either zidovudine or stavudine in the event of contraindication or toxicity. The intensive follow-up period of the trial is 12 weeks; no switches to ART for virological failure are made during this period. Participants receive ART from their ART clinic in close communication with the study team.

TB treatment is prescribed according to South African Department of Health guidelines [38] by the participant's TB clinic. Participants receive weight-based daily doses of INH, RIF, PZA, and EMB for 2 months, followed by INH and RIF for another 4 months. If TB drug-induced liver injury occurs during follow-up, participants are managed according to local clinical guidelines. In short, TB treatment is stopped and replaced with 3 drugs with no/low hepatotoxicity risk (eg, EMB, kanamycin, and moxifloxacin). In addition, other possible hepatotoxic drugs like co-trimoxazole and EFV may be temporarily stopped or replaced. Once symptoms of hepatitis have resolved and alanine aminotransferase is <100 IU/L, drugs can be rechallenged one by one with close monitoring of liver enzymes. Duration of TB treatment is individualized after rechallenge. All participants are eligible for co-trimoxazole prophylaxis unless contraindicated.

Schedule

Study visits occur at screening, enrollment, week 0 (the day the participant starts study drug and ART), week 1, week 2, week 4, week 8, and week 12. A window period of 4 days is allowed for each visit from week 1 to week 8; week 12 has a 7-day window. Assessments done at each visit are summarized in

Table 1. If the attending clinician suspects TB-IRIS, laboratory investigations including a bacterial blood culture and a chest radiograph are performed.

Outside the scheduled visits, participants can attend for unscheduled visits if they experience symptomatic deterioration or if deemed necessary by the attending clinician. For participants with ongoing TB-IRIS at week 12, follow-up is extended in order to ascertain the end date of TB-IRIS.

Table 1. Schedule of events.

Study visit	Screening	Enrollment	Wk 0	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Unscheduled visit
ART[a] day	Not specified	Aim for −7 to 0	0	7±4	14±4	28±4	56±4	84±7	Not specified
Document HIV status	x								
Screening ICF[b]	x								
Enrollment ICF		x							
Study drug dispensed			x		x				
Symptoms[c]	x	x	x	x	x	x	x	x	x
Karnofsky score	x		x	x	x	x	x	x	x
Pill count[d]				x	x	x	x	x	x
HR-QOL[e] assessments			x			x		x	
Examination	x	I[f]	x	x	x	x	x	x	x
Laboratory investigations[g]	x	I	x		x	x		x	I
CD4 count, HIV viral load	x							x	
Serum HBsAg[h]	x								
Serum CrAg[i]	x								
Urinary pregnancy test	x	I	I	I	I	I	I	I	I
Storage bloods and immunology assays			x		x	x		x	If IRIS suspected
Storage urine			x					x	If IRIS suspected
Chest radiograph	I		x						If IRIS suspected
Sputum Xpert MTB/RIF[j], TB culture, and DST[k]	x					x		x	
Initiate ART			x						

[a]ART: antiretroviral therapy.

[b]ICF: informed consent form.

[c]Symptoms and specific screening for adverse events and TB-IRIS.

[d]Pill count: ART and study drug week 1-4.

[e]HR-QOL: health-related quality of life.

[f]I: if clinically indicated.

[g]Laboratory investigations: full blood count with leucocyte differentiation, sodium, potassium, creatinine, glucose, bilirubin, alanine aminotransferase, alkaline phosphatase, C-reactive protein.

[h]HBsAg: hepatitis B surface antigen.

[i]CrAg: cryptococcal antigen.

[j]MTB/RIF: Mycobacterium tuberculosis, resistance to rifampicin.

[k]DST: drug sensitivity testing.

Protocol Change With Additional Safety Assessments

In the initial protocol, participant follow-up ended at week 12 unless there was ongoing TB-IRIS at this visit. A year after the start of our trial, the results of the IMPI trial [15] became available, showing an increased incidence of cancer in patients with HIV-related TB pericarditis prescribed prednisolone compared to those prescribed placebo. This was largely attributable to an increase in HIV-associated cancers (Kaposi sarcoma and non-Hodgkin lymphoma). The potential risk of Kaposi sarcoma associated with corticosteroid use in HIV-infected patients was known and addressed in our protocol prior to the IMPI publication: Kaposi sarcoma at screening is an exclusion criterion, Kaposi sarcoma is ascertained as a safety endpoint, and if Kaposi sarcoma occurs in patients on the trial this is an indication to immediately stop study medication.

As a study team we reviewed the implications of the IMPI findings for safety of participants in our trial. A number of considerations make the IMPI trial different from the PredART trial with respect to the risk of Kaposi sarcoma. The prednisone dose used in PredART is substantially lower and of shorter duration. All participants in the PredART trial are started on ART when they start study medication, and ART is known to reduce the risk of Kaposi sarcoma [39]; in contrast, in IMPI, 7 out of 9 of the prednisolone-treated patients who developed HIV-related cancers were not on ART at the time of enrollment and commencement of steroids (personal communication, IMPI investigators). Lastly, the PredART trial participants are not being randomized to *M indicus pranii*; this is relevant, as most of the cancers were diagnosed in participants receiving both prednisolone and *M indicus pranii* in the IMPI trial.

At the time of the IMPI publication, 89 participants had been randomized in our trial and none had developed Kaposi sarcoma. We communicated these findings and considerations to the PredART trial data safety and monitoring board (DSMB), which advised that the PredART trial should continue but that we should add extra visits for safety assesments. We added one visit at week 28 and a telephonic follow-up at one year to ascertain HIV-related cancers. During the week 28 visit, patient history is taken and clinical examination is performed specifically to assess for any history, symptoms, or signs of cancer. One year after starting ART, participants are phoned by the study team and their clinical records are assessed to review if there has been a new diagnosis of cancer subsequent to the week 28 visit. The protocol was amended accordingly and the information given during the informed consent process was updated with approval by the relevant ethics committees. The additional assessments applied to all participants, including those who had already completed their 12-week follow-up at the time of this protocol change.

Management of Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome

TB-IRIS is a diagnosis of exclusion. When TB-IRIS is suspected, investigations are performed with the main aim to exclude alternative causes of clinical deterioration. For all participants with suspected TB-IRIS, these include the laboratory investigations listed in Table 1, a bacterial blood culture, and a chest radiograph. Other investigations (eg, abdominal ultrasound, lumbar puncture) are undertaken when appropriate based on clinical presentation. Adherence to ART and TB treatment is assessed. If TB-IRIS is diagnosed (fulfilling the INSHI criteria [31]), the study drug is stopped, and open label prednisone is started at a dose of 1.5 mg/kg/day and weaned over 4 weeks or longer depending on clinical response.

Other Aspects of Clinical Management

Mild drug rashes are closely monitored with symptomatic therapy. If more severe drug rashes occur, potential causative drugs (TB medication, EFV, co-trimoxazole) are stopped and rechallenge occurs following local guidelines. All other clinical management, including treatment of new opportunistic infections, malignancies, and comorbidities, is according to South African National Department of Health guidelines.

Health-Related Quality of Life Assessments

Health-related quality of life (HR-QOL) is measured using three different questionnaires: the Patient-Reported Outcomes Quality of Life–HIV (PROQOL-HIV) [32], an adaptation of the HIV symptom index by Justice [33], and the more generic EuroQol Five Dimensions Questionnaire (EQ-5D-3L) [34]. Participants complete all three questionnaires at week 0, week 4, and week 12. Our aim is to assess HR-QOL in patients with HIV-associated TB who have recently started treatment for both conditions and to find which questionnaire best captures their HR-QOL in the acute phase of their illness. Since the PROQOL-HIV has not been used in populations with TB-IRIS in comparable settings, these data will serve to validate this instrument through triangulating the results of debriefing interviews and the two other HR-QOL instruments. Moreover, we are assessing the impact of TB-IRIS and prednisone use on HR-QOL.

Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome Endpoint Evaluation

An endpoint review committee has been established to review all cases of suspected TB-IRIS and determine whether they fulfill the INSHI case definition. This committee is comprised of 3 expert clinical investigators not active at the clinical site. Reviewers will have access to all clinical and laboratory data entered in the database, including chest radiographs and TB-IRIS narrative summaries written by the attending clinician, and they will be blinded to treatment allocation. The review will take place after completion of the clinical trial. Each reviewer will independently review the summaries and data submitted to him or her, using the INSHI paradoxical TB-IRIS case definition [31]. For those cases where there is disagreement, consensus will be sought at a meeting where investigators will also be present to provide additional clinical information when needed. If consensus cannot be reached a 2-1 vote will decide.

Statistical Analysis

The statistical analysis of the trial will be performed according to a plan prespecified before the database is locked and allocation unblinded. The primary analysis and secondary efficacy analysis will be performed using an intention-to-treat approach; safety analysis will be performed using the all-patients-treated approach. The primary endpoint will be tested comparing the proportion of patients diagnosed with

paradoxical TB-IRIS among treatment groups using a Fisher exact test. Secondary endpoints will be analyzed comparing study arms with the Fisher exact test (for categorical data) or Wilcoxon rank-sum test (for continuous data). Time to event analysis will be used to compare time from the start of ART to TB-IRIS between study arms. A prespecified subgroup analysis of those patients with a baseline CD4 count <50/μL will be performed. Adverse events will be coded following the Medical Dictionary for Regulatory Activities (MedDRA). Safety endpoints will be compared between both arms individually (eg, analysis comparing development of hyperglycemia in each arm) as well as collectively (eg, analysis comparing all corticosteroid side effects that occurred in each arm).

Data Handling and Record Keeping

The identity and information of trial participants is kept confidential. All relevant clinical information to reconstruct and evaluate the trial is kept as source documents. Data from source documents are entered into a Web-based electronic database specifically developed for the trial. The database is access-controlled and data deidentified. Point-of-entry data validation and a double–data entry system with discrepancy reporting are key measures to ensure data integrity. After completion of the first 12 weeks of the study, the electronic record of each participant is reviewed against the case report form. After completion hereof, aggregate database entries are checked for outlying data, missing data, and systematic errors according to the prespecified data management plan.

Monitoring, Oversight, and Reporting

The trial is sponsored by the University of Cape Town. which has subcontracted an independent clinical trial monitor who conducts monitoring visits once every 1 to 2 months and reports to the sponsor. An independent DSMB reviewed study recruitment, data quality, and safety endpoints twice during the trial—after 80 participants had completed their week 12 visit and again after 160 participants had completed their week 12 visit. The DSMB was constituted and conducted its tasks according to the study-specific DSMB charter. It was required to advise the sponsor of any major safety and data quality issues. At both interim reviews, the DSMB advised that trial recruitment and follow-up should continue. All adverse study drug reactions, serious adverse events, and deaths are reported to the sponsor, the University of Cape Town Human Research Ethics Committee, the Institute for Tropical Medicine Institutional Review Board, and the Medicines Control Council according to their respective reporting guidelines.

Ethical Approval

The protocol was approved by the University of Cape Town Human Research Ethics Committee (HREC 136/2013), Institute of Tropical Medicine Institutional Review Board (882/13), and the Antwerp University Hospital Ethical Committee (13/20/224). The same approval schedule is applicable to protocol amendments. The trial is conducted according to International Council for Harmonisation Good Clinical Practice standards [40], the South African Good Clinical Practice guidelines [41], and the Declaration of Helsinki [42].

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Results

The trial started enrollment at the end of August 2013; 240 participants are currently enrolled according to plan. Follow-up for the first 12 weeks was completed in June 2016, and the final safety assessments for the trial will be completed by March 2017.

Discussion

With guidelines advising that ART be started with minimal delay during treatment for HIV-associated TB, and many patients still presenting with a low CD4 count, TB-IRIS will remain a major complicating factor in patients with HIV-associated TB starting ART in sub-Saharan Africa. If corticosteroids are shown to reduce the risk of TB-IRIS without safety concerns, clinicians will have an evidence-based preventive option in patients at high risk for TB-IRIS provided they do not have a contraindication for corticosteroids. Therefore, we anticipate that the findings of this clinical trial could inform clinical practice and guidelines in sub-Saharan Africa and internationally.

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The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. The opinions, findings, and conclusions expressed in this manuscript reflect those of the authors alone.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Review by funders (EDCTP).

[PDF File (Adobe PDF File), 248KB - resprot_v5i3e173_app1.pdf]

Multimedia Appendix 2

Response to EDCTP.

[PDF File (Adobe PDF File), 245KB - resprot_v5i3e173_app2.pdf]

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Abbreviations

ABC: abacavir
ART: antiretroviral therapy
CrAg: cryptococcal antigen
CRP: C-reactive protein
DSMB: data safety and monitoring board
DST: drug sensitivity testing
EFV: efavirenz
EMB: ethambutol
EQ-5D-3L: EuroQol Five Dimensions Questionnaire
FTC: emtricitabine
HBsAg: hepatitis B surface antigen
HR-QOL: health-related quality of life
ICF: informed consent form
IMPI: Investigation of the Management of Pericarditis
INH: isoniazid
INSHI: International Network for the Study of HIV-associated IRIS
LPV/r: lopinavir boosted with ritonavir
PROQOL-HIV: Patient-Reported Outcomes Quality of Life–HIV
PZA: pyrazinamide
RIF: rifampicin
TB: tuberculosis
TB-IRIS: tuberculosis-associated immune reconstitution inflammatory syndrome
TDF: tenofovir

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Protocol

Reliable Quantification of the Potential for Equations Based on Spot Urine Samples to Estimate Population Salt Intake: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Methods based on spot urine samples (a single sample at one time-point) have been identified as a possible alternative approach to 24-hour urine samples for determining mean population salt intake.

Objective: The aim of this study is to identify a reliable method for estimating mean population salt intake from spot urine samples. This will be done by comparing the performance of existing equations against one other and against estimates derived from 24-hour urine samples. The effects of factors such as ethnicity, sex, age, body mass index, antihypertensive drug use, health status, and timing of spot urine collection will be explored. The capacity of spot urine samples to measure change in salt intake over time will also be determined. Finally, we aim to develop a novel equation (or equations) that performs better than existing equations to estimate mean population salt intake.

Methods: A systematic review and meta-analysis of individual participant data will be conducted. A search has been conducted to identify human studies that report salt (or sodium) excretion based upon 24-hour urine samples and spot urine samples. There were no restrictions on language, study sample size, or characteristics of the study population. MEDLINE via OvidSP (1946-present), Premedline via OvidSP, EMBASE, Global Health via OvidSP (1910-present), and the Cochrane Library were searched, and two reviewers identified eligible studies. The authors of these studies will be invited to contribute data according to a standard format. Individual participant records will be compiled and a series of analyses will be completed to: (1) compare existing equations for estimating 24-hour salt intake from spot urine samples with 24-hour urine samples, and assess the degree of bias according to key demographic and clinical characteristics; (2) assess the reliability of using spot urine samples to measure population changes in salt intake overtime; and (3) develop a novel equation that performs better than existing equations to estimate mean population salt intake.

Results: The search strategy identified 538 records; 100 records were obtained for review in full text and 73 have been confirmed as eligible. In addition, 68 abstracts were identified, some of which may contain data eligible for inclusion. Individual participant data will be requested from the authors of eligible studies.

Conclusions: Many equations for estimating salt intake from spot urine samples have been developed and validated, although most have been studied in very specific settings. This meta-analysis of individual participant data will enable a much broader understanding of the capacity for spot urine samples to estimate population salt intake.

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KEYWORDS

dietary salt; sodium; spot urine collection; 24-hour urine collection; meta-analysis; systematic review

Introduction

Excess consumption of salt causes high blood pressure [1-3], which is a leading risk factor for premature death worldwide [4]. The World Health Organization (WHO) recommends a maximum daily salt intake for individuals and populations of 5g/person/day [5]. Most countries (in which salt intake has been measured) exceed this recommendation, often by a large margin [6-8]. In response to the United Nations' high-level meeting on the prevention and control of non-communicable diseases in 2011, the WHO has set a target for Member States to reduce population salt consumption by 30% by 2025 [9].

To document a 30% reduction in average population salt consumption, knowledge of baseline and follow-up intake levels are required. The accepted method for measuring average population salt intake is to collect 24-hour urine samples from a subset of the population [10]. However, 24-hour urine samples are onerous for survey participants and researchers to collect, and typically the response rates in surveys are low [11]. Incomplete urine collections also represent a challenge, and although several methods have been used to identify incomplete collections (such as the use of para-aminobenzoic acid), limitations still exist with these methods [12]. Questionnaire-based dietary surveys are another method of estimating salt consumption but are even more problematic. This is principally because no robust scalable method exists for estimating discretionary salt use, which can represent a large proportion of the dietary salt consumed in many countries [13]. Systematic misreporting of foods consumed is another major challenge to questionnaire-based approaches [14].

Estimation equations based upon spot urine samples may offer a practical alternative method for measuring average population

salt consumption. This method is less burdensome for participants and response rates are markedly higher, ranging from 73-100% [11]. Individual-level correlation of urinary salt concentration in a spot sample with that of a 24-hour urinary salt is not always high [15-25] and some authors have used this observation to suggest that spot urine samples cannot be used as an alternative to 24-hour sampling [26-29]. The relatively low individual-level correlation of spot samples with 24-hour urinary salt excretion, along with the relatively large day-to-day variability of individuals' salt intake, makes it likely that spot urine sampling is inadequate for individual-level assessment in epidemiological studies. However, the method has an established role in estimating 24-hour excretion of pesticides and chemicals in the US National Health and Nutrition Examination Survey [30,31]. A strong likelihood exists that the mean salt concentration of spot urine samples for a given population is related to the mean 24-hour excretion of that same population.

A series of equations that estimate 24-hour urinary salt excretion from spot urine samples have been developed [32-36]. These equations have been derived in different populations, include a range of different covariates, and use spot urine samples voided at different times of the day. Some equations have been applied in populations external to those used for equation development, and different conclusions have been drawn about their validity [24,37-41]. It is possible that mean population 24-hour urinary salt excretion can be predicted from spot urine samples in some populations but not others, or that the different analytical approaches used have resulted in different findings. It is also possible that the small size of some studies has produced spurious findings.

We recently conducted a systematic review and meta-analysis of published aggregate data that included 10,414 participants from 35 countries, which showed that spot urine samples had excellent specificity (100%) and sensitivity (97%) at classifying mean population salt intake as above or below the WHO maximum target of 5g/day [42]. This result suggests that spot urine samples present a viable option for countries to determine salt intake levels and make objective decisions about the requirement for salt reduction strategies. Based on this meta-analysis, we identified for the first time a possible proportional bias, such that equations based on spot urine samples may overestimate consumption at lower levels and underestimate at higher levels of consumption. This proportional bias would be expected to result in an underestimation of the reduction in average salt intake if spot urine samples were used to monitor population salt consumption over time. However, due to this observation being based on a group-level meta-analysis, it should be interpreted with caution due to the possibility of confounding.

In many other areas of medical research, the combination of data at the individual participant level has enabled the resolution of comparable types of problems [43]. This is because analyses can be done in a standard way across all datasets, and because statistical precision is greatly increased by the larger volume of data available. In addition, bringing the many leaders working in this area together on a single project may synergize efforts to resolve the question at hand.

Overall Goal and Specific Objectives

The overall goal of this initiative is to identify a reliable method for estimating mean population salt intake from spot urine samples. The method should provide an estimate that is directly comparable to measurements made using 24-hour urine samples with no evidence of proportional bias. The specific aims are:

To determine the direction and magnitude of the bias of existing equations for estimating mean population 24-hour salt excretion from spot urine samples compared to 24-hour urine samples, and how ethnicity, sex, age, body mass index (BMI), antihypertensive drug use, health status, and timing of spot urine collection may modify the performance of these equations.

To investigate if equations for estimating mean population 24-hour salt excretion from sequential spot urine samples can be used to estimate the mean change in population salt intake over time.

To develop a novel equation (or equations) that performs better than existing equations to estimate mean population salt intake and changes in mean population intake over time.

Methods

This protocol involves a systematic review and meta-analysis of individual participant data. Based on the secondary analyses of existing data, separate regulatory reviews and ethics committee approvals will not be sought. The active participation of a lead investigator from every study will be encouraged, in order to maximize insight into the data included and obtain the broadest possible range of expertise available to address the research questions.

Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria:

- Original research conducted in a human population
- Report salt (or sodium) excretion based upon 24-hour urine samples and spot urine samples in the same individuals

Exclusion criteria:

- Urinary salt (or sodium) not measured in both spot samples and 24-hour urine samples
- Urinary creatinine not measured in both spot samples and 24-hour urine samples
- Spot and 24-hour urine samples not collected in the same sample

Table 1. Variables to be collected and data format.

Variable	Format
Core variables required for the analyses	
1. Unique anonymous identifier	Numerical value
2. Study identifier	Numerical value
3. Country of participant recruitment	United States, United Kingdom, Japan, etc.
4. Sex, female?	1=yes, 2=no
5. Age	Numerical value (years)
6. Height	Numerical value (cm)
7. Weight	Numerical value (kg)
8. Date of first 24-hour urine sample collection started	dd/mm/yyyy
9. Start time of first 24-hour urine collection	hhmm
10. End time of first 24-hour urine collection	hhmm
11. 24-hour urine volume first sample	Numerical value (L)
12. Sodium concentration in first 24-hour urine	Numerical value (mmol/L)
13. Potassium concentration in first 24-hour urine	Numerical value (mmol/L)
14. Creatinine concentration in first 24-hour urine	Numerical value (mmol/L)
15. Date of first spot urine sample collection	dd/mm/yyyy
16. Time of first spot urine sample collection	hhmm or 1=first morning, 2=morning, 3=afternoon, 4=evening, 5=random
17. Was first spot sample part of 24-h collection?	1=yes, 2=no
18. Sodium concentration in first spot urine	Numerical value (mmol/L)
19. Potassium concentration in first spot urine	Numerical value (mmol/L)
20. Creatinine concentration in first spot urine	Numerical value (mmol/L)
Supplementary variables that should be included when available	
21. Race	1=White, 2=Black, 3=Asian, 4=other, 5=Hispanic
22. Systolic Blood Pressure	Numerical value (mmHg)
23. Diastolic Blood Pressure	Numerical value (mmHg)
24. History of hypertension?	1=yes, 2=no, 3=unknown
25. History of diabetes?	1=yes, 2=no, 3=unknown
26. History of kidney disease?	1=yes, 2=no, 3=unknown
27. History of heart disease or stroke?	1=yes, 2=no, 3=unknown
28. Using any blood pressure lowering drug?	1=yes, 2=no, 3=unknown
29. Using diuretic therapy?	1=yes, 2=no, 3=unknown
30. Pregnancy status	1=yes, 2=no, 3=unknown
31. Start time of first spot urine collection	hhmm
32. End time of first spot urine collection	hhmm
33. Volume of first spot urine collection	Numerical value (L)

When more than one spot urine sample has been collected from the same individual, items 8-20 will be sought for the additional time-points. To assess the capacity of spot urine samples to measure changes in sodium excretion over time (change analyses), a second set of spot and 24-hour urine sodium measures (collected 1 month or more after the first sample) will be sought for the second time-point (data items 8-20). Missing data will be recorded as blank.

Study Inclusion and Exclusion Criteria

There will be no restrictions on language, study sample size, or characteristics of the study population. Inclusion and exclusion criteria are outlined in Textbox 1.

Search Strategy

Search strategies were developed in consultation with a librarian at the University of Sydney, with the goal of identifying all studies that might contribute data. The electronic databases MEDLINE via OvidSP (1946-present), Premedline via OvidSP, EMBASE, Global Health via OvidSP (1910-present), and the Cochrane Library were searched using applicable terms (Multimedia Appendix 1). A keyword search using *24-hour urinary sodium excretion* was also conducted in the China National Knowledge Infrastructure. In addition, hand searches of the reference lists of eligible studies were completed, and academic colleagues working in the field were contacted to identify unpublished data. The same search will be repeated annually to identify and include new studies as they become available.

Two reviewers independently screened the titles and abstracts of all identified articles. All potentially relevant abstracts identified by either reviewer were obtained in full text, if available. The two reviewers screened the full text papers independently to determine eligibility, with disagreements settled by discussion between the two, or via consultation with a third author when necessary. Additionally, if there was doubt about whether an article contained data that could be used for this project, the article was retained and attempts will be made to contact the study's authors. Abstracts (including conference proceedings) that were potentially eligible, but without full text available, were retained and attempts to contact the authors will be made. Non-English articles were found in the literature search, and in all cases the papers had an English abstract that was used to assess eligibility; authors will be contacted to determine eligibility for the project.

Data Request

A standard set of data in a standardized format will be sought from each participating study (Table 1). This protocol, together with an invitation letter, will be provided to the authors of all potentially eligible studies to determine their interest in participating. Data will be accepted in any form, although a standardized format will be sought. If authors are unable to share full individual participant datasets that adhere to our guidelines, efforts will be made to have analyses conducted at the collaborating site, with summary metrics shared to enable a secondary set of analyses based upon summary statistics. Two datasets will be generated for this project: one comprising the urine data collected at a single time-point; the second comprising urine data collected at multiple time-points (which will be used for the change analyses).

Statistical Analyses

Participants with suspected incomplete 24-hour urine samples (ie, <80% urinary para-aminobenzoic acid recovery [if available], or urinary creatinine <4.0 mmol/day for women or < 6.0 mmol/day for men, or a 24-hour urine collection of <500ml for either sex) and suspected over-collections (ie, urinary creatinine or a urine collection volume >3 standard deviations above the population mean) will be excluded from primary analyses. For all analyses, statistical significance will be set at $P<0.05$. Data will be analyzed using Stata V13.0 (Stata Corp, College Station, TX, USA).

Analysis One: Comparison of Existing Equations for Estimating 24-Hour Salt Intake from Spot Urine Samples with 24-Hour Urine Samples, and Assessment of the Degree of Bias According to Key Demographic and Clinical Characteristics

For each individual, the 24-hour sodium excretion (24-hour_{sodium}) value (mmol/day) based on the 24-hour urine collection will be calculated as the concentration of sodium in the urine (mmol/L) multiplied by the urinary volume (L/day). The conversion from sodium (mmol/day) to sodium (mg/day) will be made by multiplying by 23, and the conversion from sodium (g/day) to salt (g/day) will be made by multiplying the sodium value by 2.542. Estimated 24-hour salt excretion (24-hour_{salt}) from spot urine samples (24-hour_{spot}) will be calculated from currently-used estimation equations (ie, Kawasaki [36], Tanaka [33], Mage [30,31], Toft [34], and INTERSALT with and without potassium [32]; see Multimedia Appendix 2). Within-person bias (24-hour_{bias}) will be calculated as 24-hour_{spot}- 24-hour_{salt}. Pooled summary estimates across studies (24-hour_{salt}, 24-hour_{spot}, and 24-hour_{bias}) will be calculated using inverse-variance weighted fixed effects meta-analyses [44]. In cases where substantial variability across contributing studies is identified based on the I^2statistic, sensitivity analyses will be conducted using the random effects model according to DerSimonian and Laird [45].

The effects of ethnicity, sex, age, BMI, antihypertensive drug use, health status (diabetes, kidney disease, cardiovascular disease, or cerebrovascular disease), timing of spot urine collection (overnight, morning, afternoon, evening, or timed sample), and 24-hour salt (as estimated by 24-hour urine collection) on the magnitude of bias for each estimation equation will be examined by conducting multiple linear regression. The beta-coefficient resulting from the multiple linear regression will be the difference in mean 24-hour_{bias} for each unit difference for each pre-specified demographic and clinical characteristic. Beta-coefficients and their standard errors for each study will be pooled, and summary effects will be calculated using inverse-variance weighted fixed effects meta-analysis.

Within-trial proportional bias will be assessed by determining the association between level of intake (mean of 24-hour_{salt} and 24-hour_{spot}) and 24-hour_{bias}. The regression coefficients will then be meta-analyzed across the cohorts using inverse-variance fixed effects meta-analysis. In cases of substantial variability, random effects models will be used.

Analysis Two: Measuring Population Change in Salt Intake Using Spot Urine Samples

Data collected from the same person at two or more time-points at least 1 month apart (paired data), and data from the same population (but different individuals within the population) at two or more time-points (unpaired), will be sought. The capacity of spot urine samples to track population changes in salt intake will be determined by assessing the paired and unpaired data separately in the first instance. At the individual study level,

repeated measures analyses of variance will be used for analyses of the paired data, and independent samples t-tests for the unpaired data. Pooled summary estimates across studies will be calculated using inverse-variance weighted fixed effects meta-analyses for paired and unpaired data separately. To maximize the sample size, the unpaired and paired data will also be analyzed together using inverse-variance weighted fixed effects meta-analyses. The effects of covariates (ethnicity, sex, age, BMI, antihypertensive drug use, health status, and timing of spot urine collection) on equation performance will be examined by including each of these covariates in the model. Both unadjusted and adjusted analyses will be undertaken, following prior exploration of the associations between each covariate of interest.

Analysis Three: Development of an Equation (Or Equations) that Performs Better than Existing Equations to Estimate Mean Population 24-Hour Urinary Salt Excretion

Sex-specific regression equations estimating 24-hour sodium excretion will be obtained from spot urine sodium excretion, potassium, creatinine, age, BMI, and ethnicity. Inclusion of the specific variables in the models will be assessed using stepwise selection. The final model fit will be assessed using the R^2value from 5000 samples drawn using bootstrapping. The observed mean 24-hour sodium excretion will be compared with the estimated sodium excretion from the new equation (or equations) at a population level using Pearson's correlation. Bland Altman plots will also be produced to calculate the mean bias between measured 24-hour sodium excretion and estimated excretion from the spot urine samples using the new equation (or equations) [46].

Risk of Bias Assessment

Study-level risk of bias will be assessed using the Newcastle-Ottawa Scale [47]. In addition, checks of the individual participant data will be conducted to ensure that the data reflects the methods reported in the original publication [48].

Leadership and Data Curation

A Steering Committee will be established to lead the initiative, with operational support provided by a Secretariat. The Steering Committee will have final responsibility for scientific outputs and will include a representative from each study that is able to contribute individual participant data, plus members of the Secretariat. Steering Committee members will be responsible for finalizing the protocol and agreeing upon all outputs from the initiative, and will be supported by a statistician that will provide data curation and analysis services. All data provided for the initiative will be held in confidence and used only for the purposes described in this protocol or its subsequent amendments, as agreed upon by the Steering Committee. Steering Committee members will be free to withdraw their data from the initiative at any time, should they choose.

Results

The most recent search was completed in March 2016 and the results of the search are included as a Multimedia Appendix 3. Briefly, the search identified 538 records with one unpublished (but eligible) study. A total of 430 records were screened, and based on the abstracts 262 did not meet the inclusion criteria. A sample of 100 full-text articles were assessed for eligibility. Following this review, 73 studies were confirmed to be eligible (Multimedia Appendix 4), and a further 68 abstracts were identified that may be eligible for inclusion in the project (Multimedia Appendix 5). Authors from the 73 eligible studies and the 68 abstracts will be invited to contribute data.

Discussion

Multiple reports now suggest that mean population salt intake can be estimated from spot urine samples, although the robustness of the estimates obtained and the best methods for obtaining them remains unclear for many parts of the world. The recent adoption of spot urine samples for the estimation of mean population salt intake by the WHO, as part of the WHO Stepwise Approach to Risk Factor Surveillance, has placed additional priority on efforts to resolve these and related questions.

The primary objectives of this individual-participant data meta-analysis have been defined on the basis of the most pressing need, and relate to the capacity of equations based upon spot urine samples to provide results that approximate those obtained with 24-hour urine samples. The aims of this study also focus specifically on the capacity of the estimates (based on spot urine samples) to track changes in mean population salt intake over time. Studies published to date that have assessed the validity of using spot urine samples to measure average salt intake have been cross-sectional (ie, urine samples are collected at one time-point) [38-41,49-51]. Therefore, such studies only provide limited inference about the implications of using spot urine samples to monitor change over time.

A number of characteristics regarding populations and individuals might influence the capacity of different equations to provide estimates of mean population salt intake, and these issues are the focus of some of the analyses proposed. Diurnal variation in salt excretion may favor estimates based upon spot urine samples collected at a particular time of day [52]. Likewise, equations may perform differently in hypertensive compared to non-hypertensive patients, both because of reported changes in the diurnal excretion of salt and because drug therapies (eg, diuretics) affect urinary salt excretion [37,49,53-55].

The proposed analyses will also make it possible to quantify or control for the effects of methodological differences in studies, and how these effects impact on the conclusions drawn. For example, studies that use a spot urine sample collected as part of the 24-hour collection may over-estimate the coherence of population estimates based upon spot and 24-hour samples compared to studies in which the spot urine sample was collected on another day entirely. This project will also enable

standardization of the 24-hour comparator group (against which estimates based upon spot samples are compared) by applying the same set of quality criteria to the 24-hour urine samples across studies. Even with the application of rigorous quality criteria to the 24-hour samples, the 24-hour standard falls far short of being a true gold standard; even if urine collections are ascertained to be complete, salt excretion is known to vary substantially from day-to-day, and a significant proportion of salt is excreted through nonurinary routes [56]. It is, however, the current standard upon which clinical and public health decisions are made, and represents the only plausible comparator for the proposed analyses.

It is of note that several prior studies have drawn conclusions about the likely value of spot urine samples based upon metrics (such as correlation coefficients) that compare the values obtained for individuals. While high values for such metrics will typically be associated with good correlation at the population level, these are not necessarily the best means for evaluation in this setting since good correlation of data at the individual level is not a prerequisite for obtaining robust population estimates [46].

In summary, many individual studies now exist that have identified equations based upon spot urine samples as a plausible alternative to 24-hour urine samples for the estimation of mean population salt intake. There remain, however, important questions about the best approach to estimate 24-hour excretion from spot urine samples, and the capacity of estimated 24-hour salt excretion derived from spot urine samples to detect changes in population salt intake over time. This systematic review and meta-analysis should resolve much of this uncertainty and provide new data that will allow for specific recommendations to be made about the best way to measure population salt intake using spot urine samples. These findings will be a significant contribution to scientific fields and to public health.

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Authors' Contributions

Bruce Neal, Mark Woodward, Liping Huang, and Kristina Petersen conceived and designed the study. Liping Huang and Kristina Petersen drafted the article. All authors reviewed the article for critically important intellectual content and approved the submitted manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Search terms.

[PDF File (Adobe PDF File), 25KB - resprot_v5i3e190_app1.pdf]

Multimedia Appendix 2

Predictive equations used to estimate 24-hour salt intake (g) from spot urine samples.

[PDF File (Adobe PDF File), 34KB - resprot_v5i3e190_app2.pdf]

Multimedia Appendix 3

PRISMA Diagram.

[PDF File (Adobe PDF File), 33KB - resprot_v5i3e190_app3.pdf]

Multimedia Appendix 4

Identified studies with full text report available.

[PDF File (Adobe PDF File), 82KB - resprot_v5i3e190_app4.pdf]

Multimedia Appendix 5

Identified studies for which full text is unavailable and eligibility is uncertain.

[PDF File (Adobe PDF File), 68KB - resprot_v5i3e190_app5.pdf]

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Abbreviations

BMI: body mass index
NHMRC: National Health and Medical Research Council
WHO: World Health Organization

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Proposal

Use of Relational Agents to Improve Family Communication in Type 1 Diabetes: Methods

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Abstract

Background: Physiological and environmental risk factors interact to undermine blood glucose control during early adolescence. This has been documented to be associated with family conflict and poor adherence to diabetes management tasks. Family Teamwork is an efficacious program demonstrated to enhance family communication and reduce conflict during this vulnerable period. It was designed to be delivered to families in-person, which limited reach and potential impact.

Objective: The purpose of this paper is to present the protocol for adapting Family Teamwork for Web-based delivery.

Methods: Formative research with health care providers, parents, and adolescents will help modify Family Teamwork for Web-based delivery by a relational agent (ie, a computerized character with human-like features and actions). Sessions will be interactive, requiring both parent and adolescent participation, with the relational agent serving as a health coach. After programming, usability testing will be conducted to help ensure the program is easy to use. Video and instructional materials will be developed to facilitate use, and a small pilot study will be conducted to assess feasibility. Families will provide written informed consent prior to participation in any phase of the study. The Institutional Review Board at Baylor College of Medicine reviewed and approved the protocol (H-37245).

Results: Formative research is underway. No results are available at this time.

Conclusions: This research has the potential to make an important contribution to diabetes management by using technology to enhance the reach of an efficacious program.

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KEYWORDS

adolescents; family communication; pre-adolescents; relational agent; type 1 diabetes

Introduction

The incidence of type 1 diabetes (T1D) is increasing worldwide [1], and T1D is the second most prevalent chronic illness among US children, after asthma [2]. Despite the recent introduction of new types of insulin, insulin delivery systems, and innovative blood glucose (BG) monitoring technologies to improve T1D self-management and BG control, non-adherence to a diabetes management regimen remains common, especially in young adolescents with T1D [3]. Unfortunately, physiological and environmental risk factors interact to undermine BG control during pre- and early adolescence. While the physiologic insulin resistance that occurs normally during pubertal development and resulting deterioration of BG control have been well-established [4], only recently have investigators documented the significant role of the family in diabetes

adherence and BG control during this period [5]. Recent longitudinal studies [6-8] have demonstrated that poor adherence and BG control during adolescence, as well as family problems, often persist into early adulthood, amplifying the risk of long-term microvascular, macrovascular, and psychological complications. Therefore, it is increasingly clear that the pre- and early-adolescence periods are particularly critical. Intervening during this period is essential for improving both adherence and diabetes-specific family interactions, which will establish a trajectory of strong, stable self-management behavior and more optimal BG during adolescence, thus lowering the risk for long-term complications [9,10].

Family Teamwork (FT) is a clinic-based face-to-face intervention for pre- and early-adolescent youth with T1D and their parents. It targets potentially modifiable factors documented to impact glycemic control and adherence to BG monitoring, such as parent-youth conflict and communications around BG monitoring. FT was designed to increase positive parent involvement in, and reduce family conflict around, T1D management in young adolescents with T1D. Its goal was to improve adherence and BG control as reflected by hemoglobin A1c (HbA1c) [11]. The 8-session program was delivered to 10-14 year-olds and a parent during routine clinic visits by a trained research assistant. Two randomized controlled trials demonstrated its efficacy (ie, significant improvement in BG monitoring adherence and HbA1c in the FT group compared with the standard care group [11,12], as well as increases in self-reported quality of life [13]). Parents in the FT group maintained or increased involvement in diabetes management tasks, especially BG monitoring, with no increase in diabetes-specific family conflict [14]. Youth in the intervention arm improved BG monitoring adherence [11] and self-reported quality of life [13]. Furthermore, participants who received the intervention had a decrease in HbA1c from 8.4% ±1.3% to 8.2% ±1.1% compared with the deterioration from 8.3% ±1.0% to 8.7% ±1.5% (P<.05) observed in the control group, as expected during early adolescence [12].

Even though FT was proven to be efficacious, its reach was severely limited by the need for families to travel to a particular location to participate in the intervention and the costs associated with delivery by a trained research assistant. Since there is an urgent need to broadly disseminate effective interventions for the high-risk group of early adolescent youth with T1D [11], a method to deliver FT in a more convenient, lower-cost format is needed. Internet use is prevalent in today's world [15]. Therefore, adapting FT for delivery via a Web-based format, led by a relational agent (an animated computer character with human-like features and behaviors) may offer a solution.

Research has demonstrated the feasibility and acceptability of relational agents. For example, relational agents have been utilized in a variety of adult populations and with a wide array of health behaviors (eg, a virtual nurse providing discharge instructions to low health literate patients [16] and patients with depressive symptoms [17]; an exercise advisor for college students [18,19], adults [20], and low health literate older adults [16,18,21]; a health advisor promoting medication adherence to adults with schizophrenia [18,22]; a virtual coach promoting adherence to physical activity in overweight adults [23]; and a virtual agent promoting fruit and vegetable consumption to healthy adults [20]). They are also being developed for use in group settings and for multiple behaviors. Because research shows promising evidence that relational agents can establish a therapeutic relationship with patients and that they are well accepted by a variety of patient populations [18,19], this approach has potential as a method for overcoming limitations commonly associated with face-to-face behavioral interventions, such as limited reach, scheduling constraints, and variable fidelity [24,25]). Thus, incorporating relational agents into programs traditionally delivered in-person could overcome these limitations and provide a low-cost, easy-to-disseminate method for reaching families in need.

This research will convert FT to a Web-based delivery format guided by a relational agent (ie, Family Teamwork Online [FTO]) and assess the feasibility of this approach. This research addresses an important gap in the field and has the potential to enhance the reach and potential impact of a proven, efficacious intervention developed for an at-risk group. The purpose of this paper is to describe the protocol for adapting FT to a Web-based format guided by a relational agent.

Methods

Overview

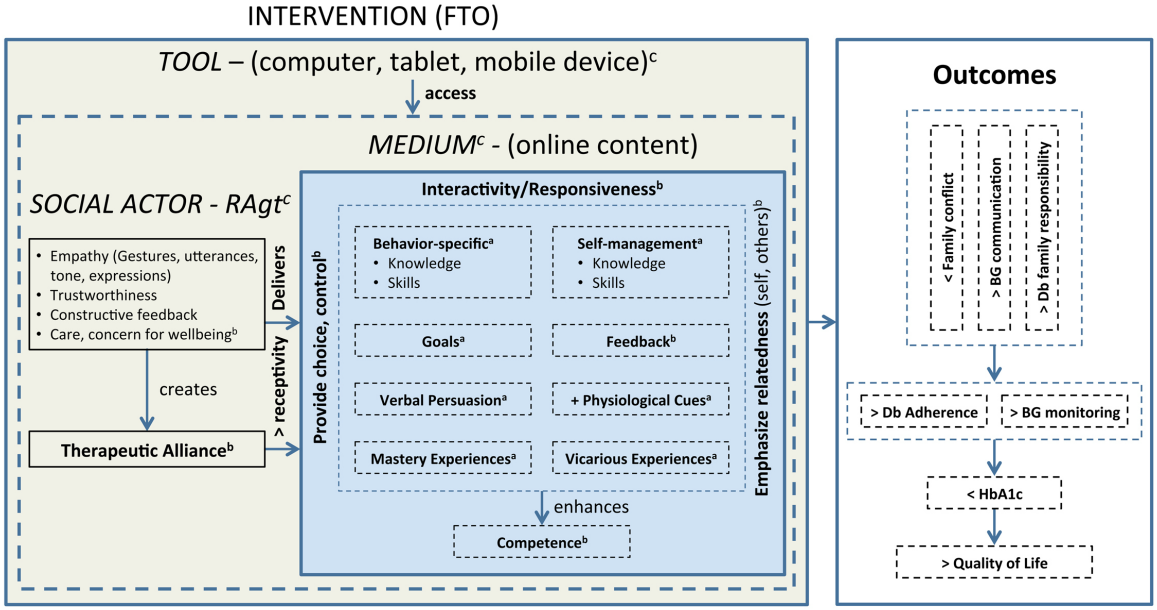
This research will be conducted in two phases: development and pilot. The purpose of the development phase is to conduct formative research with parents and adolescents with T1D and their providers in order to adapt the program to a Web-based format. The pilot phase will assess feasibility of this approach. Each phase is described below. Ethical approval was provided by the Institutional Review Board at Baylor College of Medicine (H-37245). Because the purpose of this trial is to establish the feasibility of this approach versus a randomized control trial to determine efficacy or effectiveness, the trial has not been registered with a trial registry accredited by the World Health Organization.

Theoretical Framework

The content and structure of the original FT was grounded in social cognitive theory (SCT) [26]. The adaptation of FT to FTO will be guided by Computers As Persuasive Technologies (CAPTOLOGY) [27] and self-determination theory (SDT) [28]. CAPTOLOGY provides a framework for understanding how computers can be used as a persuasive mechanism to intentionally change attitudes and behaviors. For example, computers can personalize the encounter (eg, greeting family members by name), provide an interactive versus didactic session, simulate experiences (eg, provide opportunities for the parent/adolescent dyad to practice skills taught in the session), and receive tailored feedback based on responses, problems, or issues brought up in the session [27]. The framework posits that this is achieved through the "functional triad," which is a unique combination of the tool (eg, access device, such as a computer or tablet), medium (eg, delivery mode, such as the Internet), and social actor (eg, relationship builder, such as the relational agent) [27]. SDT [28] contends that three basic needs drive behavior: competence (ie, knowledge, skills, ability to successfully perform a behavior), autonomy (ie, choice, control),

and relatedness (ie, connection to important others). A high level of need satisfaction promotes internalization and integration of the behavior into one's sense of self (ie, "I am a person who routinely monitors my BG," "I am a person who tries to understand my parent's perspective when we disagree over my diabetes"). Internalization and integration of a behavior with one's sense of self increases internally driven motivation to perform the behavior. This, in turn, increases the likelihood that the behavior will be performed and maintained over time [28]. The relational agent will be constructed to emphasize need fulfillment. For example, it will enhance effective communication among parents and adolescents around T1D self-management behaviors by presenting skills, encouraging practice (ie, competence), and emphasizing personal choice regarding how they interpret comments and respond to each other (ie, autonomy). Improved communication will provide insight into what the other person's motivations may be when they react in a certain way, and it will help establish a bond of trust and rapport with the relational agent (ie, relatedness). Figure 1 shows the conceptual model guiding the adaptation.

Figure 1. Conceptual Model of how FTO is designed to influence outcomes.



The conceptual model provides an overview of how FTO-RAgt integrates Social Cognitive Theory[a], Self Determination Theory[b], and Captology[c] to promote intentional behavior change. Note: RAgt=relational agent; Db=diabetes; BG=blood glucose; SDT=Self Determination Theory; +=positive.

Study Sample

Health care providers at a diabetes care center in a large tertiary care children's hospital in the southwestern United States are eligible if they are employed full or part time by the facility. They will be invited by email to participate in the first phase of the study.

Current patients and their primary diabetes caregivers attending a large diabetes care center in Texas are eligible to participate in this study: 10-14 year olds with T1D as defined by the American Diabetes Association criteria [29], disease duration at least 1 but not over 5 years, fluent in English with access to high-speed Internet, and a parent willing to participate in the study are eligible to participate. Adolescents are ineligible if the average HbA1c over the past year is ≥12% (due to a greater likelihood of having psychiatric conditions [30]) or 7% (excellent glycemic control), unable to attend regular clinic visits, or have a physical/mental disease or condition that may conflict with study protocol and limit ability to complete data collection activities or participate in the intervention.

Eligible parents must be the primary caregiver of a child with T1D enrolled in the study, be willing to participate in study activities, be fluent in English, have access to high-speed Internet, and not be planning to leave the geographic area.

Recruitment

To identify families, a research coordinator experienced in working with families with diabetes will screen the clinic appointment schedule to identify families who meet the eligibility criteria. Eligible families will be invited by letter to participate. Within a week of sending the letter, study staff will contact the families to answer questions, ascertain interest, and screen for eligibility. If families are interested and eligible, written informed consent and child assent will be obtained.

Development Phase

The purpose of this phase is to conduct formative research to adapt FT for Web-based delivery by a relational agent. It consists of in-person interviews with health care providers, Web-based surveys and telephone interviews with parents and adolescents, in-person usability testing with parents and adolescents, and development of a brief instructional video and supporting materials to facilitate intervention completion.

Sample Sizes

A purposive sampling approach will be used to identify sample sizes for the formative research [31]. We selected this approach expecting that it would provide key insights from stakeholders (health care providers, families who have a child with T1D) that could be used to update the content and develop a program sensitive to the needs of families enrolled in the study. In this

sampling approach, sample size is driven by the number of participants needed to address key research questions. Therefore, formative research will involve 10 health care providers and up to 24 parent/adolescent dyads. Usability testing will be conducted with a different sample of up to 12 parent/adolescent dyads. If analysis does not yield adequate information with which to address the research questions, additional data will be collected until this point is attained.

Health Care Providers

Health care providers will participate in a scripted, semistructured interview to identify their general thoughts about FTO, diabetes management concerns, and issues often seen in clinic related to family conflict. Interviews will be digitally recorded and transcribed verbatim. Data will be coded and analyzed using thematic analysis [32]. A priori codes will provide the initial coding framework; they will be augmented with additional codes that emerge during analyses. Codes will be examined to identify themes and patterns. Discrepancies will be discussed and resolved.

Parent/Adolescent Dyads

Formative research with families will include up to two Web-based surveys, each followed by a telephone interview to clarify, expand, and understand survey responses. Parents and adolescents will participate in this phase separately. They will be asked to provide feedback on the relational agent (eg, looks, clothing, skin tone, hair style, name, facial expressions), issues their family commonly faces surrounding diabetes management, usual reactions, and suggested session topics. This information will be used to adapt FT for Web-based delivery (FTO) and to develop the relational agent. Sample questions will include, regarding relational agent mock-ups, "Which virtual health educator appeals to you the most?" (response options will include Male, Female with curly hair, Female with straight hair); relating to structure, "The sessions will be delivered online through your computer. Parents and children will view the program together. In your opinion, about how long should each session last?" (response options will range from 15 minutes-1 hour); and regarding content, "What is your [parent's/teen's] usual reaction to high blood glucose readings?" (response options will include Calmly talks about it, Refuses to talk about it, Gets upset or angry, Gets frustrated, Gets defensive, None apply).

Creating Family Teamwork Online

The information presented in each content segment, including content, questions, response options, and feedback will be adapted from the original FT for Web-based delivery by a relational agent based on feedback from health care providers and families. Each session will focus on a specific topic informed by the original FT and the formative research. Sessions will be scripted and will include (1) didactic components where the relational agent conveys content, components where "typical" family scenarios are demonstrated, and (2) interactive components where the relational agent poses a question for the families, parent, and/or adolescent, they select a response, and the relational agent responds. Parents and adolescents will view the sessions together. Session delivery will mimic the original FT delivery by a trained research coordinator as closely as possible. For example, during each session, the relational agent will convey the session content in segments, rather than all at once. Similar to in-person delivery, after presenting content, the relational agent will ask the family a question. The family will have several response options from which to select. Then feedback will be provided. Responses will be made via mouse click. This pattern will continue until the end of the session, which ends in a joint goal-setting task specific to family communication around T1D management. The relational agent's verbal and nonverbal behaviors will be generated using pre-rendered three-dimensional animated video clips. The video clips will be based on scripts generated for each session. Responses will trigger the next video clip in the sequence. The list of questions is set and will not branch.

FTO will be programmed to be viewed over a high-speed Internet connection, from a desktop, laptop, tablet, or mobile device. It will include high-resolution graphics and vocal tracks, animation, and interactivity. Because it is being programmed to be viewed online, the program will not be device dependent.

Usability Testing

After development, FTO usability (ie, ease of use) will be assessed with up to 12 new families to identify technical issues and ease of navigation (ie, do parents/adolescents understand what to do and can they do it without assistance). Following standard usability procedures [33], research staff will observe and keep a log of difficulties as participants (parent/adolescent dyads) work through sessions. On completion, the retrospective think-aloud technique will be used to guide the family through a description of what they did, why, problems they encountered, and how they addressed them as they navigated the program. The research coordinator will take notes of their comments. When the parent/child dyad has finished, using the retrospective probing technique, the research coordinator will ask questions about their thoughts and actions based on the notes taken during the observation and think aloud sessions. Each parent and adolescent will also complete the System Usability Scale [34]; a score of >80.3 will be interpreted to mean that the system has a high level of usability [35].

Instruction

A brief video and colorful print information guide will be developed demonstrating how to navigate FTO. These materials will be written at a 5th grade reading level to facilitate comprehension by both parents and adolescents.

Pilot Phase

Sample Size

Feasibility studies are designed to contribute to a well-informed main trial [36-38] and are the first step in intervention development [37-39]. Although the literature does not offer consistent guidance, an appropriate sample size should represent the minimum number of participants needed to adequately assess the feasibility criteria [40]. A sample size of 24 dyads would provide a reasonable evaluation of feasibility; it would also be large enough to examine trends in HbA1c over time.

Design

The feasibility study will use a one-group design with three data collection periods: baseline, post 1 (immediately after completion of the online program, ie, approximately 3 months after baseline), and post 2 (approximately 3 months after post 1, ie, approximately 6 months after baseline). Because the primary outcome in a future efficacy study will include HbA1c, the pilot study will encompass 6 months. This will enable an examination of trends in intervention effects on HbA1c over time.

Procedure

FTO will be completed online using procedures from other online studies [41,42]. Parents/adolescents will complete the sessions together; they will each be given unique passwords to log on to the program. Both parent and adolescent will need to log on to view a new session. Families will receive email reminders when eligible to log on to the next session. Clinical data collection will occur during the usual clinic visits, online, and as parents/adolescents navigate FTO. Each session will be led by the relational agent who will work with the parent/adolescent dyad during the program. At the end of each session, families will have the option to print their goal and a tip sheet offering suggestions for ways to enhance goal attainment. Families can replay previously viewed sessions unlimited times.

Data Collection Procedure and Measures

Several types of data will be collected during this study. Self-report questionnaires will be completed by parents/adolescents separately over a secure, password-protected website at baseline, post 1, and post 2. Trained research staff will extract clinic data needed for the study from the medical record following approved clinic procedures. Program use data will be automatically collected as families navigate FTO. Staff logs will be maintained to assess key process evaluation variables (see Table 1; [17,43-49]).

Feasibility Outcomes

FTO will be considered feasible if (1) recruitment goals are met, (2) families complete ≥75% of the sessions (ie, login rate), (3) attrition rate is ≤10%, (4) program satisfaction with FTO is high (average score of ≥16/20), (5) therapeutic alliance with the relational agent is high (average score of 5/7), (6) families express positive attitudes toward the relational agent (average score of 5/7), (7) ≥80% of data are collected at post 1 and post 2, and (8) few technical issues (<10%) with intervention delivery occur.

Analysis Plan

Feasibility

Analysis for the feasibility study will be mainly descriptive. To enrich understanding of the FTO process, descriptive statistics will be calculated and compared to the target goals. FTO will be considered feasible if target goals are met.

Exploratory

Using a within-subject design, linear effect mixed models will examine change in HbA1c and self-report psychosocial measures over time (ie, baseline to post 1, post 2), controlling for potential confounders (eg, gender, race/ethnicity). Separate models will be conducted for psychological and behavioral outcomes. Self-report outcomes will be analyzed separately for parents and adolescents. Although statistical significance is not expected due to the small sample size, changes will be examined to determine if they are in the expected directions. Analyses will be calculated with SAS 9.4 [50].

Anticipated Results

We anticipate that feasibility criteria will be met and that families in the FTO group will have favorable changes in the expected directions.

Table 1. Pilot study measures.

Who	What	Method	Prior	Baseline	Intervention	Post 1	Post 2
Adolescent	Diabetes Self-Management Questionnaire [43]	Self-report		x		x	x
	Peds QL Diabetes Module 3.2 [44]	Self-report		x		x	x
	Revised Diabetes Family Conflict Scale [45]	Self-report		x		x	x
	BG Monitoring Communication Survey [46]	Self-report		x		x	x
	Diabetes Family Responsibility Questionnaire [47]	Self-report		x		x	x
	Program satisfaction [41,48]	Self-report				x	
	Therapeutic Alliance [49]	Self-report				x	
	Attitudes toward Relational Agent [17]	Self-report				x	
	Program reactions	Interview				x	x
	BG meter/insulin pump readings	EHR[a]		x		x	x
	HbA1c	EHR		x		x	x
	Height	EHR		x		x	x
	Weight	EHR		x		x	x
	Treatment regimen	EHR		x		x	x
	Severe hypoglycemia/ketoacidosis	EHR		x		x	x
	Emergency room visits/hospitalizations	EHR		x		x	x
Parent	Revised Diabetes Family Conflict Scale [45]	Self-report		x		x	x
	BG Monitoring Communication Survey [46]	Self-report		x		x	x
	Diabetes Family Responsibility Questionnaire [47]	Self-report		x		x	x
	Demographics	Self-report		x			
	Program satisfaction	Self-report				x	
	Therapeutic Alliance [49]	Self-report				x	
	Attitudes toward Relational Agent [17]	Self-report				x	
	Program reactions	Interview				x	x
Program	Logins	Program			x		
	Responses	Program			x		
	Technical issues	Program			x		
	Recruitment	Staff logs	x				
	Attrition	Staff logs		x	x	x	x
Health care providers	Opinions to help develop FTO	Interview	x				

[a]EHR: electronic health record.

Discussion

Principal Considerations

The Diabetes Control and Complications Trial and its findings heightened awareness of the critical importance of maintaining near-normal BG levels to delay and/or prevent T1D complications [51]. Adolescents are particularly affected by poor adherence to the demanding T1D regimen. Family conflict and negative communication around diabetes management, especially around BG monitoring, are barriers to adolescent adherence to their treatment plan [14]. A meta-analysis of pediatric T1D interventions with adherence-promoting components concluded that behavioral interventions focusing "on direct, behavioral processes and neglected emotional, social and family processes are unlikely to have an impact on BG control" (p. 1658) [52]. The most efficacious interventions addressed both [52]. The FT intervention meets these criteria: it targets interactions of the parent and adolescent with T1D and addresses T1D management behaviors (eg, BG monitoring, administering insulin, carbohydrate counting).

Although face-to-face interactions with health care providers have historically been thought of as the most effective method for achieving health behavior change and are considered the

"gold standard" [18,53], limited reach [53], time [18], and consistency in intervention delivery can reduce effectiveness [18]. Relational agents may help overcome these limitations. They simulate characteristics of face-to-face interactions with a health care provider, including verbal and nonverbal behaviors that contribute to trust, rapport, and relationship-building. Programs delivered by relational agents are also convenient, accessible, and likely cost effective, particularly when delivered online [18].

Relational agents have been utilized in a variety of populations and health behaviors [16-23] . However, to our knowledge, they have not been used to enhance family communication around T1D in adolescence. Because research shows promising evidence that relational agents can establish a therapeutic relationship with patients and that they are accepted by a wide variety of patient populations [18,19], relational agents have the potential to enhance reach and public health impact of efficacious interventions by overcoming limitations associated with face-to-face delivery. Thus, if proven feasible, this research has the potential to ultimately impact how health education programs are delivered to families of adolescents with T1D and other chronic diseases in which effective family communication is essential.

Limitations

Limitations of this research include conducting the research in one geographic region of the United States, which may limit generalizability. However, this is a pilot study, seeking to establish feasibility and proof of concept, which somewhat overcomes this concern at this stage of intervention development. The sample size is also small; however, once feasibility is established, fully powered efficacy and effectiveness trials can be conducted with larger, more diverse samples. Self-report questionnaires are also used to report psychological information. However, objective measures of adherence will be captured by retrieving BG meter readings and other health outcomes, such as lab values of glycemic control (HbA1c), from the electronic health record. However, whenever possible, gold standard measures will be used in order to obtain the best information possible.

Conclusions

In conclusion, this research is novel and has the potential to make an important contribution to the scientific literature by expanding the reach and thus the public health impact of programs typically delivered in-person to families that have a child or adolescent with T1D.

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Conflicts of Interest

None declared.

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Abbreviations

BG: blood glucose

CAPTOLOGY: Computers as Persuasive Technology
EHR: electronic health record
FT: Family Teamwork
FTO: Family Teamwork Online
HbA1c: hemoglobin A1c
SAS: Statistical Analysis Software
SCT: social cognitive theory
SDT: self-determination theory
T1D: type 1 diabetes

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Proposal

Technology-Enabled Remote Monitoring and Self-Management — Vision for Patient Empowerment Following Cardiac and Vascular Surgery: User Testing and Randomized Controlled Trial Protocol

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Abstract

Background: Tens of thousands of cardiac and vascular surgeries (CaVS) are performed on seniors in Canada and the United Kingdom each year to improve survival, relieve disease symptoms, and improve health-related quality of life (HRQL). However, chronic postsurgical pain (CPSP), undetected or delayed detection of hemodynamic compromise, complications, and related poor functional status are major problems for substantial numbers of patients during the recovery process. To tackle this problem, we aim to refine and test the effectiveness of an eHealth-enabled service delivery intervention, TecHnology-Enabled remote monitoring and Self-MAnagemenT—VIsion for patient EmpoWerment following Cardiac and VasculaR surgery (THE SMArTVIEW, CoVeRed), which combines remote monitoring, education, and self-management training to optimize recovery outcomes and experience of seniors undergoing CaVS in Canada and the United Kingdom.

Objective: Our objectives are to (1) refine SMArTVIEW via high-fidelity user testing and (2) examine the effectiveness of SMArTVIEW via a randomized controlled trial (RCT).

Methods: CaVS patients and clinicians will engage in two cycles of focus groups and usability testing at each site; feedback will be elicited about expectations and experience of SMArTVIEW, in context. The data will be used to refine the SMArTVIEW eHealth delivery program. Upon transfer to the surgical ward (ie, post-intensive care unit [ICU]), 256 CaVS patients will be reassessed postoperatively and randomly allocated via an interactive Web randomization system to the intervention group or usual care. The SMArTVIEW intervention will run from surgical ward day 2 until 8 weeks following surgery. Outcome assessments will occur on postoperative day 30; at week 8; and at 3, 6, 9, and 12 months. The primary outcome is worst postop pain intensity upon movement in the previous 24 hours (Brief Pain Inventory-Short Form), averaged across the previous 14 days. Secondary outcomes include a composite of postoperative complications related to hemodynamic compromise—death, myocardial infarction, and nonfatal stroke— all-cause mortality and surgical site infections, functional status (Medical Outcomes Study Short Form-12), depressive symptoms (Geriatric Depression Scale), health service utilization-related costs (health service utilization data from the Institute for Clinical Evaluative Sciences data repository), and patient-level cost of recovery (Ambulatory Home Care Record). A linear mixed model will be used to assess the effects of the intervention on the primary outcome, with an a priori contrast of weekly average worst pain intensity upon movement to evaluate the primary endpoint of pain at 8 weeks postoperation. We will also examine the incremental cost of the intervention compared to usual care using a regression model to estimate the difference in expected health care costs between groups.

Results: Study start-up is underway and usability testing is scheduled to begin in the fall of 2016.

Conclusions: Given our experience, dedicated industry partners, and related RCT infrastructure, we are confident we can make a lasting contribution to improving the care of seniors who undergo CaVS.

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KEYWORDS

technology-enabled self-management; remote automated external monitoring; usability testing; randomized controlled trial

Introduction

Background

Cardiac and vascular surgeries (CaVS) are performed on seniors [1] to improve survival and health-related quality of life (HRQL). Unfortunately, chronic postsurgical pain (CPSP), delayed detections of hemodynamic compromise, complications, and related poor functional status are major problems for substantial numbers of recovering patients [1]. This reflects the inadequacy of current systems for patient monitoring after CaVS, both on hospital surgical wards and at home. The current approach (eg, manually checking vital signs every 8-12 hours on postsurgical wards) results in thousands of cases of delayed detection of hemodynamic compromise (eg, low blood pressure and hypoxia) leading to severe complications (eg, myocardial infarction and stroke) [2] and drastically reduced HRQL. To tackle this problem, our aim is to refine and test the effectiveness of the eHealth-enabled service delivery intervention, TecHnology-Enabled remote monitoring and Self-MAnagemenT—VIsion for patient EmpoWerment following Cardiac and VasculaR surgery (THE SMArTVIEW CoVeRed), which combines remote automated monitoring, education, and self-management training to optimize recovery in seniors undergoing CaVS, internationally.

Population, Challenges, Gaps, and Inefficiencies to be Addressed

Overview

Collectively as an innovation community we have completed, or are conducting, prospective outcome studies with >65,000 surgical patients, including CaVS patients [3-12]. Based upon the collective research and literature syntheses [13-15], CaVS can be currently characterized by several clinical inefficiencies, resulting in the key challenges discussed in the following sections.

Chronic Postsurgical Pain and Related Consequences

CaVS surgeries affect pain-sensitive structures as they invade muscle and visceral tissues, and involve the harvesting and manipulation of vessels. Such surgical tissue insults lead to pathological nervous system changes, collectively known as sensitization [16]—a function of neuronal modifiability [17]. Sensitization increases pain sensitivity (ie, hyperalgesia), augments the normal duration (ie, hyperpathia) and amplitude of pain, and results in abnormal interpretation of nonpainful stimuli as painful (ie, allodynia) [16]. In all cases, CPSP is, in part, a function of unrelieved acute postoperative (postop) pain that involves a transition phase [18] by virtue of these pathological mechanisms. In our review of 26 studies (n=2033; mean age 65.1 years) across 15 countries, CPSP prevalence following CaVS [11,12,18-41] ranged from 17-56%. The 2013 Canadian prospective Cardiac (CARD) pain study (n=1010) [11] reported more modestly varying CPSP prevalence rates of 40%, 22%, and 17% at 3, 6, and 12 months following surgery, respectively; pain was most commonly located along the sternal incision and saphenous vein harvesting sites. But other studies have reported 1-year CPSP prevalence rates as high as 39% [39] and 45% [40]. Rates of CPSP following vascular surgery are similar in range (25%), with moderate to severe pain typically presenting along the femoropopliteal bypass tunnel [42].

The deleterious consequences of CPSP in CaVS—amidst divergent surgical populations—are well-known, with numerous studies reporting associations of CPSP with poor HRQL and depressive disorder [11,12,18-43]. We meta-analyzed available data [11,25,26,29,32,33,35] (see Multimedia Appendix 1) and found that among seniors who undergo CaVS, there is a statistically and clinically significant relationship between acute postop pain and CPSP development (standardized mean difference 0.28; 95% CI 0.12-0.44) (see Table 1). This emphasizes the decades of research [44-53] which indicate that CaVS patients have erroneous pain and pain medication beliefs that obstruct acute postop pain management. In 2004, Watt-Watson et al [46] found that up to 83% of CaVS patients do not ask for pain medication when requiring it and that, on average, <35% of prescribed analgesic dosages are routinely administered [46]. Current studies indicate that this unfortunate scenario remains unchanged. Cogan et al [53] recently found, for example, that 36% of CaVS patients believed that “pain medication should be spared until the pain is very severe” and 20% believed that “good patients do not speak of their pain.” A gap revealed from this meta-analysis regarding CPSP was that unrelieved acute postop pain requires more effective intervention. A solution to this gap is that postop education, support, and acute pain monitoring and management at home are needed to prevent transition from acute postop pain to CPSP.

Table 1. Meta-analysis: Differences in acute postoperative pain scores between those who do and do not develop chronic postsurgical pain.

Study	Standardized mean difference (SE)	Weight (%)	Standardized mean difference inverse variance random effects (95% CI)
Choiniere et al 2014 [11]	0.14 (0.04)	24.2	0.14 (0.06 to 0.22)
King et al 2008 [25]	0.07 (0.11)	17.3	0.07 (-0.15 to 0.29)
Lahtinen et al 2006 [26]	0.13 (0.06)	22.7	0.13 (0.02 to 0.25)
Lee et al 2010 [35]	0.96 (0.39)	3.8	0.96 (0.19 to 1.74)
Steegers et al 2007 [29]	0.86 (0.17)	12.3	0.86 (0.53 to 1.19)
van Gulik et al 2011 [33]	0.31 (0.17)	12.6	0.31 (-0.02 to 0.63)
van Gulik et al 2012 [32]	0.27 (0.25)	7.1	0.27 (-0.25 to 0.79)
Total	N/A[a]	N/A	0.28 (0.12 to 0.44)

[a]N/A: not applicable.

Undetected Hemodynamic Compromise

CaVS are among the highest-risk surgeries and are associated with substantial postop morbidity and mortality. Following an immediate postop period of intensive care unit (ICU) hemodynamic surveillance, vital signs monitoring after ICU discharge is lacking. Most patients on surgical wards will have vital signs evaluated once per 4-12 hours [54,55]. Such limited in-hospital monitoring—followed by no daily monitoring at home—is significantly associated with poor clinical outcomes. For example, in a study from the Cleveland Clinic [56], nurses blinded to continuous pulse oximetry for monitoring peripheral oxygen saturation (SpO_2) assessed their postop patients (n=594) according to normal practice and detected a 5% incidence of hypoxemia (SpO_2< 90%). Blindly captured study oximetry, however, detected that 37% of patients had one or more continuous episodes of hypoxemia for ≥1 hour, and that 10% of patients had at least one continuous episode (≥1 hour) of hypoxemia where SpO_2 was <85% [56]. Given that hypoxemia for >5 minutes is associated with increased risk of myocardial ischemia, suboptimal monitoring on surgical wards elevates risks for patients. Studies have also demonstrated that continuous electrocardiographic ST segment monitoring after surgery can identify asymptomatic ischemia that is independently associated with myocardial infarction [57-59]. A study of postop ST segment depression followed 151 consecutive patients undergoing major vascular surgery and assessed for postop myocardial ischemia [57]. Approximately 85% of patients who suffered postop cardiac events had preceding long-duration ST segment depressions [57]. These data suggest that remote, continuous, noninvasive ST segment monitoring systems can identify impending cardiac events much sooner than the usual practice of checking vital signs manually every 4-12 hours. The same is true for cardiac postop arrhythmias. The incidence of atrial fibrillation, in particular, is 20-40% after cardiac surgery, with even higher rates (30-50%) after valvular surgery [60-62]. While most patients spend the first 12-24 hours after surgery in the ICU, 70% of postop atrial fibrillation occurs over the first 4 days following surgery, suggesting that many occurrences will be missed on surgical wards [63]. This common scenario is risk elevating, given that atrial fibrillation imposes a three-fold increase in hypotension and stroke [64,65].

Data from large randomized controlled trials (RCTs) also suggest that blood pressure is a particularly important independent predictor of postop cardiac complications and death. The PeriOperative ISchemic Evaluation (POISE) trial [4] randomized 8351 patients to extended-release metoprolol (mean age 68.9 years) or placebo (mean age 69.1 years). Along with a reduction in myocardial infarction, a clinically significant increase in hypotension with metoprolol use was found (hazard ratio [HR] 1.55; 95% CI 1.38-1.74). Overall, clinically significant hypotension is associated with the largest population-attributable risk for perioperative death and perioperative stroke [4]. Following POISE, POISE-2 was an international RCT of 10,010 patients with, or at risk of, vascular disease undergoing noncardiac surgery, including vascular surgery [5]. Analyses demonstrated that clinically important hypotension was an independent predictor of subsequent risk of myocardial infarction during 30-day follow-up (adjusted HR 1.37; 95% CI 1.16-1.62) [5]. A gap revealed from this analysis was that current monitoring of patients after CaVS is inadequate, with significant harm resulting from undetected postoperative hypoxemia, arrhythmia, and hypotension. A solution to this gap is remote automated noninvasive postoperative monitoring, for 30 days following discharge, to enhance detection of hemodynamic compromise and reduce adverse event risk.

Surgical Site Infections

CaVS options are changing, with many patients choosing percutaneous coronary interventions (PCIs) to address vasculature blockages. This results in those undergoing CaVS manifesting disease that is either too advanced or too complicated for PCI. As such, CaVS patients—often with multiple comorbidities—are at high risk for surgical site infections (SSIs). In England, for example, SSIs occurred in 4.4% of patients (n=29,144) who underwent coronary artery bypass grafting and 2.2% of patients (n=7256) who underwent vascular surgery—in National Health Service hospitals from April 2008 to March 2013 [66]. The median time to infection identification was 12 days and 11 days after cardiac and vascular surgery, respectively [66]. A recent systematic review—57 studies—has corroborated the commonality of these infection rates and that SSIs, furthermore, have major consequences including mortality, repeated surgical procedures, hospital readmissions, and health-related economic burden [67].

Evidence from established daily postoperative surveillance systems in the United States suggests that daily wound monitoring can prevent SSI progression—superficial/incisional to deep wound/organ/space [68]. A gap revealed from this analysis is that postop SSIs often manifest at home following discharge and are potentially preventable [69]. A solution to this gap would be daily postop wound monitoring for early detection of, and to prevent progression of, SSIs that require hospitalization.

Hospital Readmissions and Summary of Key Issues

Not only are CaVS among the highest-risk surgeries, they are associated with high rates of hospital readmission. A 2014 prospective, multicenter cohort study—10 centers, 5185 patients—in Canada and the United States reported the rate of all-cause 30-day readmission following cardiac surgery at 18.7% [69]. Recent data (2014) from a large US registry (N=11,246) showed comparable rates of 30-day unplanned readmissions among major vascular surgery patients: 15.7%, infrainguinal bypass [70]. Our particular focus on the aforementioned issues is due to the unequivocal association with poor postoperative functional recovery resulting in CPSP [11,12,18-41]; adverse cardiac events due to hemodynamic compromise [54-59]; and high rates of hospital readmission due to infection [66,69]. Postoperative infection, for example, is the most common reason for readmission in Canada following cardiac surgery (17.1%) [69]. Other important recovery challenges for seniors, requiring intervention, include psychological morbidity (eg, anxiety and depression) [71-77] and medication reconciliation [78].

Proposed eHealth Innovation-Enabled Care Delivery Program

Intervention in Canada and the United Kingdom

This project is being undertaken in Canada and the United Kingdom because (1) the gaps and inefficiencies following CaVS are similar and (2) implementations of eHealth innovations require attention to agile/scalable designs which can be realized through efficient (ie, parallel) integration and effectiveness testing across two health systems.

Targeting Seniors Recovering From Cardiac and Vascular Surgery

Guided by the Integrated Vascular Health Blueprint for Ontario [79] and the UK Department of Health Cardiovascular Disease Outcomes Strategy [80], our aim is health service integration. The fragmented nature of cardiac/vascular care threatens the sustainability of health systems due to inefficiencies and waste. Given that factors associated with poor recovery are common to both sets of CaVS patients, we are aligned with the Canadian Vascular Health Coalition strategy—see page 7 of the Integrated Vascular Health Blueprint for Ontario [79]—of mapping and implementing more integrated ways of addressing cardiac and vascular disease-related burden.

Partnership Process and Technology Partners

Initial discussions have centered on eHealth Innovation Partnership Program objectives, CaVS recovery challenges, and potential partners' orientation to improving patient experience, willingness to codesign, and their match with desired partner criteria. Further discussions reviewed respective technology innovations and desired scope of involvement. As a result of this process, we are fortunate to be working with Philips Canada, QoC Health, XAHIVE, and mPath. These partners are drivers of innovation, ranging from small to medium enterprises, to a multinational organization.

Guiding Principles, Work to Date, and Patient-Oriented Approach

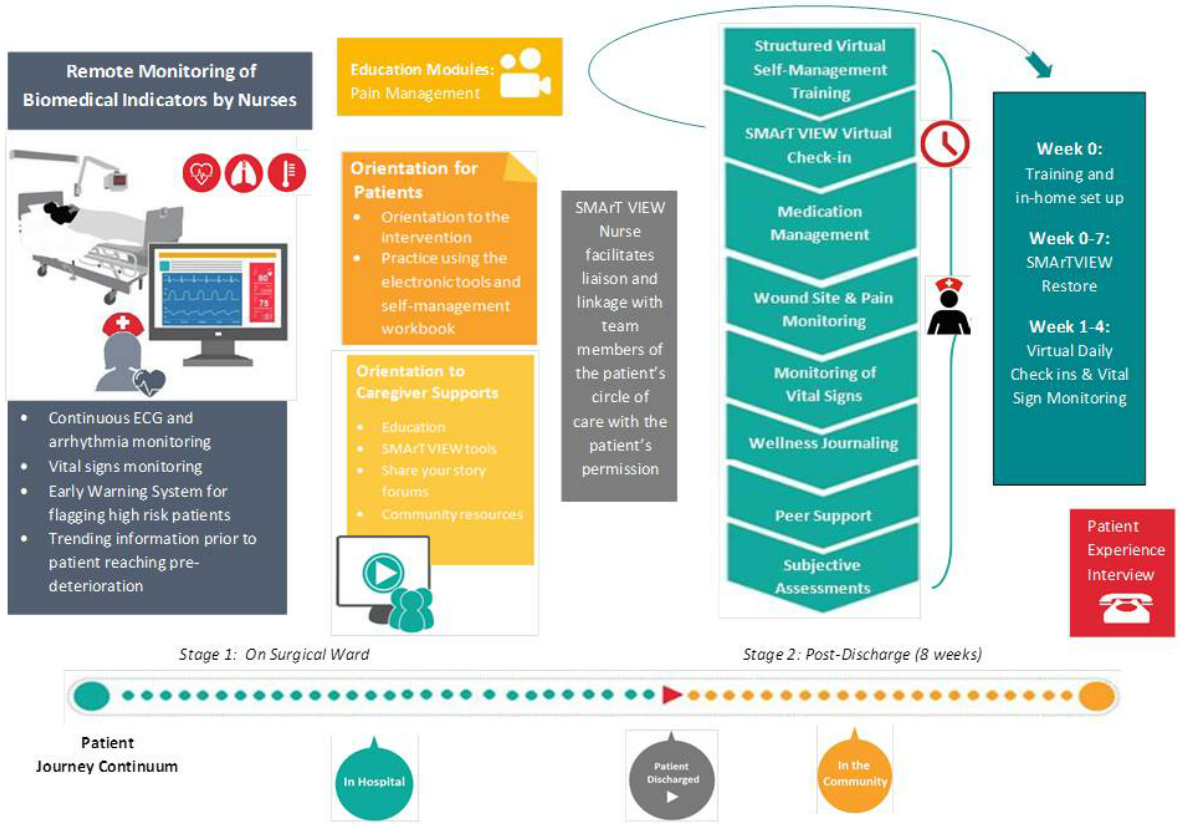
The intervention has been designed according to *Patients First: Action Plan for Health Care* [81]. Grounded in commitment to efficiency and integration of care, the following tenets of Patients First serve as our guiding principles: (1) Improve access: provide faster access to the right care by removing barriers to full scope of practice and coordinating care, (2) Connect patients to services: deliver integrated care that is home based when possible, (3) Protect public health care system: innovate based on evidence and capacity to engage patients, and (4) Inform: provide education and transparency. With Patients First as our framework, our leadership team and technology partners jointly applied for, and secured, competitive seed funding from the Michael G DeGroote Institute for Pain Research and Care at McMaster University. With these funds, a 2-day, international SMArTVIEW meeting was held for the purposes of intervention codesign, systems integration planning, and change management/scalability plan development. A professional facilitation company, Guiding Star Communications, led us through structured patient journey mapping and analysis. Divided into working groups—each with scientists; clinicians; CaVS patient representatives; engineers; and information technology, policy, and knowledge translation experts—we worked from stems of real CaVS cases to map the typical senior patient's recovery journey, based on experience. We then engaged in facilitated analysis of what "must change." Once "must change" items were distilled and validated by patient representatives, the technology partners showcased their evidence-based innovations for change. Using consensus techniques, we mapped partners' solutions to "must change" items in a codesign of the SMArTVIEW intervention. Three subgroups worked intensively on systems integration.

Intervention Program, Technologies, and Effectiveness

Overview

SMArTVIEW is an eHealth-enabled service delivery program—based on existing implementable technology and validated interventions—which combines remote monitoring, education, and self-management training (see Figure 1). The following review of SMArTVIEW components as a whole identifies key members of the health care team as well as key phases and technology enablers.

Figure 1. The Self-MAnagemenT—VIsion for patient EmpoWerment (SMArTVIEW) eHealth-enabled service delivery program. ECG: electrocardiogram.



Health Professionals Involved, Phases, and Technology Enablers

Multiple clinicians are involved in seniors' circles of care in the hospital and the community. Successful implementation, however, requires centralized coordination. Therefore, the "SMArTVIEW Nurse" (SVN), a registered nurse with SVN training, is central. SMArTVIEW is a two-stage intervention program. Stage 1 supports seniors after CaVS in hospital on surgical wards post-ICU, with a view to seamless transition, while Stage 2 supports patients at home during the first 8 weeks of recovery (see Figure 1). Across stages, our clinical technology enablers include Philips' IntelliVue Guardian [82] and Transition to Ambulatory Care (eTrAC) Program [83], and QoC's Engagement Platform [84].

Stage 1

Stage 1 includes remote automated postoperative monitoring (Protect) and pain management education (Protect, Inform).

Monitoring

On the ward, remote monitoring will be implemented by the SVN via Philips' IntelliVue Guardian early warning system, which includes a centrally located monitor, a portable spot check monitor, and four lightweight cableless devices worn by the patient, with connectivity via short range radio and hotspot transmitters. The four devices are as follows: (1) MX40,a telemetry pack for 8-lead continuous electrocardiogram monitoring; (2) Acquire SpO_2, a wrist-worn device applied to the index finger, which provides continuous SpO_2 saturation values under various artifact conditions, including motion and low perfusion, as well as pulse rate; (3) Acquire Blood Pressure, a noninvasive blood pressure cuff worn on the brachial aspect of the arm; and (4) Acquire Respiration Pod, a small patch-like device, attached to the left costal arch of the patient's chest, which derives respiration rate and patient posture via 3D accelerometer [82]. Receiving data from each device, IntelliVue Guardian software employs a deterioration notification algorithm to facilitate early intervention. This algorithm automates hospital early warning score (EWS) systems, normally performed manually by clinicians. EWSs track vital sign deviations from normal and trigger increasing attention to care, proportional to the deviation. By virtue of automation, IntelliVue Guardian efficiently verifies the accuracy of vital signs data by repeating measurements at customized intervals [82]. If early signs of deterioration are detected, IntelliVue Guardian will inform the SVN via mobile device. Moreover, clinicians on the ward are able to visualize EWS on the central monitor and spot check monitor, which is kept at the patient's bedside. As identified previously, remote automated monitoring is needed to identify undetected hemodynamic compromise and allow for early intervention to prevent adverse events following CaVS; IntelliVue Guardian provides a comprehensive, evidence-based solution [85] to meet this need.

Education

Education (Inform) is critical to prevent transition from acute postop pain to CPSP. To empower seniors to know how to communicate their postop pain experience and understand options for pain management (Protect), we employ, on ward

day 2, Watt-Watson et al's Pain Relief After Surgery educational intervention [46]. Adapted as an animated video module, Pain Relief After Surgery is a 20-minute education tool, validated for CaVS patients—comprehension level: Grade 6—and designed to address common misbeliefs preventing patients from asking for improved pain relief. Content also emphasizes the individuality of pain responses and the importance of good pain relief for optimal recovery at home. RCT evidence supports the effectiveness of Pain Relief After Surgery for reducing pain-related interference during recovery as well as misbeliefs about analgesics [46]. In conjunction with Philips' eTrAC program, this video module will be issued to the patient on ward day 2.

Stage 2

Stage 2 includes SVN hospital-to-home remote monitoring and support and self-management training.

Hospital-to-Home Remote Monitoring and Support

The eTrAC program is a tablet-based solution that combines clinical software for effective care management with Bluetooth-enabled, patient-monitoring devices measuring SpO_2, blood pressure, temperature, blood glucose, and weight [83]. Philips eTrAC allows clinicians to monitor discharged (ie, at-home) patients' vital signs status from the hospital (Protect), and then prioritize them for required interventions (eg, signs of sepsis evident) based upon a combination of customized/standardized intervention rules [83]. eTrAC also features customizable, interactive patient symptom and self-report surveys to inform postoperative support and management. SMArTVIEW-specific surveys include postop daily symptoms, wound monitoring, sleep, nutrition, medication, quality of life, and patient satisfaction. Interactive modules assisting patient orientation to the system are also included. The clinician interface for the eTrAC program is eCare Coordinator (eCC), a cloud-based software tool designed to maximize efficiency through risk prioritization— patients are assigned overall scores calculated from weighted scores of self-report surveys, measurements, issues, risk of readmission, and discharge date if within the last 30 days. The overall score generated allows clinicians to manage large patient populations by triaging their interventions based on potential patient need (ie, those with the highest scores are seen first). Through eCC, clinicians can remotely manage patients, view and interpret results (eg, vital signs and symptom and reflexive surveys), follow up and intervene as needed, conduct video visits with patients, and document all patient interventions and observations.

The SVN will employ the eTrAC program to facilitate daily virtual check-ins and counseling, daily vital signs monitoring and triage, and review of interactive symptom and reflexive surveys (Access, Inform, Protect, Connect) [83].

Self-Management Training

As with Stage 1, we are committed in Stage 2, combining improved monitoring with education and support that empowers seniors to proactively prevent transition to CPSP and prevent poor functional recovery. As a team we are experienced in the development/testing of self-management models for people with coronary artery disease [86-88], other forms of chronic illness [89,90], and CPSP [91]. In conjunction with postoperative monitoring and support, participants will engage in SMArTVIEW Restore. Restore is a virtual self-management program, to be delivered in 2-hour sessions weekly, over a 7-week period, from week 0 (week of discharge) to week 6 postoperation (at home).

Figure 2 presents an overview of the Restore curriculum, based on seniors' CaVS recovery needs identified during patient journey mapping, as well as lessons learned from our previous self-management experience [86-91]. Both content and process elements of Restore are grounded in the fear-avoidance beliefs model [92], which shows how catastrophic pain perceptions can lead to fear, hypervigilance, avoidance, disability, and depression. The curriculum is designed to provide patients with requisite cognitive, emotional, and behavioral skills to manage their postop pain experience in a productive and positive way, leading to optimal functioning. Restore will be run on a time-release basis; interactive features will include weekly recovery goal setting, interactive reflexive activities, wellness journaling, a peer support forum, and a gratitude "wall."

Both the online interactive elements as well as self-efficacy-enhancing features of Restore will be adapted specifically from the Coventry University Help to Overcome Problems Effectively (HOPE) and Internet-based (iHOPE) programs. As one of the first self-management interventions combining positive psychology and cognitive behavioral therapy theory, iHOPE includes evidence-based and positive psychological activities such as goal setting, action planning, identifying personal strengths, scheduling pleasant activities, mindfulness, relaxation training, and reviewing successes [93]. Feasibility trials have shown that HOPE has the potential to improve important quality-of-life outcomes for people living with and affected by a range of long-term conditions [94,95]. Recently, Coventry University and Macmillan Cancer Support—the United Kingdom's leading charity and source of cancer support—tested a Web-based version of HOPE (iHOPE) for cancer survivors, comprised of six interactive Web-based sessions, which combine cancer self-management information and education with self-monitoring tools, worksheets, audio- and video-based materials, interactive goal setting and gratitude "walls," and social networking via email and discussion forums. Feasibility trial results showed that participants' depression, anxiety, fatigue, fear of cancer returning, positive mental well-being, hope, and gratitude all significantly improved [95]. Participants' course experience and usability ratings were high, with all of the participants willing to recommend iHOPE to other users [95].

To facilitate our adaptation of iHOPE interactive elements, QoC Health's Engagement Platform will be leveraged to customize and integrate the validated modules (ie, feature sets) from their existing platforms and to develop customized modules to transform Restore from concept to a codesigned interactive digital solution. QoC will apply the principles of user interface and user experience design to create a user-friendly and intuitive solution with reduced interface friction. An iterative, user-centered design framework featuring participatory design will be used to develop the Web-based solution, which will be

optimized for tablet. QoC will facilitate codesign development sessions with our patient representatives to ensure Restore is aligned with their recovery needs and that it considers their technical capabilities (eg, digital literacy and technology-savvy level) and design preferences. The cognitive load on users will be minimized by abating unnecessary decisions/steps and inconsistencies in the interface. To offer the end user an enhanced e-learning experience throughout Restore, the design will feature "digital resting spaces." This will be achieved by applying the concepts of e-learning (eg, pacing and quantity and diversity of content) and using the principles of white space to balance content and segregate sections.

In summary, our technology partners are cutting-edge eHealth innovators for change with evidence-based solutions. For example, Philips' IntelliVue Guardian has been shown to significantly increase timely clinical response in hospital, based on abnormal vital signs detection, as well as survival after rapid response treatment [85]. Emerging evidence also suggests that solutions developed through QoC's Engagement Platform are feasible, acceptable, and beneficial to postop patients and surgical teams [96,97].

Figure 2. The Self-MAnagemenT—VIsion for patient EmpoWerment (SMArTVIEW) Restore curriculum. CaVS: cardiac and vascular surgery.

Module	Week 0	Week1	Week2	Week3	Week4	Week5	Week6
Orientation to the SMArTVIEW self-management system	•						
Overview of post-operative self-management	•						
Listening to your heart		•	•	•	•	•	•
Managing your post-operative wounds		•	•	•	•	•	•
Gratitude diary		•	•	•	•	•	•
Weight tracking for fluid management after surgery		•	•	•	•	•	•
Solution-focused goal setting and action planning		•	•	•	•	•	•
Managing your medications		•	•	•	•	•	•
Share your story forum for caregivers		•	•	•	•	•	•
Getting a good night's sleep after CaVS surgery		•	•				
Instilling hope and other positive emotions after CaVS surgery			•				
Dealing with depression and difficult emotions during recovery			•				
Staying active during recovery			•				
Solution-focused goal feedback			•				
Preventing falls during recovery & Vitamin D			•				
Mindfulness			•				
Avoiding chronic pain and pain misbeliefs after CaVS			•				
Better breathing after cardiac surgery			•				
Wellness journaling			•	•	•	•	•
Pacing and energy conservation				•			
Healthy eating I, general introduction				•	•	•	
Relaxation				•			
Prority setting				•			
Fear avoidance					•		
Physical activity and exercise					•	•	•
Healthy eating II, nutrition recovery					•		
Stress management					•		
Medication usage during recovery						•	
Weight management						•	
Communication skills						•	
Sexuality and intimacy						•	
Prevent setbacks and dealing with setbacks when they occur during recovery							•
Communication skills I, working with your health care professional and organization							•
Moving forward, leading a happy, flourishing life							•

Systems Integration

SMArTVIEW deploys a highly integrated "system of systems." Multiple decentralized and heterogeneous subsystems, with operational and managerial independence, are required to provide our end-to-end SMArTVIEW solution. Our end goal for clinical data management is to ensure that the right information is provided to the right person, at the right time. We have consulted extensively with our information technology and clinical informatics experts to leverage existing assets through systems architecture, as opposed to duplicating functionality or existing data. Moreover, our technology partners' solutions meet Health Level 7 [98] industry standards for seamless connection and bidirectional data exchange with

our hospital information and electronic medical record systems. We will also use application programming interfaces for the extraction of data. We are confident we can achieve integrated exchange of information, from hospital to home.

Privacy and Data Aggregation

Our additional partners, XAHIVE and mPath, serve as our chief stewards of privacy and data aggregation, respectively. With privacy paramount, we espouse a "privacy by design" approach [99]. Privacy will be role based, highly configurable, and will include the entire circle of care, including formal and informal caregivers and supports by patient consent. To achieve these objectives, we will employ XAHIVE's secure communication service platform, extensible using a custom off-the-shelf model. The XAHIVE communication protocol does not require servers in order to operate, nor does it require specific hardware devices; these two factors give our team an advantage in the arena of scalability of our deployments. XAHIVE will interface with hospital information systems at both sites—Canada and the United Kingdom—in order to realize (1) consistent security across all communication touch points in the SMArTVIEW system, and (2) a clear chain of custody on the privacy of data per legislative requirements. SMArTVIEW involves multiple "moving parts" that will generate data about recovering seniors' status and behavior via peripheral devices. Additionally, the solutions we use will generate and aggregate clinical measurements in discrete locations. Third-party data sets (eg, health services utilization data) will also be accessed, allowing for correlations to be made beyond the scope of our integrated systems. There are multiple considerations in the way data is aggregated (eg, efficiency of architecture, reduction of redundancy, and optimization of data accessibility). As leading experts, mPath will govern our data aggregation practices.

Scalability

With scalability central to our vision, all partner solutions are at technology readiness Level 9, with next to zero time to solution required. Our scalability report will include documentation of (1) unforeseen issues as they arise and problem solving strategies, (2) patient and SVN experience, and (3) results of our comprehensive econometrics evaluation plan, distilled into a projected model of total cost of 1-year SMArTVIEW patient throughput, based on site surgical volumes.

Evaluation Plan Objectives

The objectives of the evaluation plan are to refine SMArTVIEW (Phase 1) and conduct an RCT to examine its effectiveness.

Settings

Both evaluation plan phases will take place at Hamilton Health Sciences, Hamilton, Canada, and Liverpool Heart and Chest Hospital, the United Kingdom; the coordinating center is the Population Health Research Institute, Hamilton, Canada.

Methods

Phase 1: Usability Testing

Participants

Included participants will be (1) aged ≥65 years, (2) undergoing major CaVS with predicted admission >48 hours, and (3) able to read, speak, and understand English such that reflexive intervention surveys generated by eTrAC can be completed (ie, Grade 6 reading level). Those excluded will have planned postop admission or readmission to a nursing home or long-term care facility.

Design and Procedures

Overview

Rogers' methods for usability testing [100] will guide SMArTVIEW refinement in the first 9 months. Patients and clinicians will engage in two cycles of focus groups and usability testing at each site, as described in the following sections.

Focus Groups

Two focus groups, one at each site, will each be conducted with 5 CaVS patients and 5 SVNs via an adapted semistructured interview guide [101]. With well-established technology partner solutions (ie, applications and devices), our focus is refining overall system intervention flow and staging. After viewing still images of each SMArTVIEW stage, feedback will be elicited about (1) what is seen in each still, (2) expectations for engaging with the SVN and eTrAC solutions at each stage, (3) what each stage should accomplish, and (4) if conceptualization of SMArTVIEW aligns with participants' mental models of required tasks.

Usability Testing

High-fidelity user testing of SMArTVIEW, focused on intraoperability and flow of information, will involve a human factors analyst, a research assistant (RA) with design ethnography training, and the leadership team. Focus group findings will be embedded into test (ie, simulated) clinical scenarios, representing CaVS recovery issues. Using think-aloud [102,103] protocols and task completion checklists, this usability testing cycle—conducted twice, once at each site—will have SVNs and patients rehearse all scenarios wherein information coming from either player can be communicated, via automated monitoring or self-report. Scheduled for 2 hours in the hospital and 2 hours in the patient's home soon after, but not on the same day, rehearsals will be observed by the human factors analyst and the RA. Through analysis of recorded usability testing data to identify patterns of use, areas of satisfaction or frustration, and system efficiencies and problems, the human factors analyst and the RA will determine actions for system refinement [104,105]. The entire cycle will be repeated, this time observing real-time-based interaction.

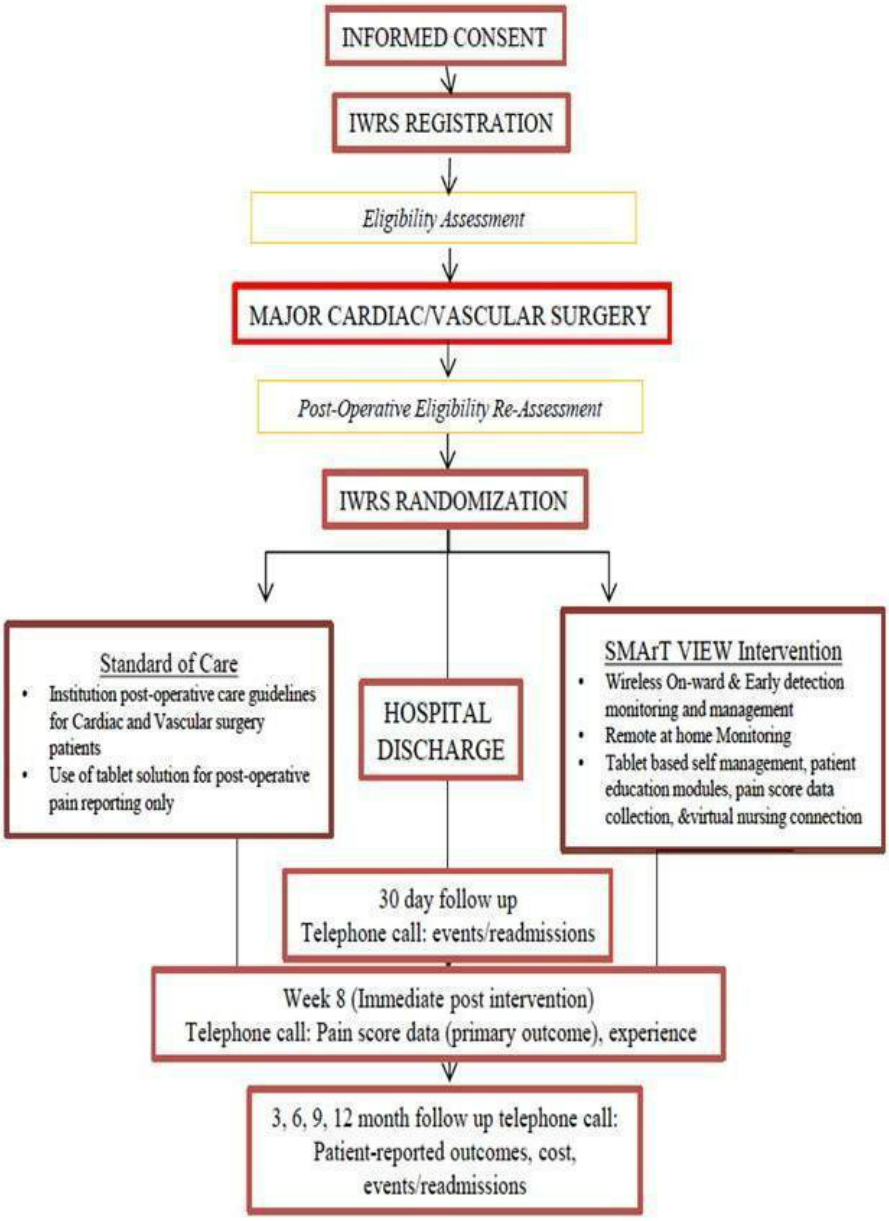
Phase 2: Randomized Controlled Trial

Methods

Trial Design

Research questions to be addressed in a two-group, parallel-arm RCT (see Figure 3) include effectiveness of the intervention to (1) improve postop pain at 30 days (primary outcome) and (2) composite of major postop complications related to hemodynamic compromise, HQRL, depressive symptoms, health service utilization costs, and patient-level cost of recovery (secondary outcomes).

Figure 3. Randomized controlled trial flow diagram. IWRS: Interactive Web Randomization System.



Participants

Participants will be included according to the inclusion/exclusion criteria outlined in Phase 1, with two additional exclusion criteria: (1) participation in Phase 1 and (2) positive Confusion Assessment Method (CAM) screening upon transfer to the surgical ward.

The Self-Management—Vision for Patient Empowerment Intervention

The components of the SMArTVIEW intervention will be as described under the Intervention Program, Technologies, and Effectiveness section. The intervention delivery protocol, by stage, is presented in Table 2. This protocol features SVN support from the surgical ward 24 hours/day, 7 days/week.

Table 2. SMArTVIEW[a] intervention delivery protocol by stage.

Stages	Details
Stage 1: In hospital	
IntelliVue Guardian setup (ward day 1)	
	Upon transfer to the ward, the IntelliVue Guardian early warning system is established by the SVN[b] on duty, who connects patient to peripheral, cableless devices; establishes baseline/normal vital signs with spot check monitor; activates IntelliVue Guardian; and performs system checks every shift.
	The SVN will receive alerts via mobile device; alerts will be set according to surgeon-sanctioned vital signs parameters programmed into IntelliVue Guardian, which allow for tailoring of profiles for day or night, as well as pre-existing comorbid conditions (eg, atrial fibrillation).
	Upon alerts, SVN assessment, intervention, and escalation of care will be according to usual hospital protocols.
Patient and family pain education and hospital-to-home orientation (ward day 2)	
	The SVN will facilitate a 2.5-hour hospital-to-home orientation session implemented at the convenience of the patient, supports (eg, family, friends, and caregivers), and clinical workflow.
	This orientation will focus on the eTrAC[c] tablet-based applications, the PRAS[d] educational video, and Restore.
	Following the orientation, the SVN will invite and answer questions.
Receipt of SMArTVIEW hospital-to-home package and skills rehearsal (day prior to discharge)	
	On the day prior to discharge, patients will receive their hospital-to-home packages from the SVN, including eTrAC tablet-based solutions, instructions for monitoring vital signs at home, eTrAC 30-day application schedule for monitoring vital signs, SVN video visits, and daily recovery symptom and reflexive surveys.
	Upon receipt of this hospital-to-home package, the SVN will facilitate a 30-minute checklist-oriented rehearsal of all eTrAC features; the SVN will also invite and answer questions.
Stage 2: In the community	
Setup (week 1 postdischarge)	
	Philips' in-home installation team will work with the SVN to establish the Bluetooth-enabled vital signs monitoring system.
	The SVN will then commence monitoring of all incoming data from eTrAC via eCC[e].
Patient monitoring and virtual check-ins (first 30 days postdischarge)	
	The SVN will perform daily 15-minute virtual check-ins—eTrAC video visits—with patients at home from the hospital via eCC, per hospital-to-home package instructions.
	Virtual check-ins will include review of priorities flagged in eCC, review of vital signs and symptom and reflexive survey data, postop pain assessment, and discussion of any patient/SVN concerns.
	Issues identified—via eCC risk stratification or SVN assessment—that require intervention, but are out of the scope of SVN practice, will be escalated to the most responsible clinician.
SMArTVIEW-Restore (0 to 7 weeks postdischarge)	
	During recovery, participants will engage the Restore time-release, self-guided, online curriculum (described previously).
	Restore is structured according to seven weekly asynchronous modules, consisting of two to seven activities each.

Stages	Details
	Restore is designed to constitute 2-3 hours of online activity, weekly.

[a]SMArTVIEW: Self-MAnagemenT—VIsion for patient EmpoWerment.

[b]SVN: SMArTVIEW Nurse.

[c]eTrAC: Transition to Ambulatory Care.

[d]PRAS: pain relief after surgery.

[e]eCC: eCare Coordinator.

Outcome Measures

Primary Outcome

The primary outcome is *worst* postop pain intensity upon movement in the previous 24 hours—at 30 days after randomization—averaged across the previous 14 days. This will be assessed using the Brief Pain Inventory-Short Form (BPI-SF), which has well-established reliability and validity in surgical groups, including CaVS [15,106,107]. Common to studies with postop pain as a primary outcome [15,106,107], patients will report *worst* pain-intensity rating both upon rest and movement in the past 24 hours. The primary outcome of worst pain *upon movement* is a more reliable indicator of suboptimal pain management and pain-related interference with recovery-related activities than worst pain *upon rest* [15,106,107].

Secondary Outcomes

Postoperative Complications Related to Hemodynamic Compromise

We will capture a composite of complications related to hemodynamic compromise up to 30 days postrandomization, including death, myocardial infarction, and nonfatal stroke. The number of events for the overall composite, as well as number of events per component within the composite, will be reported.

All-Cause Mortality and Other Postoperative Complications

All-cause mortality will be captured up to 1 year postrandomization. We will also monitor for new-onset atrial fibrillation and SSI up to 30 days postrandomization.

Functional Status

The Short-Form 12 version 2 (SF-12v2) is an established, reliable, and valid tool [108,109] to measure functional status [108,109]. The SF-12v2 provides both physical component summary and mental component summary scores [9,11,46,109].

Depressive Symptoms

The five-question version of the Geriatric Depression Scale (GDS-5) will be used to measure depressive symptoms. This tool is a well-validated instrument in the assessment of depression in hospitalized older adults, with high levels of sensitivity and specificity [110,111].

Chronic Postsurgical Pain

Development of CPSP is defined [112] as (1) pain that developed after the surgical procedure, (2) being different from pain experienced before surgery, and (3) being present for at least 3 months. Patient responses in the affirmative to each of these questions indicate patients have developed CPSP. For patients who have developed CPSP, pain intensity and related interference with usual daily activities will be measured via the BPI-SF [106,107].

Heath Service Utilization-Related Cost

Data on hospital readmission and health care utilization and costs of health service utilization data from the Canadian arm of the trial will be linked with the health administrative Institute for Clinical Evaluative Sciences data repository. Administrative databases used to describe the health service utilization include (1) Registered Persons Database—demographics and vital statistics of all legal residents of Ontario, (2) Discharge Abstract Database—records of inpatient hospitalizations—from the Canadian Institute for Health Information (CIHI), (4) Ontario Health Insurance Plan Database—physician billing claims, and (5) the National Ambulatory Care Reporting System—information on emergency department visits—from CIHI. In addition, to capture data on times spent on the portal by health providers (eg, pharmacists and nurses), costs of health providers' time will be captured in the system reporting. Costs of health providers' time on the portal will be calculated by multiplying the time with unit costs from standard costing sources in Ontario.

Patient-Level Cost of Recovery

The Ambulatory and Home Care Record (AHCR) [11,113-117] will be used to comprehensively measure patient-level cost of illness from a societal perspective (Canada and the United Kingdom). This approach gives equal consideration to health system costs and costs borne by patients and unpaid caregivers (eg, family members and friends). AHCR items can be categorized as publicly financed (eg, public sector paid resources) or privately financed care (eg, all out-of-pocket and third-party insurance payments, and time costs incurred by caregiver). Face validity and reliability of the AHCR is well-established in multiple groups, including CaVS patients [11,113-117].

Baseline Measures to Inform Subgroup Analyses

Aside from baseline clinical and demographic information, gender-based pain expectations [118] will be assessed to inform subgroup analyses as evidence suggests that gender-based pain expectations may lead to differences in the experience of pain and related response to interventions [118]. These expectations will be captured using the Gender Role Expectations of Pain (GREP) tool, which captures stereotypic attributions regarding pain endurance, pain sensitivity, and willingness to report pain. The GREP tool has been used in multiple pain investigations [118-123] with acceptable test-retest and internal consistency reliability [118].

Baseline digital literacy will also be assessed using an adapted version of the informational and instrumental support domains of the Patient-Reported Outcomes Measurement Information System (PROMIS) measures. This approach, previously pilot-tested with cardiovascular patients [124], employs five items to examine current level of engagement with mobile and digital technologies.

Follow-Up

The SVN will collect outcome data for intervention and control groups following random allocation through discharge. Once in the community, patients in both groups will record their BPI-SF pain scores daily for 8 weeks using the tablet-based solutions. Data on 30-day event rates (ie, major postop complications) and hospital readmissions for both groups will be collected by a blinded RA via telephone interview at 30 days postoperation. At 3, 6, 9, and 12 months, additional telephone interviews conducted by the RA will assess (1) functional status, (2) depressive symptoms, (3) CPSP, and (4) patient-level cost of recovery (ie, AHCR).

Qualitative Data Collection

To understand patient experience with CaVS recovery and involvement with the SMArTVIEW intervention, we will conduct telephone interviews with 60 patients and 60 primary support persons in the intervention and control groups and with all SVNs (n=20) using a semistructured interview guide. The interviews will focus on perceptions of usability and ethical, social, and legal issues. Our sample size should ensure data saturation [125].

Sample Size

Assuming a two-sided type I error (alpha) of .05 and a standard deviation of 20 points in BPI-SF numeric rating scale scores (range 0-100), a total of 128 participants (ie, 64 individuals in each group) are required to provide 80% power to detect a minimally important difference of 10 points. This difference represents a moderate effect size (Cohen's d=0.50) [126]. Assuming a 10% loss to follow-up, 144 total patients (or 72 per group) is required. We will use this sample size for each site, to allow for site-specific analyses with equal and sufficient power. If there is sufficient homogeneity between the Canadian and UK samples, the combined sample (eg, 256 patients with complete data) would provide 80% power to detect a difference in pain intensity scores of 8.6 points (Cohen's d=0.43), assuming a generous design effect [127] of 1.5 due to the clustering of participants within the site.

Recruitment

Strategies previously developed will be applied [3,6]; RAs will screen preoperative surgical patient lists daily. Anesthesia, CaVS, and medicine services will contact the RAs for all CaVS admissions through emergency and new consultations. Eligible patients will be approached and invited. Patients providing informed consent will be registered via the Interactive Web Randomization System (IWRS), a 24-hour, central, computerized, secure (ie, password-protected), Web-based registration/randomization service at the Population Health Research Institute, and baseline data will be collected. Patients undergoing urgent surgeries will be approached postoperation.

Randomization and Allocation

Blocked randomization (ie, randomly assigned block sizes) will be used to achieve balanced allocation of intervention and control groups. The randomization allocation list will be prepared by Population Health Research Institute statisticians and integrated into the IWRS system. Upon transfer to the surgical ward (ie, post-ICU), the SVN will assess consented patients using the CAM. If CAM scores do not indicate cognitive impairment or delirium and the patient remains eligible, they will be randomly allocated by the IWRS.

Feasibility

Our technology partners have contributed equipment and personnel time, in-kind, such that we are able to intervene and follow up on 15 patients at one time per site throughout the study until 30 days follow-up, at which time equipment will be returned to each hospital site for cleaning and reset. Therefore, the RCT (Phase 2) will be executed in five serial, parallel waves of approximately 30 patients per site. In 2014, there were 2311 and 1974 CaVS performed at Hamilton Health Sciences, Canada, and the Liverpool Heart and Chest Hospital, the United Kingdom, respectively. Planned recruitment will occur at a rate feasible for SVN time and access to the surgical populations at both sites. Patients will be enrolled during a 3-week period, with the last week of each recruitment month available for additional patient registrations as needed to accommodate those not meeting postop eligibility. Each site will target recruitment of 14 cardiac and 16 vascular patients during 3 weeks of recruitment—10 patients per week, per site. Allowing for a 25% refusal rate, lost opportunities, and competing studies, this still provides access to 20 patients at Hamilton Health Sciences and 17 patients at the Liverpool Heart and Chest Hospital. Since participant recruitment is only limited by prototype availability, our proposed recruitment target and timeline is feasible and recruitment of 300 participants will be completed in 10 months' time.

Data Analyses

Primary Analyses

Table 3 summarizes all data analyses. Using the intent-to-treat principle [128], all patients will be included in the final analysis and according to the group to which they were randomly allocated. Descriptive statistics will be used to describe sample characteristics using measures of central tendency and dispersion for continuous factors, and frequencies and proportions for categorical factors. A two-sided significance level of .05 will be used for all inferential analyses. Statistical methods used will depend on the type and distribution of data for the outcome variable under study. If outcome data meet requirements for parametric statistics, a linear mixed model [129] will be used to assess the effects of the intervention on the primary outcome. An a priori contrast of the weekly average worst score for the BPI-SF numeric rating scale *upon movement* (previous 24 hours) will be used to evaluate the primary endpoint of acute postop pain at 30 days postrandomization.

Linear mixed models, using an autoregressive [130] covariance structure—allowing for correlations between measurements to decline as they are further apart in time—will be used to evaluate

within-patient variation in patient-reported outcomes over 12 months of follow-up. Linear mixed models are a flexible and powerful approach to the analysis of data with a complex variance structure, such as correlated data [129-131]. Unlike traditional repeated-measures designs, these models do not require complete data on each patient and have increased statistical power [132]. Nonlinear mixed models will be used in the following cases: (1) if continuous data violate assumptions of normality [132] and (2) for categorical secondary outcomes (eg, adverse event). Chi-square tests of association will be used to assess the association between categorical secondary outcomes identified in the administrative data and intervention. Given that the data is derived from an RCT, complex modeling for these outcomes will not be performed, as potential confounders are considered to be adjusted for in the design. Finally, we will examine patterns of missing data and determine demographic and/or clinical characteristics that are related to missing data at each time point, and the potential impact on the primary findings.

Secondary Analysis

A secondary analysis will aim to establish the cumulative impact of the components of the intervention (eg, remote monitoring and self-management training) on outcomes and assess "digital retention" and sustained digital device usage in visual and time-sensitive analyses using an N-of-1 design (see Table 3). N-of-1 designs use a patient as their own control and can assess the impact of incremental changes with respect to the intervention with frequent and repeated measurements of the outcome variable of interest (ie, pain over time) and are particularly applicable to digital health and mobile phone-based clinical trials [133]. An N-of-1 design allows for association of causality to interventions in real time and direct methods to estimate individual treatment effects and variation per patient. Using the funnel approach, an individual patient is observed repeatedly to graphically demonstrate the variation in pain and HRQL over time [134].

Subgroup Analyses

Two types of separate subgroup analyses are planned to determine the impact of gender-based pain expectations and patient sex on intervention effectiveness (see Table 3):

1. Patients will be stratified into high versus low GREP scores. The primary analyses examining the effect of the intervention on the worst score for the BPI-SF numeric rating scale *upon movement* (previous 24 hours) will be conducted. An interaction term for GREP score (low versus high) and the group allocation will be incorporated into the analyses to determine if gender-based pain expectations are associated with differences in the effect of the intervention on the primary outcome. If a significant interaction is identified, the primary analysis in these two groups will be performed.

2. Similarly, interaction between the intervention and patient sex will be examined.

Cost-Effectiveness Analyses

The cost-effectiveness of implementing the intervention will be determined from two perspectives: (1) the Ministry of Health and Long-Term Care (MoHLTC) (Canada) and (2) society (Canada and the United Kingdom) (see Table 3). Separate analyses will be conducted from each perspective. MoHLTC costs will include costs associated with health service utilization over the study period (eg, hospitalization, emergency room visits, day surgery or procedure, laboratory services, outpatient visits, prescription drugs, and home care services from the Institute of Clinical Evaluative Sciences). Time that health providers (eg, pharmacists) spent on the SMArTVIEW portal will be calculated by multiplying the time with unit costs from standard costing sources in Ontario. From the societal perspective, costs will include those from the MoHLTC perspective, including costs incurred to patients and family members (eg, travel cost and productivity loss), which will be captured through the AHCR.

The first economic analysis outcome is the incremental cost of the intervention compared to usual care. We will analyze the total cost as a dependent variable, using a regression model to estimate the difference in expected health care cost between the two groups. The intervention will be the primary independent variable and the regression model will adjust for potential confounding variables. In theory, an ordinary least squares model produces unbiased estimates even if the data are skewed [135,136]; however, additional estimation methods (eg, generalized linear models) and different uncertainty methods (eg, parametric and nonparametric bootstrapping) will be explored to facilitate investigation of the impact of various cost assumptions.

As a secondary cost objective, we will compare the cost and quality-adjusted life years (QALYs) between the two groups using the net benefit regression framework (see Table 3). QALY is a preference-based utility measure of HRQL, as perceived by the patient, that incorporates both length of life and quality of life into a single measure [137,138]. We aim to determine the incremental net benefit of interventions versus usual care. To estimate QALYs gained, we will convert SF-12v2 data collected to utility scores using a validated algorithm. We will also estimate the incremental cost per QALY gained. A cost-effectiveness acceptability curve (95% CI) will be used to characterize the uncertainty of our findings [139].

Uptake of Technology

Data on uptake of the SMArTVIEW intervention will be used to explain differences in the outcome measures, determine patterns of use to predict outcomes, and identify users who may require escalated care. Session frequency (ie, times the technology is accessed) and session length (ie, length of time users interact with the technology) [140] will be determined via daily metrics of both device and application use. During Phase 1, mPath will identify all key actions of SMArTVIEW to generate a template for relevant data collection at a granular, individual user level.

Table 3. Summary of outcomes, hypotheses, measures, and methods of analysis.

Analyses	Outcome	Hypothesis	Outcome measure	Method of analysis
Primary outcome				
	8-week worst postop pain intensity *upon movement* score in the past 24 hours	Intervention > control	Measured by Brief Pain Inventory-Short Form (BPI-SF[a])	Linear mixed model or nonlinear mixed models (if assumptions of normality are violated)
Secondary outcome				
	Functional status	Intervention > control	Short-Form 12 version 2	Linear mixed model or nonlinear mixed models (if assumptions of normality are violated)
	Depressive symptom scores	Intervention > control	Five-question version of the Geriatric Depression Scale	Linear mixed model or nonlinear mixed models (if assumptions of normality are violated)
	Postop complications related to hemodynamic compromise	Intervention > control	Myocardial infarction and stroke	Nonlinear mixed models
	Other relevant postop complications	Intervention > control	Surgical site infection, presence of CPSP[b]	Nonlinear mixed models
	Heath service utilization-related cost	Intervention > control	Linked with health administrative Institute for Clinical Evaluative Sciences data repository	Linear mixed model or nonlinear mixed models (if assumptions of normality are violated)
	Patient-level cost of recovery	Intervention > control	Ambulatory and Home Care Record	Linear mixed model or nonlinear mixed models (if assumptions of normality are violated)
Subgroup outcomes				
	All outcomes	Effect will differ by gender (male versus female)	Worst postop pain intensity *upon movement* score in the past 24 hours measured by BPI-SF numeric rating scale	Interaction test
	All outcomes	Effect will differ by GREP[c] scores (low versus high)	Worst postop pain intensity *upon movement* score in the past 24 hours measured by BPI-SF numeric rating scale	Interaction test

[a]BPI-SF: Brief Pain Inventory-Short Form.

[b]CPSP: chronic postsurgical pain.

[c]GREP: Gender Role Expectations of Pain.

Qualitative Analyses

Qualitative Description

Data will be digitally recorded, transcribed verbatim, and managed in NVivo 11 (QSR International). Concepts that relate to the usability and value of the intervention will be coded [141] and reviewed by investigators to resolve differences and minimize biases [141]. Revisions to the interview guide and codebook will reflect emerging themes.

Critical Qualitative Analysis

To reveal the ethical, legal, and social implications of the intervention, we will apply methods used successfully in previous research [142]. Following this, data will be re-examined using four bioethical concepts—relational autonomy, care, social justice, and privacy—to draw out the normative implications of the intervention which are sensitive to ethical issues common to at-home care for seniors [143]. A *retroductive* process will be used that involves moving between observations and concepts and allows the interplay between individuals' lives and larger social and contextual forces to be understood [144,145]. The four concepts will not be used simply as containers to categorize data uncritically to aid in the social and ethical analysis of the data. Rigor will be maintained by keeping a reflexive journal and audit trail [141] and ensuring that the purpose of the research, theoretical assumptions, and method of data analysis are congruent [146].

Controls for Bias

To limit sampling bias, a recruitment schedule randomly generated to ensure representation from each surgical group will be used. Contamination should not exist between groups as we will control who interacts with the SVN and intervention features. Those allocated to the intervention group will be asked not to share their tablets or demonstrate application features to any peers assigned to the control group. To evaluate

cointervention, we will track participant receipt of any monitoring or recovery support-related interventions, outside of expected usual care up to 8 weeks postoperation. RAs responsible for outcome data collection will be separated from randomization procedures, will have no permitted access to IWRS, will not be involved in intervention delivery, and will be blinded to group allocation. An event adjudication committee responsible for adjudication of all clinical outcome data will be blinded to randomized allocation. The team has extensive experience with assiduous follow-up procedures to minimize losses to follow-up.

Knowledge Translation

Integrated knowledge translation strategies will continue to involve stakeholder groups during the project. As part of integrated and end-of-grant knowledge translation, stakeholders will assist in interpreting findings, identifying key results, and reviewing and revising the end-of-grant knowledge translation plan at a final meeting for review of investigator results. End-of-grant knowledge translation goals—generate interest, discussion, and awareness; impart knowledge; and inform research—will be addressed via tailored implementation strategies.

Results

Study start-up is underway and usability testing is scheduled to begin in the fall of 2016.

Discussion

THE SMArTVIEW, CoVeRed innovation community brings together an international, dedicated group of well-known clinical and eHealth researchers; health economists; clinicians; administrators; patient representatives; engineers, information technology, and clinical informatics experts; as well as leaders in the arenas of health policy, big data and data aggregation, bioethics, knowledge translation, and privacy. Collectively, we possess the requisite skills, experience, and track record to execute the proposed evaluation, disseminate what we learn, and plan for diffusion of innovation.

We are actively engaged in systems integration and change management at both study sites. As a result of planned, shared stewardship of our vision, we have fostered a milieu of co-ownership and investment in SMArTVIEW usability and effectiveness testing. With respect to end-user engagement, we understand well from experience that innovation is not a linear process. We are committed to recursive coinnovation between "solutioner" and end users. Hence, corefinement of SMArTVIEW— via usability testing in context—was a key objective identified during team debriefing, following our patient journey mapping exercise. Akin to the use of "experimentation suites" in the industry sector, our process, as outlined within the Usability Testing section, will be to immerse with participants in high-fidelity rehearsal of SMArTVIEW activities in order to uncover ways we can refine our processes to optimize the experience of recovery for seniors following CaVS. Our team, including patient representatives, is organized into both content and governance committees (see Table 4).

In collaboration with our industry partners, Canadian and UK hospital sites, we are confident that we have the experience, expertise, infrastructure, and support to realize THE SMArTVIEW, CoVeRed. A copy of our Canadian Institutes of Health Research (CIHR) reviews can be found in Multimedia Appendix 2.

Table 4. SMArTVIEW[a] team committees.

Committee type	Committee name
Content	
	Clinical Transformation/Change Management
	Clinical Monitoring
	Patient Engagement and Experience
	Economics
	Knowledge Translation
	Systems Integration
	Self-Management
	Clinician and SVN[b] Training
	Ethics
Governance	
	Project Office Operations
	International Operations
	Steering
	Outcomes Adjudication
	External Safety
	Efficacy and Monitoring
	Substudy and Publications

[a]SMArTVIEW: Self-MAnagemenT—VIsion for patient EmpoWerment.

[b]SVN: SMarTVIEW Nurse.

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Conflicts of Interest

In-kind industry support is provided by the following industry partners: Philips, QoC Health, XAHIVE, and mPath. The following authors are employed by Philips: Karsten Russell Wood, Michael Weber, Jolene McNeil, and Robyn Alpert. Sarah Sharpe is Co-Founder and shareholder, QoC Health; Sue Bhella is employed by QoC Health. David Mohajer is Co-Founder, Chief Executive Officer, and Vice President, XAHIVE; Sem Ponnambalem is Co-Founder, Chief Operating Officer, and President, XAHIVE. Naeem Lakhani and Rabia Khan are Co-Founders, mPath.

Multimedia Appendix 1

Approach to meta-analysis.

[PDF File (Adobe PDF File), 27KB - resprot_v5i3e149_app1.pdf]

Multimedia Appendix 2

Canadian Institutes of Health Research (CIHR) reviews.

[PDF File (Adobe PDF File), 313KB - resprot_v5i3e149_app2.pdf]

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Abbreviations

AHCR: Ambulatory Home Care Record
BPI-SF: Brief Pain Inventory-Short Form
CAM: Confusion Assessment Method
CARD: Cardiac
CaVS: cardiac and vascular surgery
CIHI: Canadian Institute for Health Information
CIHR: Canadian Institutes of Health Research
CPSP: chronic postsurgical pain
eCC: eCare Coordinator
ECG: electrocardiogram
eTrAC: Transition to Ambulatory Care
EWS: early warning score
GDS-5: five-question version of the Geriatric Depression Scale
GREP: Gender Role Expectations of Pain
HOPE: Help to Overcome Problems Effectively
HR: hazard ratio
HRQL: health-related quality of life
ICU: intensive care unit
iHOPE: Internet-based Help to Overcome Problems Effectively
IWRS: Interactive Web Randomization System
MoHLTC: Ministry of Health and Long-Term Care
N/A: not applicable
PCI: percutaneous coronary intervention
POISE: PeriOperative ISchemic Evaluation
postop: postoperative
PRAS: pain relief after surgery
PROMIS: Patient-Reported Outcomes Measurement Information System
QALY: quality-adjusted life year
RA: research assistant
RCT: randomized controlled trial
SF-12v2: Short-Form 12 version 2
SpO2: peripheral oxygen saturation

SSI: surgical site infection
SVN: SMArTVIEW Nurse
THE SMArTVIEW, CoVeRed: TecHnology-Enabled remote monitoring and Self-MAnagemenT—VIsion for patient EmpoWerment following Cardiac and VasculaR surgery

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Protocol

Using Tablet Computers to Increase Patient Engagement With Electronic Personal Health Records: Protocol For a Prospective, Randomized Interventional Study

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Abstract

Background: Inadequate patient engagement in care is a major barrier to successful transitions from the inpatient setting and can lead to preventable adverse events after discharge, particularly for older adults. While older adults may be less familiar with mobile devices and applications, they may benefit from focused bedside training to engage them in using their Personal Health Record (PHR). Mobile technologies such as tablet computers can be used in the hospital to help bridge this gap in experience by teaching older, hospitalized patients to actively manage their medication list through their PHR during hospitalization and continue to use their PHR for other post-discharge tasks such as scheduling follow-up appointments, viewing test results, and communicating with providers. Bridging this gap is especially important for older, hospitalized adults as they are at higher risk than younger populations for low engagement in transitions of care and poor outcomes such as readmission. Greater understanding of the advantages and limitations of mobile devices for older adults may be important for improving transitions of care.

Objective: To better understand the effective use of mobile technologies to improve transitions in care for hospitalized, older adults and leverage these technologies to improve inpatient and postdischarge care for older adults.

Methods: We will compare an intervention group with tablet-based training to engage effectively with their PHR to a control group also receiving tablets and basic access to their PHR but no additional training on how to engage with their PHR.

Results: Patient enrollment is ongoing.

Conclusions: Through this grant, we will further develop our preliminary dataset and practical experience with these mobile technologies to catalyze patient engagement during hospitalization.

ClinicalTrial: ClinicalTrials.gov NCT02109601; https://clinicaltrials.gov/ct2/show/NCT02109601 (Archived by WebCite at http://www.webcitation.org/6jpXjkwM8)

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KEYWORDS

mobile health; patient engagement; older adults

Introduction

Engagement in Hospital Care and Personal Health Records

Low engagement in discharge planning and poor understanding of discharge medications are major barriers to promoting successful transitions of care for older adults at many US hospitals. As many as 1 in 5 older patients experience an adverse event after discharge, many of which are likely preventable [1-3]. The overall impact of these poor transitions on costs and outcomes of care is also substantial: 15% to 30% of Medicare patients experience unplanned readmissions with related cost exceeding $17 billion annually [4]. Accordingly, a new Medicare policy to reduce readmission rates was introduced as a core cost-saving component of the Affordable Care Act in 2012, and many hospitals have initiated intense efforts to improve transitions of care [5,6]. Many hospitals have deployed discharge coordinators and extended discharge training for hospital staff to improve transitions, but uses of mobile technologies to add or extend the value of these human interventions have been understudied [7,8].

Many existing technology-enabled interventions have relied heavily on provider uses of the electronic medical record (EMR) to increase the completion and accuracy of key transition tasks such as scheduling appointments, communicating with providers, and completing medication reconciliation [9-11]. While EMR-based interventions have been successful in reducing preventable adverse drug events from inaccurate medication reconciliation, they are clinician-centered and do not actively engage patients. This is a missed opportunity not only to enhance patients' understanding of their medication list but also to learn about using their personal health record (PHR) to continue actively monitoring their medication list after discharge. Furthermore, interventions focused only on medication reconciliation do not address other important aspects of care transitions such as managing follow-up appointments, viewing test results, and communicating with providers. An ideal patient-centered mobile health intervention would facilitate patients' ability to view and interact with their medication list as well as empower patients to engage in these other aspects of postdischarge care through active use of their PHR.

Mobile Technology, Hospital Care, and Older Adults

The widespread use of mobile computers (laptops, tablets, and smartphones) in everyday activities has prompted surprisingly few studies of mobile devices in the care of hospitalized patients. Health care provider use of tablet computers to collect clinical registration data, distribute educational materials to patients, or do clinical work (eg, check labs, write notes) has been studied primarily in outpatient settings [12-17]. To date, however, there are very few studies of tablet use by *patients* in the *inpatient* setting, and none have focused on challenges specific to older, hospitalized adults [18]. To address these knowledge gaps, we propose two aims that will create data needed to assess advantages and limitations of these devices and develop a preliminary dataset and practical experience to build and scale innovative approaches to patient engagement during hospitalization.

Study Aims and Project Impact on Patient Care

We propose a structured, tablet-based intervention targeted to older patients (aged 50 years or more) admitted to the medical service to enhance PHR use in both inpatient and postdischarge settings for specific tasks. All participants will receive study tablets and access to their PHR. Intervention patients will receive additional training related to using their PHR for specific tasks such as medication management, making appointments, viewing test results, and communicating with providers.

Aim 1: To Promote Inpatient Engagement With Their PHR During and After Hospitalization.

We will analyze patients' use of their PHR throughout hospitalization and also for 7 days after discharge to determine if our intervention affects likelihood of PHR use to view medications, check lab results, view appointments, or send a provider message.

Aim 2: To Compare Effects of an Inpatient PHR Engagement Intervention to a Virtual Cohort.

We will compare PHR engagement of our study participants to a virtual cohort of patients who were hospitalized but who were already regular users of their PHR. Patients in this virtual cohort will be identified through review of EMR data only and receive no intervention—they will serve as a benchmark for all participants (both intervention and control) in our study.

We hypothesize that those in the intervention group will be more likely than the control group to use their PHR while they are inpatients and after discharge and that patients in both the intervention and control groups will be more likely to use their PHR in these settings than the virtual cohort. In addition to testing these hypotheses, our project is designed to have significant impact on patient engagement with their care during hospitalization at our hospital. We will also add significant value to existing efforts by our health system to increase patient use of existing technologies: our system uses the PHR application called MyChart (Epic Systems Corp), a Web-based patient portal that allows patients to access to their PHR and perform health care tasks such as sending messages to providers, requesting appointments, viewing test results, and reviewing their medications. The overall objective of this research is to study the use of mobile platforms to improve transitions in care for older, hospitalized adults.

Methods

Study Design, Participants, and Setting

This is a prospective, randomized interventional study of tablet computers (iPad 16 GB 3rd generation Model A1430) as a new platform to engage older patients in actively using their PHR during and after hospitalization. We focused on tablet computers because they are light and mobile, which is helpful in the inpatient setting (eg, patients laying in gurneys for hours, patients with limited strength). The PHR used at our institution is mobile-friendly and easily accessible via Web browsers commonly used on tablets, desktops, laptops, and smartphones. We plan to enroll 100 hospitalized patients over 12 months on two general medical units at a large, academic teaching hospital

(University of California, San Francisco [UCSF] Medical Center). We will also leverage EMR data to compare these 100 patients to a virtual cohort of 400 patients with the same inclusion/exclusion criteria who were already engaged in PHR use; patients in this virtual cohort will have no direct involvement in the study and will serve only as a benchmark for engagement by the 100 patients who actively participate in the study.

Each morning, research assistants will screen for new patients through UCSF's electronic medical records by searching for medical service. While our study focus is on older patients (aged 50 years or more), we will also enroll patients younger than 50 years in order to compare and contrast patterns of use between these groups. We will include adult, English-speaking, cognitively intact patients on the medical service. To ensure patients selected will be able to use the iPad, we will exclude patients who are reported by the medical team to be cognitively impaired, blind, deaf, or involuntarily hospitalized because of mental illness. We will also exclude those who are unable to understand the study and consent to participation or who are otherwise excluded at the discretion of their medical team.

Randomization and Intervention

To randomize patients into intervention and control groups, we used an Internet-based coin toss random number generator (Random.org). The research assistant performs this randomization process after patient screening and consent. If the result of the coin toss is heads, the patient is enrolled in the intervention arm; if the result is tails, the patient is enrolled in the control arm. Patients were enrolled Monday through Friday only, no weekends or holidays.

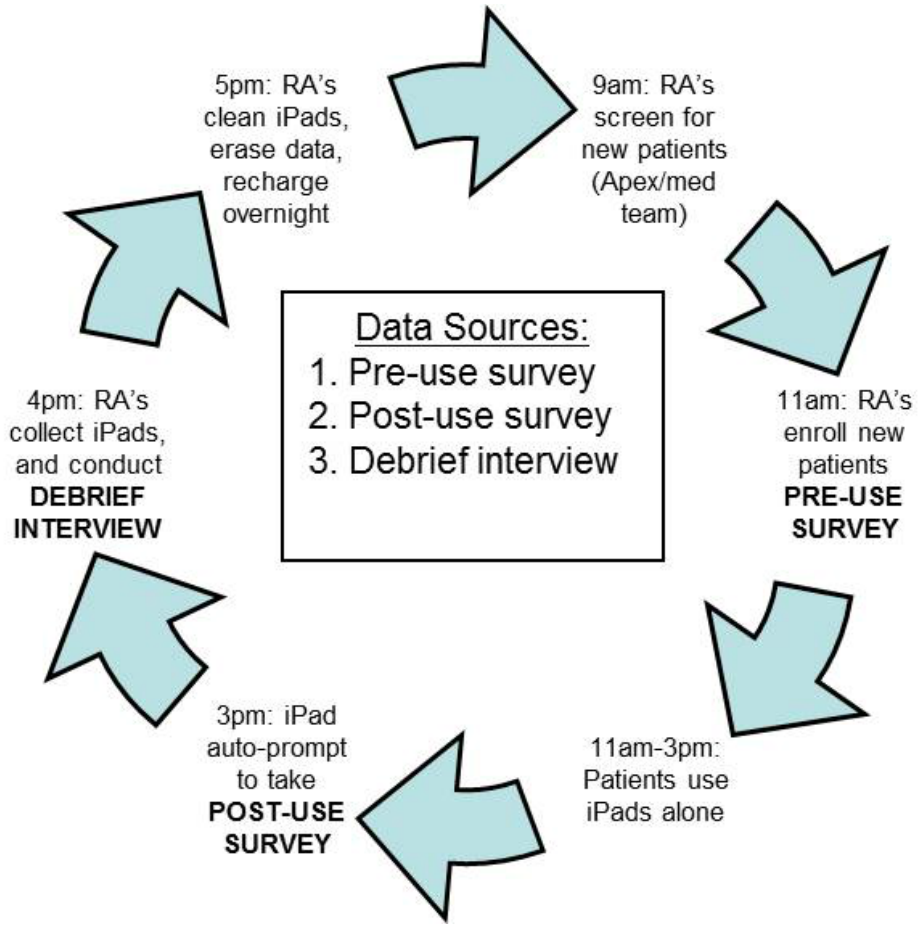
Our project will provide all study participants with tablets and access codes to MyChart while they are hospitalized. Intervention patients will also receive bedside training from study research assistants on key functions of MyChart including how to view medication lists (see Multimedia Appendix 1). Through our preliminary work, we have created a semistructured tutorial for this bedside training that assistants can administer to patients. While this tutorial allows for a basic level of content uniformity for all patients, it is flexible enough to allow assistants to speed up or slow down or otherwise tailor the depth of explanation to the needs of each individual patient (see Multimedia Appendix 2). This study was approved by the UCSF Institutional Review Board and registered at Clinicaltrials.gov [NCT02109601].

Data Collection and Sources of Data

After creating a list of eligible patients, research assistants will approach medical teams during rounds (9:00 AM to 11:00 AM) to ensure that screened patients do not have exclusion criteria (Figure 1). The assistants will then approach patients to explain the study, including basic instructions for tablet use (on/off, opening/closing applications, and typing with touchscreen); intervention patients only will receive additional instruction in the form of the semistructured tutorial. The assistant will then leave the device with the patient and return to recollect it after about 4 to 5 hours. The assistant will perform a debrief interveiw upon return and ask patients to view and verify their preadmission medications using the medication list in their PHR. Success (gross pass/fail) in this task will be defined as patient ability to independently log in, locate their medication list, and verify their prehospitalization prescriptions (MyChart does not show inpatient medications unless they are continued at discharge). We will not require patients to correctly describe indications for every medication to receive credit; they will only be asked to identify which medications are familiar to them and which are not. We will use frequency analysis to compare the percentage of intervention group who are able to complete this task with the control group.

Sources of data will include surveys that will be administered on the device, semistructured debrief interviews administered by assistants, and data on postdischarge access to the PHR from our EMR data repositories. All patients will answer basic questions about demographics, health literacy, and technology use in a preuse survey. The postuse survey will ask about satisfaction with the device to access their PHR and any technical issues. We have developed an interview tool for assistants to use to collect information about patient-reported problems with devices and ask open-ended questions about the overall experience using the tablet. During the debrief interview, the assistant will also ask the patient to demonstrate ability to access their PHR to view and verify their preadmission medications using their PHR medication list. Data about patient use of their PHR is compiled by our EMR in a searchable database (Clarity). We will query Clarity at 7 days to determine access and specific PHR tasks accomplished by all patients both during their hospital stay and for 7 days after discharge. We will also use the Clarity database to identify our virtual cohort of patients who were already engaged with their PHR (1 or more log-ins in the month prior to hospitalization) and were hospitalized during the same 12-month period of our study.

Figure 1. Inpatient iPad tablet daily workflow.



Data Analysis

Our overall objective is to assess whether inpatients can successfully use iPads for clinically useful tasks such as viewing their medications or labs or messaging their providers by using their PHR. First, we will assess this overall goal using descriptive statistics (frequency analysis) to describe time required to orient patients to tablets and basic use metrics for PHR (time spent using PHR, number of PHR tasks observed by assistant, etc). Next, we will determine the total number of log-ins to the PHR and number of clicks on different domains of the PHR (medications, labs, appointments) by querying the PHR database. We will extract basic information about whether each patient has accessed their PHR (successful log-in), when they first logged in (time from discharge), and how many times they logged in. Additionally, we will extract information about specific tasks accomplished at any point during both inpatient and postdischarge periods. We will use frequency analysis to compare the following for intervention versus control patients: rates of PHR access, time to first log-in, total number of log-ins, and number of specific tasks (refill prescription, make/change appointment, view test result, or send message to provider) accomplished within 7 days. Finally, we will assess patient satisfaction with devices overall and PHR use specifically. We will perform bivariate analyses (chi-square tests) to determine whether ability to perform key PHR tasks (eg, view medications or lab results) vary according to demographics such as age, gender, health literacy, or technology usage (eg, types of devices owned, frequency of Internet use). Although most of our findings will be descriptive, we plan to enroll 100 patients to enable detection of a 10% difference in ability to perform a key inpatient task (medication verification) and one of several key postdischarge PHR tasks (80% power, 2-sided alpha 0.05).

Results

Preliminary data from our protocol are show in Table 1. To date, we have enrolled 45 patients; approximately half our sample comprises older adults (50-79 years, 22) and about half (24) are female. Most participants reported owning a laptop computer (34, 75%) or smartphone (29, 64%); desktop and tablet computer ownership were lower at 54% (24) and 51% (23), respectively. A strong majority of patients (39, 86%) indicated they access the Internet daily. While 82% (37) reported looking up health information for themselves on the Internet in the past 12 months, only slightly more than half (27, 59%) had used the Internet to communicate with a health care provider and few had used it to schedule a medical appointment (18, 40%) or refill a prescription (17, 37%).

Table 1. Participant characteristics (n=45).

	n (%)
Age (years)	
18-39	9 (19)
30-49	14 (32)
50-79	22 (49)
Gender	
Female	24 (53)
Male	19 (42)
Declined/no response	2 (4)
Device ownership	
Desktop computer	24 (54)
Laptop computer	34 (75)
Smartphone	29 (64)
Tablet computer	23 (51)
Internet use	
Daily	39 (86)
Several times a week	3 (6)
Once a week or less	1 (3)
Prestudy online health tasks	
Looked up health information	37 (82)
Communicated with provider	27 (59)
Scheduled medical appointment	18 (40)
Refilled prescription	17 (37)
Orientation to iPad	
Required 15 minutes or less	36 (81)
Required 16 to 30 minutes	4 (9)
Required 30 minutes or more	5 (10)
Independently access/navigate PHR on iPad	
Log in/verify info	28 (62)
Medications list page	34 (76)
Medications refills page	18 (40)
Scheduled appointments page	38 (85)
Test results page	38 (85)
Secure messaging page	37 (82)

Among older adults, 70% (15) owned a laptop, 58% (13) owned a desktop computer, 52% (11) owned a smartphone, and 42% (9) owned a tablet. Thus, mobile technologies pose an excellent venue to interact with this patient population. Trained research assistants spent at least 30 minutes with those patients who needed more assistance to become familiar with the tablets, but the majority needed 15 minutes or less, suggesting that most of them felt comfortable with using this technology. Indeed, our findings to date suggest that inpatients of all ages in both intervention and control groups require only minimal orientation from research assistants to use basic (eg, access Internet, check email) as well as more advanced functions (watch videos, complete tasks requiring more advanced navigation): 90% (41) of patients required 30 minutes or less for device orientation and 81% (36) required 15 minutes or less. Additionally, we found that after focused bedside teaching, most patients in our study were able to perform one or more key function in their PHR. These key functions included viewing their medication list (34, 76%), viewing scheduled appointments (38, 85%), viewing test results (38, 85%), and sending a secure message to their primary care provider (37, 82%). Additionally, 75% (34) reported they were satisfied or very satisfied with iPad

tablet use for bedside access to their PHR to accomplish these tasks.

Because data is still being collected to compare patient groups within our study (intervention vs control), we compared PHR use among all participants (to date) in both groups to a virtual cohort of patients identified as regular users of their PHR prior to hospitalization. In most areas, both groups were similar, but our study group had significantly higher activity in medication list views (mean 2.12 views vs 1.07) and the virtual cohort had significantly higher use of the provider messaging function (mean 4.34 views vs 1.63) (Table 2).

Table 2. Patient characteristics and PHR use in study participants compared to a virtual cohort of regular PHR users.

	Study group (n=45)	Virtual cohort (n=400)	*P* value
Inpatient characteristics			
Hospital length of stay, days	5.79	4.51	.37
Previous PHR experience, n (%)	22 (50)	400 (100)	<.01
PHR use during hospitalization			
Logins per person, mean	2.74	2.99	.64
Medication tab views, mean	2.12	1.07	<.01
Test results tab views, mean	1.42	2.21	.28
Appointments tab views, mean	0.69	1.34	.11
Provider messaging inbox views, mean	1.63	4.34	.04
PHR use after hospitalization (up to 7 days after discharge)			
Logins per person, mean	4.04	3.87	.83
Medication tab views, mean	2.93	1.46	<.01
Test results tab views, mean	6.28	4.29	.37
Appointments tab views, mean	2.72	2.01	.32
Provider messaging inbox views, mean	3.91	6.11	.36

Table 3. Adjusted PHR use during hospitalization by study group compared to virtual cohort group.

	Multivariable logistic regression[a]	
	OR for study group vs virtual cohort group mean	95% CI
Medication tab views	2.4	1.5-4.2
Test results tab views	1.1	0.7-1.8
Appointments tab views	0.71	0.5-1.1
Provider messaging inbox views	0.70	0.5-1.1

[a]Adjusted for age, gender, race/ethnicity, length of stay, and prior PHR experience.

In analyses adjusted for confounding, the higher rate of provider messaging seen in Table 3 disappeared with adjustment; however, the higher rate of medication list views persisted (odds ratio [OR] 2.4) (Table 3). In adjusted analyses of PHR use after discharge, there were no significant differences between the virtual cohort and the study group.

Discussion

Principal Findings

Our preliminary findings demonstrate relatively high ownership and use of mobile devices among all patients (including those over age 50 years) and relatively low use of these devices for specific health care tasks that can be accomplished via patient PHRs. This gap between high device ownership/use and low engagement in PHR confirms a pattern seen in our previous work and suggests an opportunity to intervene in order to increase PHR engagement during and after hospitalization [19]. Regarding device use, national data from the Pew Research Center show that 55% of all adults own a smartphone and 43% own a tablet; our study shows higher rates, at 64% (29/45) for smartphones and 51% (23/45) for tablets [20]. Although this is only half of our planned total enrollment, this difference in level of tech-savviness may limit the generalizability of our results to less tech-savvy populations if these trends persist in our final sample.

Although we do not yet have data to report on differences between our intervention and control group, we are able to do some preliminary comparisons between both groups (all of whom received a tablet and assistance logging into their PHR) and a virtual cohort of patients who were regular PHR users but received neither tablets nor PHR assistance during

hospitalization. Our findings to date show that patients in our study were more likely to use their PHR for viewing the medications during hospitalization. These findings suggest that providing tablets and even basic PHR assistance for patients in the hospital may be an intervention that can improve engagement among inpatients to resemble patterns seen in a group of patients who were already engaged in using their PHR before hospitalization. Once final data collection and analysis are complete for our study, we will explore differences between intervention and control patients and compare each group separately to the virtual cohort as a benchmark for PHR engagement.

Strengths

While our results are preliminary, we believe this project has potential to be innovative in several ways. First, our study will be one of the first to explore a patient-centered mobile health approach to engage adult patients in hospital and postdischarge settings. Furthermore, by exploring patient experiences with mobile devices, our research will enable us to carry out future projects to engage hospitalized patients in a variety of tasks. For example, we would like to build on experience from the current project to use patient PHRs at bedside in the hospital for more advanced discharge planning in coordination with multidisciplinary team rounds. Finally, our focus on older adults is especially important as they represent a large portion of our health system's inpatient population, they are at particularly high risk for poor outcomes of transition care, and they are the least likely to be familiar with their PHR or to use it meaningfully without targeted interventions.

Limitations

Despite these strengths, our study has several limitations which will be important to contextualize our preliminary and final results. First, this is a relatively small study (planned enrollment of 100) which may limit our ability to detect small differences between the intervention and control groups. Second, there may be participation bias in our sample as our preliminary data suggest participants to date have been more tech-savvy than national data (ie, it may be that less tech-savvy patients are less inclined to agree to participate). Third, we did not include education or income in our survey instruments so we will not be able to determine to what extent these factors explain the tech-savviness of our participants, although we will be able to extract other traditional determinates of low technology use such as race/ethnicity and payer status (eg, Medicaid vs Medicare or private insurance) from our EMR for final analysis. Finally, we did not conduct postdischarge interviews so we do not know how patient perspectives on using their PHR might change over time; this is an important question for future studies. Future studies may also consider following patients for longer than 7 days after discharge (eg, 30 days), although we did not find any significant results at 7 days so stronger postdischarge reinforcement may be needed for future hospital-based interventions to create lasting impact.

Conclusions

We have designed a protocol to examine whether the provision of tablet computers and varying levels of PHR assistance (log-in only for control, extensive guidance for intervention) can improve inpatient use of their PHR to engage in hospital care. Our preliminary results suggest that learning about the device is not a significant barrier and that all patients actively enrolled (intervention and control) use their PHR at rates similar to a passively enrolled virtual cohort of patients who were already engaged with their PHR. Our final results will examine whether the intervention patients are different than control patients in terms of inpatient and postdischarge use of their PHR or whether the mere provision of tablets and log-in assistance in the hospital might be enough to explain higher PHR engagement in these patients. Our results are designed to have real-world impact at our medical center and may have important applications for many other medical centers and health systems that are searching for effective implementation strategies to increase patient engagement with PHR systems already in use in their facilities.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Study protocol details.

[PDF File (Adobe PDF File), 54KB - resprot_v5i3e176_app1.pdf]

Multimedia Appendix 2

Debrief interview data collection tool example.

[PDF File (Adobe PDF File), 59KB - resprot_v5i3e176_app2.pdf]

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Abbreviations

EHR: electronic health record
OR: odds ratio
PCR: personal health record
UCSF: University of California, San Francisco

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Protocol

Dementia and Traffic Accidents: A Danish Register-Based Cohort Study

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Abstract

Background: As a consequence of a rapid growth of an ageing population, more people with dementia are expected on the roads. Little is known about whether these people are at increased risk of road traffic-related accidents.

Objective: Our study aims to investigate the risk of road traffic-related accidents for people aged 65 years or older with a diagnosis of dementia in Denmark.

Methods: We will conduct a nationwide population-based cohort study consisting of Danish people aged 65 or older living in Denmark as of January 1, 2008. The cohort is followed for 7 years (2008-2014). Individual's personal data are available in Danish registers and can be linked using a unique personal identification number. A person is identified with dementia if the person meets at least one of the following criteria: (1) a diagnosis of the disease in the Danish National Patient Register or in the Danish Psychiatric Central Research Register, and/or (2) at least one dementia diagnosis-related drug prescription registration in the Danish National Prescription Registry. Police-, hospital-, and emergency room-reported road traffic-related accidents occurred within the study follow-up are defined as the study outcome. Cox proportional hazard regression models are used for the main analysis.

Results: Our study protocol has 3 phases including data collection, data analysis, and reporting. The first phase of register-based data collection of 853,228 individual's personal information was completed in August, 2016. The next phase is data analysis, which is expected to be finished before December 2016, and thereafter writing publications based on the findings. The study started in January 2016 and will end in December 2018.

Discussion: This study covers the entire elderly population of Denmark, and thereby will avoid selection bias due to nonparticipation and loss to follow-up. Furthermore, this ensures that the study results are reliable and generalizable. However, underreporting of traffic-related accidents may occur, which will limit estimation of absolute risks.

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KEYWORDS

dementia; accidents; traffic; comorbidity; epidemiology; public health

Introduction

Background

The elderly population is rapidly increasing globally as a result of extended life expectancy due to the success of social, medical, and economic development [1,2]. Consequently, ageing brings societal challenges due to the increase in the proportion of elderly people with chronic diseases including dementia [3].

Dementia is one of the major causes of functional disabilities and dependency among elderly people [4-6]. It is a symptomatic decline in cognitive ability severe enough to affect daily activities, and is usually irreversible, accumulative, and age-dependent [7]. Alzheimer disease and vascular dementia are the most common causes of dementia, other diseases and injuries to the brain are also contributing factors [8].

The prevalence of dementia is expected to increase substantially in parallel with elderly population growth [9]. By 2050, there will be a projected 135 million people suffering from dementia worldwide [3]. Denmark is facing the brunt of the dementia epidemic, an approximately 150,000 Danes are estimated to be afflicted with dementia by 2040, which is nearly doubled than of 2015 [10].

Elderly people in Denmark tend to choose cycling, walking, and private motor vehicles, as their daily mode of transportation [11]. Hence, leading society to a growing concern regarding road traffic-related accidents risk among those suffering from dementia in the coming years. The Statistics Denmark (DST) reported a total of 3375 road traffic-related accidents, including 182 fatal accidents occurring in 2014. Of those accidents, 15% of total and 32% of fatal accidents occurring among people aged 65 or older [12]. Dementia-related accidents within this group of people have never been well reported in Denmark.

However, older people do not necessarily pose an increased risk of traffic accidents as compared with other age groups, as age itself is a poor indicator of movement competence due to individual practice, experience, and general functioning skills being different [13]. However, dementia as a cognitive impairment disorder may affect vision, balance, judgement, perception, motor skills, and problem-solving, therefore it could increase the risk of traffic accidents [14]. Certain people with mild dementia however may still be capable of conducting themselves safely in traffic, at least for a certain period of time [15]. But, it is worth noting that motor skills are deteriorating, depending on the type and the severity levels of the dementia onset, and therefore the risk of accidents may vary [16,17].

Relatively limited numbers of studies have investigated dementia for the risk of traffic accidents, but with inconsistent results. Among published studies, approximately 2 to 10 times higher risks of crashes for people with dementia have been reported [18-21]. However, some others have reported no significant risk difference between people with dementia and their controls [22,23]. Despite traffic accidents being infrequent among elderly people, heterogeneity, small study population, and the quality of accident reporting, justify further studies into dementia and traffic accidents. Nationwide cohort studies with register-based information including exposures, confounders, and various health-related outcomes may fill these gaps.

A population-based Swedish study from 2013 with a sample size of more than 6.9 million people aged 20 years or older, found that the risk of total accidental deaths, including falls, suicides, transport accidents, and accidental poisoning, was 6- to 7-fold higher among people with dementia compared with the general population during 8 years of follow-up [24]. However, the Swedish study only measured accidental death, and therefore this study was not able to identify risk for nonfatal traffic accidents. Additionally, the Swedish study did not adjust for chronic illnesses and possibly harmful medications (eg, tranquillizers and sleeping medication) that may potentially affect the accidental risk [25].

Dementia is often comorbid with other chronic diseases, and the risk of having multiple morbidity increases with age [2,26]. In primary care in America, there is an average of 2.4 additional chronic diseases and above 5 prescribed medications associated with dementia patients aged 65 or older [27]. In Scotland, only 5.5% people with dementia had no other chronic diseases [28]. Sharing some common risk factors and pathophysiological mechanisms such as inflammation and endothelial dysfunction may be one of the reasons for coexistence of multiple chronic diseases, other factors may also play a role [29].

National prevalence of dementia-related comorbidity in the elderly population in Denmark is unclear. However, depression, Type 2 diabetes (T2D), ischemic heart disease (IHD), and chronic obstructive pulmonary disease (COPD), are among the 10 most common chronic diseases among Danish patients, and have been found as independent risk factors for the development of dementia, and can even exacerbate dementia [30-37]. For instance, a systematic review with 17 cohort studies reported that depression, especially late-life depression, was associated with a significant risk of dementia (pooled risk=1.59, 95% confidence interval (CI)=1.41-1.80) [32]. Another meta-analysis with 19 population-based longitudinal studies found a 2- to 3-fold higher risk of developing dementia with diabetes [38].

Moreover, these chronic diseases have also been reported as independent risk factors for traffic accidents [24,39-41]. A structure review with 7 studies found increased odds, or risk ratios of crashes ranging from 1.9 to 7.7 for people with post stroke [42]. Given that the combined effects of those chronic diseases are higher than single or additive effects [43,44], it is possible that dementia accompanied with other chronic disorders can pose an even higher risk of traffic accidents, and chronic disease-related medications may modify the risk estimations. However, to date, those issues have not been studied in much detail elsewhere, or in Denmark.

Aims of the Study

This study protocol overall aim is to investigate the risk of road traffic-related accidents for people aged 65 years or older with diagnosis of dementia in Denmark. The following will be investigated: (1) the risk of road traffic-related accidents among older people with and without dementia, (2) the effect modification of dementia and association with the risk of road traffic accidents by comorbidities, and (3) the effect modification

of dementia and association with the risk of road traffic accidents by sedative prescription medications.

Methods

Study Design and Population

The study is designed as a register- and population-based cohort study consisting of all residents in Denmark aged 65 years or older as of January 1, 2008 (n=853,228). These people are followed for 7 years from baseline until December 31, 2014 to assess the incidence of road traffic-related accidents attributable to a dementia diagnosis. The follow-up period of 7 years is chosen because (1) the median survival time for people with dementia in Denmark is 6.6 years; this is slightly longer than other countries (median ranged 3.2-6.6 years) [45,46], and (2) the validity of the dementia diagnosis in recent years has increased and therefore is more accurate from 2008 compared with earlier registration [47-50].

Data Sources

Personal-level data are available in the Danish Civil Registration System (CRS) [51]. This registry electronically records the name, address, migration, marital status, date of birth, place of birth, date of death, and other basic information on all residents in Denmark since 1968. Using a unique 10-digit Civil Personal Register (CPR) number assigned to each individual at birth, or to a person who holds a Danish residence upon immigration, one can access an individual's information in all national registers, hospitals, general practitioners, police offices, and other authorities in Denmark.

Assessment of Dementia and Comorbidity

Dementia and subtype of dementia including Alzheimer's disease [52], vascular dementia [53], frontotemporal dementia [54], dementia with Lewy bodies [55], mixed dementia [56], Parkinson's disease [57], and dementia without specification, are identified by any primary and secondary diagnosis in the Danish National Patient Register (NPR) (Table 1), or in the Danish Psychiatric Central Research Register (PCRR) [58,59].

International Classification of Diseases versions 10 codes (ICD-10) are used for disease classification in the registers. Additionally, the prescription of antidementia drugs and the corresponding Anatomical Therapeutic Chemical (ATC) codes (Multimedia Appendix 1) from the Danish National Prescription Registry (DNPR) are also used to identify people with dementia disorders [60].

To more accurately define the earliest date of a dementia diagnosis, the diagnosis is dated back to either the first inpatient or outpatient record ever mentioning dementia or the first prescription of antidementia medication since the inception of the DNPR, whichever comes first. A person is identified with dementia if this person meets at least one of the following criteria: (1) a diagnosis of disease in NPR or in PCRR, and/or (2) at least one antidementia drug registration in DNPR.

Table 1. *International Classification of Diseases*, Tenth Revision (ICD-10) codes for dementia and other chronic disease[a] diagnoses in Danish health registers.

Diseases		ICD-10 codes
Dementia		
	Alzheimer's disease	F00.0, F00.1, F00.2, F00.9, G30.0, G30.1, G30.8, G30.9
	Vascular dementia	F01.0, F01.1, F01.2, F01.3, F01.8, F01.9
	Frontotemporal dementia	F02.0
	Dementia with Lewy bodies	G31.83
	Mixed dementia	
	Parkinson's disease	F02.08
	Dementia without specification	F03.9
Other chronic diseases		
	Type 2 diabetes	E11
	Chronic obstructive pulmonary disease	J44
	Ischemic heart disease	I20–I25
	Depression	F32-F33
	Hypertension	I10, I15
	Stroke	I60-I69
	Atrial fibrillation	I48
	Asthma	J45

[a]The inclusion criteria for the chronic illness are based on the 10 most common chronic conditions among Danish patients [61], as well as prior studies that found that those diseases are both linked to dementia [62-67], and traffic accidents [42,68].

In this study, comorbidity is defined as a person with at least 2 chronic diseases as listed in Table 1. For chronic disease ascertainment, we apply a similar assessment procedure as with dementia. A person is identified with a specific chronic disorder if this person had a diagnosis of disease in NPR or in disease-specified register if available (Multimedia Appendix 2). Because there is no such registration regarding the exact time when the chronic disease symptoms began, we use the date of registration and/or drug prescription as the initial time point for dementia onset and the comorbidity. Therefore, if the date of registration for any of the comorbidities has been recorded prior to the date of dementia registration, we consider the comorbidity has occurred before onset of dementia, and vice versa.

Study Outcomes Ascertainment

The primary outcome (time to first road traffic-related accident event) is Danish police-reported road traffic accidents including minor injuries, serious injuries, and fatal accidents caused by road traffic during the study follow-up interval. The information such as the date, location, and type of traffic accident is recorded in DST. Because some traffic injuries may only be registered by the hospital or emergency room without being reported to the police, any hospital or emergency room diagnosis representing road traffic accident (ICD-10 codes V00-V89, V98-V99) within the study follow-up period in NPR is supplementary being assessed.

Other Covariates

Age, sex, education, marital status, geographic location, and living in a nursing home are examined as predictors and adjustment variables based on prior knowledge in the present study. Those data are available in CRS and in DST. Driving experience (eg, the years of holding a valid driver license) as one of the potential confounders will also be included in the sensitivity analysis if possible. The chronic disease-related medications that impair ability to drive are addressed as covariates in our study and ascertained by the information of side effects from the drug labelling (Multimedia Appendix 3). If medication involvement in the analysis gets too complicated, we will begin with the most common drugs for the listed chronic diseases.

Statistical Analyses

For aims 1, 2, and 3, the relation between a diagnosis of dementia, or of selected comorbid chronic diseases, as well as antidementia medication, and the incidence of traffic accidents, will be analysed in Cox proportional hazard (Cox) regression models. The total period at risk for a person is the time from January 1st, 2008 until the first occurrence of a traffic accident, death, emigration or end-of-follow-up at December 31st, 2014, whichever comes first; the latter 3 occurrences are censoring events. Dementia, and the other selected comorbid conditions, will be modelled as time-varying covariates in that persons contribute to “nondiagnosed” person-years before and “diagnosed” person-years after the first occurrence of the corresponding diagnosis.

The magnitude of the associations will be reported as hazard ratios (HRs) with 95% CIs. The associations of dementia and other selected comorbid conditions with a traffic accident incidence will be adjusted for several potential confounders in multivariable Cox regression models: age, sex, education, marital status, geographic location, living in a nursing home, medication, and Charlson comorbidity index (CCI) [69]. The proportional hazard assumption will be evaluated by adding interaction terms between the logarithm of time and the independent variables to the model; a joint test for these interaction terms evaluates the proportional hazard assumption.

By the addition to the model of interactions between the selected chronic disorders and the dementia diagnosis, we will investigate a possible differential effect of dementia on the incidence of traffic accidents depending on the aforementioned factors. The different impacts of dementia for the different levels of the corresponding interacting variable will be recorded, and the differences will be evaluated for statistical significance.

Study Power Calculation

There were 6323 road traffic accidents (including injuries and fatalities) in 2008 in Denmark, which represented 1.16‰ (6323/5,475,791) of the total population (DST 2008). If we assume that there is a 1% prevalence of dementia in the Danish population (which is lower than the 1.53% that Alzheimer Europe has estimated for 2012) [70], we can, with nationwide data, detect a traffic accident incidence increase from 1.16‰ for those without dementia to 1.60‰ for those with dementia with 80% power and 5% significant level.

There were 661 road traffic accidents in 2008 among people aged 65 years and over in Denmark, which represented 0.78‰ (661/853,041) of people aged 65 and over in Denmark (DST 2008). If we assume that there is a 7% prevalence of dementia in this age group [10,71,72], we can, with these data, detect a traffic accident incidence increase from 0.78‰ for those without dementia to 1.13‰ for those with dementia with 80% power and 5% significant level.

All statistical tests will be two-sided and use a significance alpha level of 5%. STATA 14.0 will be used for all statistical analysis.

Ethical Consideration and Dissemination

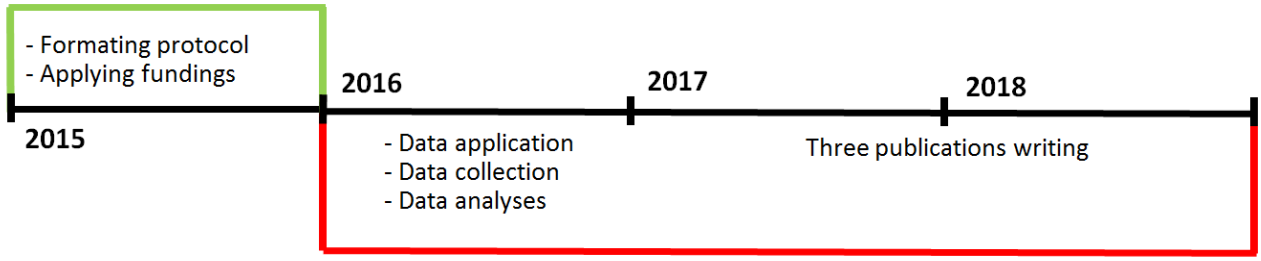
The study protocol was approved by the Danish Data Protection Agency for data permission as well as for ethical considerations (J.no. 2016-41-4674).

Results

This 3-year PhD study is planned from January 1, 2016 to December 31, 2018. The study timeline is illustrated in the Figure 1. At the current stage, we have finished the data collection, and are beginning the data analysis.

Three publications are planned within the protocol. The publication titles at the current stage can potentially be: (1) The risk of road traffic-related accidents among people with dementia, (2) The modification of the dementia and association with the risk of road traffic accidents by comorbidities, or (3) The modification of the dementia and association with the risk of road traffic accidents by sedative prescription medications.

Figure 1. The study timeline.



Discussion

Strengths and Limitations

This is the first study to evaluate elderly people with dementia and the link to transport safety injuries in Denmark. With our objectives, we are expecting to find an association between the onset of dementia and the risk of traffic-related accidents among people aged 65 or older.

Denmark is internationally recognized for having rigorous registrations of data regarding many activities. Using nationwide register data to examine the association between dementia and the risk of traffic-related accidents with an entire national elderly population is a major strength of our study, as selection bias due to nonparticipation or loss to follow-up is negligible [47]. The health care system is free of charge and all citizens have equal access to it. Hence, our study results are more reliable and generalizable than those of previous studies with limited sample sizes or case-control designs.

However, underreported traffic-related accidents might occur, and this may limit our risk estimation. It seems a common social norm is that, with very minor traffic accidents such as scratches, the drivers tend to negotiate between each other rather than to rush to report to the police. Nevertheless, using police and hospital, as well as emergency room-registered road traffic accidents, the present study has much more complete data than previous studies on a similar topic.

Implications

Transportation in an ageing society is a general challenge, and it is considered appropriate to actively engage people with dementia and their families in social chores. But the traffic risk has not been well assessed. Therefore, this study may identify the magnitude of traffic accident risk among people with dementia in order to provide initiatives for reducing this potential risk.

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Authors' Contributions

Frans Boch Waldorff initiated the project and guided throughout the protocol writing process. Jindong Ding Petersen wrote the protocol. Volkert Siersma advised and drafted the statistical analysis including a power calculation. Connie Thurøe Nielsen and Mikkel Vass gave academic suggestions for the project. All the authors have approved the protocol for publishing.

Conflicts of Interest

None declared.

Multimedia Appendix 1

ATC-codes for drugs in the Danish National Prescription Registry.

[PDF File (Adobe PDF File), 31KB - resprot_v5i3e191_app1.pdf]

Multimedia Appendix 2

Overview of databases and indicators for data assessment.

[PDF File (Adobe PDF File), 24KB - resprot_v5i3e191_app2.pdf]

Multimedia Appendix 3

Medicines labelled with side-effects as impaired driving ability.

[PDF File (Adobe PDF File), 47KB - resprot_v5i3e191_app3.pdf]

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Abbreviations

ATC: anatomical therapeutic chemical

CCI: Charlson comorbidity index
CI: confidence interval
COPD: chronic obstructive pulmonary disease
Cox: Cox proportional hazard
CPR: Civil Personal Register
CRS: Danish Civil Registration System
DNPR: Danish National Prescription Registry
DST: Statistics Denmark
HRs: hazard ratios
ICD-10: *International Classification of Diseases, Tenth Revision*
IHD: ischemic heart disease
NPR: Danish National Patient Register
PCRR: Danish Psychiatric Central Research Register
T2D: type 2 diabetes

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Protocol

A Cross-Sectional Comparison of Druggable Mutations in Primary Tumors, Metastatic Tissue, Circulating Tumor Cells, and Cell-Free Circulating DNA in Patients with Metastatic Breast Cancer: The MIRROR Study Protocol

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Abstract

Background: Characterization of the driver mutations in an individual metastatic breast cancer (MBC) patient is critical to selecting effective targeted therapies. Currently, it is believed that the limited efficacy of many targeted drugs may be due to the expansion of drug resistant clones with different genotypes that were already present in the primary tumor. Identifying the genomic alterations of these clones, and introducing combined or sequential targeted drug regimens, could lead to a significant increase in the efficacy of currently available targeted therapies.

Objective: The primary objective of this study is to assess the concordance/discordance of mutations between the primary tumor and metastatic tissue in MBC patients. Secondary objectives include comparing the genomic profiles of circulating tumor cells (CTCs) and circulating free DNA (cfDNA) from peripheral blood with those of the primary tumor and metastatic tissue for each patient, evaluating these mutations in the signaling pathways that are relevant to the disease, and testing the feasibility of introducing liquid biopsy as a translational laboratory tool in clinical practice.

Methods: The multicenter, transversal, observational MIRROR study is currently ongoing in three participating hospitals. All consecutive patients with MBC confirmed by radiologic findings will be screened for eligibility, either at first relapse or if tumor regrowth occurs while on treatment for metastatic disease.

Results: Patient recruitment is currently ongoing. To date, 41 patients have a complete set of tissue samples available (plasma, CTCs, and formalin-fixed, paraffin-embedded primary tumor and metastatic tumor). However, none of these samples have undergone nucleic acids extraction or targeted deep sequencing.

Conclusions: The results of this study may have a significant influence on the practical management of patients with MBC, and may provide clues to clinicians that lead towards a better stratification of patients, resulting in more selective and less toxic treatments. Additionally, if genomic mutations found in metastatic tissues are similar to those detected in CTCs and/or cfDNA, liquid biopsies could prove to be a more convenient, non-invasive, and easily accessible source of genomic material for the analysis of mutations and other genomic aberrations in MBC.

Trial Registration: ClinicalTrials.gov NCT02626039; https://clinicaltrials.gov/ct2/show/NCT02626039 (Archived by WebCite at http://www.webcitation.org/6jlneVyoz)

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KEYWORDS

breast neoplasm; drug therapy; genetics; molecular targeted therapy; sequence analysis.

Introduction

Characterization of the driver mutations in an individual metastatic breast cancer (MBC) patient is important for several reasons. First, effective targeted therapies for patients with certain genomic alterations, such as in the human epidermal growth factor receptor 2 (HER2), are available if such a mutation is identified. Second, drugs targeted against molecules such as the estrogen receptor (ER) and specific signaling pathway proteins, such as poly-adenosine diphosphate ribose polymerase, cyclin-dependent kinase (CDK) 4/6, phosphoinositide-3-kinase (PI3K), mammalian target of rapamycin (mTOR), and others are similarly available or under development. Companion diagnostic studies are underway, and are aimed at identifying the specific genomic sequences that can predict the response to these targeted agents, which could aid in the selection of a population of patients who would receive the maximum benefit from specific therapies [1-3]. Third, the expansion of drug-resistant clones with different genotypes compared to the primary tumor, that were already present at the initiation of therapy, may be responsible for the limited efficacy of some targeted drugs in terms of *time to treatment failure*. Identifying the genomic alterations of these clones could indicate that combined or sequential targeted regimens could be used against them, which would lead to a significant increase in the efficacy of currently available targeted therapies.

Tumor Heterogeneity: Primary Tumor and Metastases

Most cancers are ecosystems of evolving clones with different genotypes [4]; a phenomenon defined in 1976 by Peter Nowell as *tumor heterogeneity* [5]. Tumors arise and develop through a Darwinian clonal evolution [6], and phenotypic heterogeneity is a well-recognized phenomenon described in many cancer types. Numerous comparative genomic hybridization studies, and more recent massively parallel sequencing studies, have generated clear evidence of intratumor heterogeneity in renal and breast cancers [7,8]. Phenotypic heterogeneity was first attributed exclusively to genomic diversity secondary to mutations resulting from clonal evolution. More recently, the study of gene mutations in advanced cancer disease, with acquired resistance to treatments, has evidenced a potential role of the therapy as a selective pressure in the natural clonal evolution of cancer [9-11]. Conversely, the cancer stem cell (CSC) hypothesis postulates that differences between cells can also be due to differences in their differentiation status, which has added an additional perspective to tumor heterogeneity [6].

The initiation and development of cancer are dependent on genetic factors, particularly on the acquisition of multiple *driver* mutations associated with a large number of *passenger* mutations that do not confer any selective advantage. This could, however, be a misleading classification, since passenger mutations might interact with driver mutations in advanced cancer stages and become a reason for resistance to therapy. Additionally, phenotypic heterogeneity may be due to non-genetic factors. According to the CSC hypothesis, phenotypic heterogeneity in cancer is a reflection of differentiation hierarchies that already exist in normal tissues [6]. High expression of stem cell markers, indicating an early stage of differentiation, confers clinically important properties on the tumor cell, such as resistance to therapy and seeding ability.

Genomic Alterations in Primary Tumors Versus Metastases

An increasing number of studies have identified the existence of genetically distinct clonal subpopulations in some primary tumors [12]. Breast cancers have been classified by means of microarray-based comparative genome hybridization in single cells as either monogenomic or polygenomic, the latter having several clones that are evident in the primary tumor; polygenomic diagnoses carry a poorer prognosis [13,14]. Individual breast cancer tumor cell clones may harbor unique genetic alterations in addition to the founder mutations [15,16]. Distinct populations of breast cancer cells appear to interact in a competitive manner, both in the primary tumor and the micrometastatic environment. The selective pressure of therapeutic interventions can allow resistant cell clones to persist (usually as *dormant* cells) in distant organs. For unknown reasons these clones may expand, first in a silent way and later generating overt metastases, usually several years after the primary diagnosis. A substantial number of subdominant somatic mutations present in the primary tumor can evolve to become dominant in metastatic sites due to a selection process that is a consequence of the therapy [8,10]. Thus, the biology of metastases may be quite different from that of the primary tumor. This phenomenon can be particularly relevant in tumors that relapse after adjuvant treatments, especially if the relapse occurs years after the removal of the primary tumor.

The traditional view of cancer spread and metastasis is that metastatic cells arise from the most aggressive and dominant clone in the primary tumor and, therefore, primary tumors can serve as adequate diagnostic proxies when selecting therapies for metastatic disease. This theory holds true in tumors that are induced by chemicals and those that are associated with short patient survival, such as non-small cell lung cancer [17]; whether this is true in tumors of different etiology, biology, and behavior (such as breast cancer) remains to be established. This traditional view has been challenged by recent studies, in which substantial genetic divergence has been described not only between the primary tumor and metastases, but also between different metastatic sites. The *parallel progression model* considers that breast cancer metastases arise from the primary tumor very early

in the evolution of the disease, both evolving in parallel and acquiring different genomic alterations [18]. In reality, it is plausible that both models coexist, with a close clonal relationship between primary tumor and metastases in some breast cancer patients, and marked divergences in others.

Based on these findings, we speculate that breast cancer metastases and primary tumors could harbor both common and unique genomic aberrations. To test this hypothesis, we propose to compare the genomic status of paired breast cancer primary tumors and metastases from the same patients. Obtaining metastatic tumor tissue can be challenging in routine practice, and since different metastatic sites could harbor different alterations, other potential sources of genomic information, such as circulating tumor cells (CTCs) and circulating free DNA (cfDNA), will also be analyzed and compared with the genomic status of the primary and metastatic tumor tissues [19,20]. We will specifically look at the status of the ER/progesterone receptor (PR) pathway, the HER2 pathway, CDK 4/6 activation, phosphatase and tensin homolog, the p53 gene, fibroblast growth factor receptor, and the PI3K pathway, since one or more of these genes/pathways are typically altered in almost all tumors [21].

Methods

Study Design and Objectives

This is a multicenter, transversal, observational study performed by the Medical Oncology departments of three hospitals in Madrid, Spain: University Hospital Gregorio Marañón (UHGM), University Hospital Clínico San Carlos, and University Hospital Infanta Cristina. The primary objective of this study is to assess the concordance of mutations and other genomic findings between the primary tumor tissue and metastatic tissue in patients with MBC. Secondary objectives include determining the genomic profiles of CTCs and cfDNA from peripheral blood (liquid biopsy) and comparing these genomic profiles with those from the primary tumor and metastatic tissue for each patient, in order to assess the mutations in the genes of the signaling pathways that are relevant to the disease (ER/PR, HER2, PI3K/RAC-alpha serine/threonine-protein kinase [AKT1]/mTOR, and MAPK pathways, and CDK 4/6 activation) in the various tissues. Additionally, a final objective is to test the feasibility of introducing liquid biopsies as a translational laboratory tool in clinical practice.

Ethical Considerations and Regulatory Approvals

Approvals for the MIRROR study have been obtained from the ethics committees in all participating hospitals (Study No. Identifier GOMHGUGM092013; ClinicalTrials.gov Identifier: NCT02626039). This study will be carried out in accordance with the guidelines of the Declaration of Helsinki, the principles of Good Clinical Practice as defined by the International Conference on Harmonization (ICH-E6, 17/07/1996), as well as specific regulations in Spain regarding research issues (Spanish Law 14/2007 on Biomedical Research). Before any study procedure, patients will need to provide written informed consent, and allow for the use of tissue samples (metastatic and primary tumor tissues) as well as blood samples for genomic studies and biobanking. Specifically designed case report forms will be used to collect patient information, which will be safely and confidentially stored at the Translational Oncologic Research Unit of each participating hospital.

All recruited patients will follow the therapy prescribed by their oncologists, according to individual clinical practices. No additional treatment or change in treatment is required for participation in this study.

Patient Selection

All consecutive patients with MBC who visit the Oncology Services of the participating hospitals will be screened for eligibility. To participate in the study, patients must be over the age of 18 with MBC (all subtypes) confirmed by radiologic findings, either at first relapse or if tumor regrowth occurs while on treatment for metastatic disease since November, 2013. Additionally, patients will have a formalin-fixed paraffin-embedded (FFPE) tissue sample isolated from the primary tumor, and a clinical indication for biopsy of the metastatic relapse. Patients will be excluded if they are unable or unwilling to give informed consent, have metastatic bone disease only, have coagulation disorders, are unable to have peripheral blood drawn, or have an Eastern Cooperative Oncology Group performance status of 3 or 4.

Patients who sign the informed consent form and enter into the study, but fail to undergo the biopsy (or for whom primary tumor tissue is not available), will be ineligible and considered recruitment failures. Patients for whom biopsies are not successful due to failure of tumor tissue retrieval will be also considered recruitment failures.

Study Procedures

After the patient is enrolled, baseline demographic characteristics, medical history, and a complete physical examination will be recorded, and metastatic tissue and blood specimens will be obtained. Additionally, a paraffin block of the primary tumor tissue will be obtained and archived. Investigators will be trained in the specimen collection protocol of the Translational Oncology Research Unit of UHGM for the genomic studies. Biopsies of both the metastatic tissue and the blood sample must be taken close together in time; if the metastatic tumor tissue is obtained by puncture, the blood sample must be taken no more than 15 days before or after the biopsy. If the biopsy procedure is surgical, a peripheral blood sample must be taken on the same day as (or the day before) the biopsy procedure. Biopsy procedures will be guided using imaging technology as per clinical practice, unless metastasis is cutaneous. The biopsied tissue will then be formalin-fixed and sent for examination by the Pathology Service of the participating hospital. Whenever possible, a separate sample of the tissue will be sent directly to the Translational Oncology Research Unit of UHGM within 24 hours.

At the time of the biopsy, an assessment of any adverse events (AEs) possibly related to the biopsy procedure will be recorded. Those patients who do not return for a biopsy follow-up visit will be contacted by telephone for an AE safety evaluation during the 20 days following their most recent biopsy procedure. All AEs suspected to be related to the biopsy procedure will be

followed up weekly, or as clinically indicated, until resolution or stabilization.

Patients (or parents/guardians in the case of disabled participants) may voluntarily withdraw from the study or be lost to follow-up, and patients may be dropped from the study at the discretion of the investigator at any time.

Biobanking and Sample Analysis

All specimen analyses will be performed at the laboratory of the Translational Oncology Research Unit of UHGM. For each patient, five types of biological samples will be obtained and analyzed, namely FFPE from primary tumor, FFPE from one metastatic site, plasma, white blood cells (WBCs), and CTCs. Parameters to be studied in each specimen are shown in Table 1.

Table 1. Genomic studies per sample and specimen.

Specimen	Sample	Study	Biobanking
Formalin-fixed paraffin-embedded primary tumor	Tissue section	Immunohistochemistry for ER/PR, HER2, P53, Ki67	Formalin-fixed paraffin-embedded block
	DNA	Mutation profile and copy number variation	DNA
	RNA	PAM50 intrinsic subtype	Aliquot for RNA sequencing
Formalin-fixed paraffin-embedded metastases	Tissue section	Immunohistochemistry for ER/PR, HER2, P53, Ki67	Formalin-fixed paraffin-embedded block
	DNA	Mutation profile and copy number variation	DNA
	RNA	PAM50 intrinsic subtype	Aliquot for RNA sequencing
White blood cells	DNA	Mutations and copy number variation in germinal line	DNA
Circulating tumor cells	Circulating tumor cells	Number	DNA
	RNA	PAM50 intrinsic subtype	Aliquot for RNA sequencing
	DNA	Mutation profile and copy number variation	DNA
Plasma	Circulating free DNA	Quantification, mutation profile, and copy number variation	DNA

For primary tumor and metastatic tissues, a hematoxylin and eosin section of FFPE sample will be assessed by the pathologist, with the aim of selecting areas of tumor with >70% cellularity. Two unstained sections will be macrodissected and processed for both DNA extraction using the QIAamp DNA FFPE Tissue Kit (Qiagen) and RNA extraction using the RNeasy FFPE kit (Qiagen). Somatic mutations will be assessed by targeted deep sequencing applied to plasma DNA (cfDNA test), tumor DNA (sDNA test) and, CTC-DNA (ctcDNA test). For each patient, genomic DNA from normal peripheral blood leukocytes will be assayed. Fully customized amplicon-based assays will be used to include genes of the ER/PR, HER2, PI3K/AKT1/mTOR, and MAPK pathways, and CDK 4/6 activation. The somatic mutation profile of the DNA extracted from all samples will be assessed according to the techniques developed as proof of concept by Forshew [20], Dawson [19], and Mutarza [22]. Structural variants of DNA will be assessed by applying the copy number variation (CNV)/CNV-FFPE nCounter Analysis System. RNA will be assayed for the PAM-50 expression profile to determine the subtype of breast cancer in the primary tumor, while the metastatic tissue and CTCs will be analyzed using the nCounter Analysis System.

Blood collected in ethylenediaminetetraacetic acid tubes will be processed within one hour to separate plasma, WBCs, and CTCs. Samples will be frozen at -80ºC until the nucleic acids extraction is scheduled. Following the method described by Dawson et al [19], DNA will be extracted from plasma using the QIAamp Circulating Nucleic Acid kit (Qiagen). The total amount of cfDNA will be quantified using previously described methods [19,23]. After collection of plasma, the remaining buffy coat-containing WBCs will be removed. DNA will be extracted using adsorption methods. Peripheral blood mononuclear cells will be obtained from blood by density gradient centrifugation, which will then be mixed with CTC beads and loaded onto a microfluidic cartridge following the ISOFLUX-CTC procedures (Fluxion Biosciences Inc). Enriched CTCs will be processed for enumeration or be stored for further DNA and RNA extraction.

Sample Size and Statistical Analyses

Analyses of genomic DNA sequencing data are considered exploratory in nature, and will generate new hypotheses. For this study, we have estimated that three patients per month will be enrolled, reaching a final sample size of 40 patients with complete data to proceed for further analyses.

According to Hart et al [24], a sample size calculation comparing two groups involves five factors, namely (1) the depth of sequencing and consequent expected count for a given transcript, (2) the coefficient of variation of counts within each of the two groups, (3) the fold-change that we wish to detect, (4) the target false positive rate and the false negative rate, and (5) the sample

size in each group. Setting 3000x as the sequencing depth and 0.4 as the coefficient of variation, we estimate there is enough statistical power (80%) to detect effects higher than 1.29.

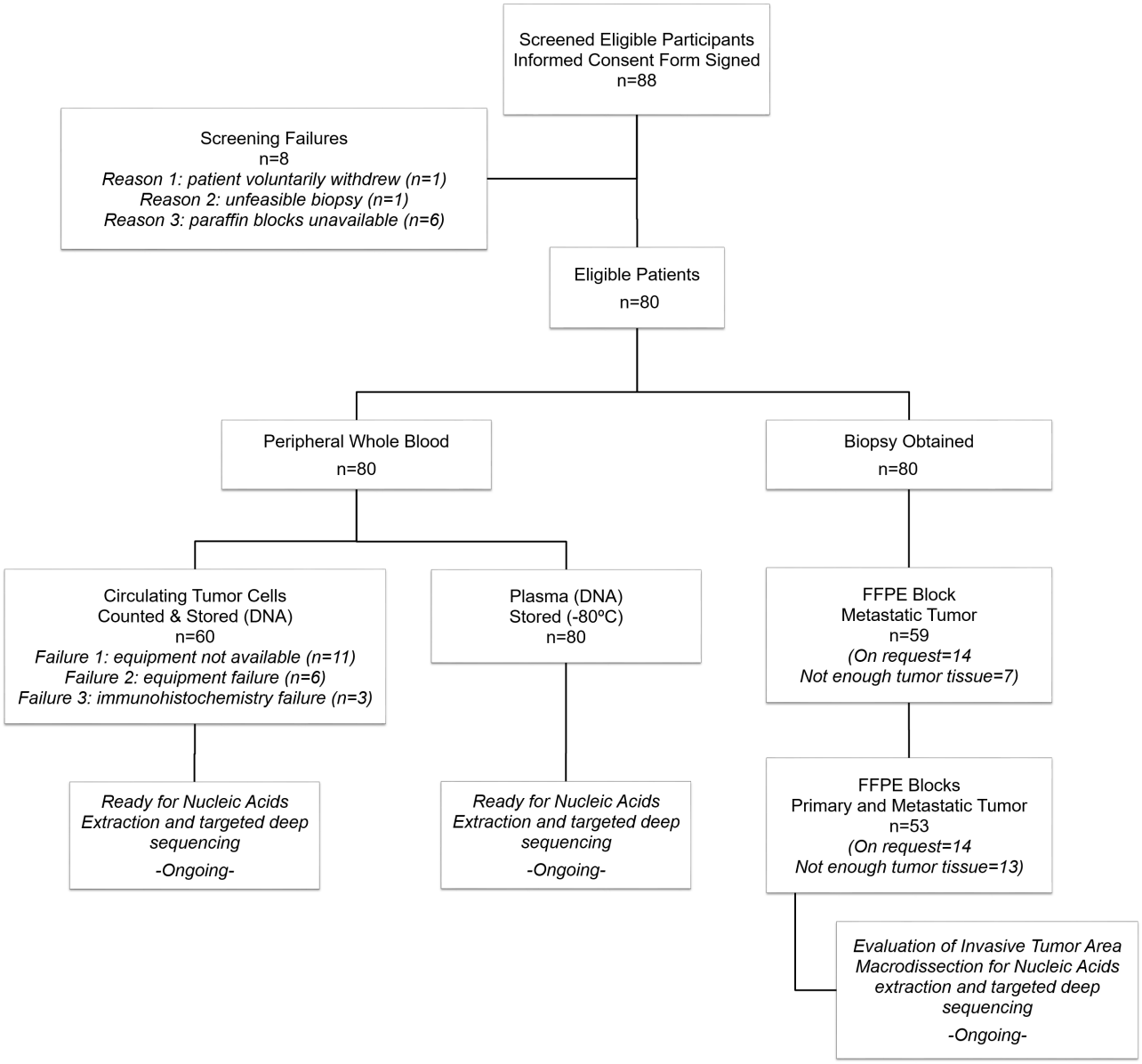
Clinical and demographic characteristics of patients will be described using descriptive statistical methods. Univariate analysis will be performed in order to describe the distribution, central tendency, and dispersion of the variables. Bivariate analysis will be used to find relationships between different variables. Analyses will be performed using the Statistical Package STATA version 12.1 or the newest version of R, according to the requirements of the analyses. Additionally, a scoring algorithm will be established in order to compare the mutation/CNV status in cfDNA/CTC-DNA against primary tumors, metastases, and germinal line DNA.

The genome sequencing data will be analyzed using bioinformatics tools. Sequencing reads will be aligned to the human reference genome building hg38 (GRCh38) to generate a list of potential genomic variations through variant-calling procedures. The alignments will be run using tools based on the Burrows-Wheeler Transform such as Burrows-Wheeler Aligner or Bowtie2. The aligned results will be processed using the SAMtools suite in order to obtain sorted, indexed, and binary files. If necessary, duplicate reads will be marked with Picard and removed before single nucleotide variation (SNV) identification with softwares such as SAMtools, mpileup, and MuTect. These programs will be used to detect low-frequency variants, as data cannot be expected to follow normal ploidy models. Additional steps will be performed if needed, such as the recalibration and realignment using BaseRecalibrator and IndelRealigner, both in the GATK suite. In recent years, a number of important algorithms and implementations have been designed for specific SNV detection tasks in matched samples. Depending on the number and nature of the detected SNVs, it may be appropriate to filter the results in order to keep only those located in exon junctions, or those leading to nonsynonymous changes. Moreover, germinal DNA will be taken as a control to assess background noise, and establish sample-specific thresholds for SNVs to be accepted. Identified and confirmed SNVs will be annotated with broadly-used tools such as SIFT, Variant Effect Predictor, or MutationAssessor. Finally, self-contained pathway and functional analyses will be applied to the obtained results, in order to check that a specific pathway has different genomic or expression patterns between compared samples. The high throughput sequencing raw data will be stored as clinical research files for further reevaluations. All reference genomic files containing the genes, transcripts, and annotated mutations will be used as the control genomic profile of each sample.

Results

Patient recruitment started in November, 2013 and is currently ongoing. To date, 41 patients have a complete set of tissue samples available (plasma, CTCs, and FFPE of primary tumor and metastatic tumor). However, none of these samples have undergone nucleic acids extraction or targeted deep sequencing. Due to the high standards of the quantity and quality of DNA required to perform these procedures, the recruitment period is still open (it is expected that some of the tissue samples will not be valid). Final study results are expected to be available in December, 2016. Additional information regarding the progress of this study is described in the Figure 1.

Figure 1. Flowchart of participants, specimens, and samples through the study.



Discussion

The MIRROR study is one of the first observational studies to test the hypothesis that breast cancer metastases and primary tumors harbor different genomic profiles (related to genomic regions of interest) in a clinically relevant proportion of MBC patients, while concurrently assessing whether genomic aberrations found in the metastatic tissue are detectable in CTCs and cfDNA. Our study is a descriptive observational trial in the clinical setting. Genomic data will be described along with the clinical course of the disease for each patient. Therefore, data will include the type and the time of recurrence, and the different therapies received until the biological samples were collected.

Most registration trials examining new targeted agents involve companion diagnostic studies that are implemented in parallel with the efficacy study. In the majority of these studies, tumor biopsies are required prior to enrollment in order to characterize the genomic status of the patient. However, for practical reasons, some studies are accepting primary tumors as appropriate material for genomic testing. When biological samples of the current disease status are not available, two hypotheses have to be assumed: (1) all the genomic aberrations that are present in the metastases were already present in the primary tumor, and (2) all metastatic sites are genomically homogeneous. However, these hypotheses may not be true or, more precisely, they could be true in some patients but not in others. In this study, we intend to shed some light onto this issue.

The results of the present study may have a significant influence on the practical management of patients with MBC, and may guide clinicians towards a better stratification of patients, resulting in more effective and less toxic treatments. Additionally, if genomic mutations found in metastatic tissue are similar to those detected in CTCs and/or cfDNA, liquid biopsies could prove to be a more convenient, non-invasive, and easily accessible source of genomic material for the analysis of mutations and other genomic aberrations in MBC.

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Authors' Contributions

MGR conceived and designed the study, and wrote the study protocol and manuscript. AP and EA conceived and designed the bioinformatics and biostatistics, and reviewed the manuscript. MM conceived and designed the study, patient recruitment, and clinical study coordination, and reviewed the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AE: adverse event
AKT1: RAC-alpha serine/threonine-protein kinase
CDK: cyclin-dependent kinase
cfDNA: circulating free DNA
CNV: copy number variation
CSC: cancer stem cell
CTCs: circulating tumor cells
ER: estrogen receptor
FFPE: formalin-fixed paraffin-embedded
HER2: human epidermal growth factor receptor 2
MBC: metastatic breast cancer
mTOR: mammalian target of rapamycin
PI3K: phosphoinositide-3-kinase
PR: progesterone receptor
SNV: single nucleotide variation
UHGM: University Hospital Gregorio Marañón
WBC: white blood cell

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Protocol

Protocol for Autologous Fat Grafting for Immediate Reconstruction of Lumpectomy Defects Following Surgery for Breast Cancer

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Abstract

Background: For women undergoing breast conservative surgery or lumpectomy for early stage breast carcinoma, there are limited options for reconstruction. Options include the use of flap surgery and/or implants, and have a significant associated morbidity and cost. Autologous fat grafting is a new alternative that can achieve a good cosmetic result, while reducing patient morbidity and cost by avoiding more extensive surgery.

Objective: The primary objectives are to assess patient satisfaction using the Breast-Q questionnaire and to evaluate fat graft volume. The secondary objectives are fat survival and assessment for complication (eg, fat necrosis, cysts), local recurrence, and the number of sessions needed for a satisfactory outcome.

Methods: This study is a case series of 100 patients, at a single-center institute spanning one year. The inclusion criteria include: female sex, age 18 to 75, early state breast cancer (confirmed on ultrasound/ positron emission tomography-computed tomography and cytology), amenable to breast conservative surgery, and at least 6 months post-completion of radiotherapy/ hormone/chemotherapy. Exclusion criteria include patients with more advanced stages of breast cancer necessitating total mastectomy, those unsuitable for surgical excision, and those in whom lumpectomy is not feasible. The patients will have follow-up data collected at 6 months, 12 months and 5 years post-operatively.

Results: This study will begin enrolment in January 2017. We anticipate that there will be good patient satisfaction with fat grafting. The risk for long-term breast cancer recurrence hasn't been evaluated extensively in literature, however some clinical studies have shown no increased risk of breast cancer in appropriately selected patients at one year. Although some patients may develop complications from fat grafting (eg, necrosis/cysts) this should not confuse the radiological detection of breast cancer recurrence.

Conclusions: Fat grafting is proving to be a viable option for reconstruction of lumpectomy defects with good patient satisfaction. The heterogeneous methods of reporting the harvesting of fat in literature may account for the variable outcomes described, and makes it difficult to compare results with similar studies. The long-term risk of breast cancer recurrence with fat grafting for lumpectomy defects is unknown.

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KEYWORDS

Fat grafting; lumpectomy defects

Introduction

Disease Background

Women undergoing breast conservative surgery or lumpectomy for early stage breast carcinoma currently have limited options for breast reconstruction. Surgical options include the use of flaps and implants, and have a significant associated morbidity and financial cost.

Autologous fat grafting is a new alternative technique that can achieve a good cosmetic result, while reducing patient morbidity and cost by avoiding more extensive surgery. There is limited literature describing the role of autologous fat grafting for lumpectomy defects. There is, however, a prospective case controlled study (the RESTORE 2 trial) that has demonstrated adequate graft survival, good breast contour, patient satisfaction, and low complication rates [1-3]. Another large retrospective study followed patients who underwent autologous fat grafting, following breast conservative surgery for breast cancer or subsequent breast reconstruction, over a period of 10 years. This study also demonstrated a low complication rate and no long-term increased risk of breast cancer recurrence [4].

Rationale for Performing the Study

The aim of our study is to establish the feasibility of autologous fat grafting for lumpectomy defects in a large cohort of patients, and to identify factors associated with improved graft survival and better patient satisfaction.

Methods

Primary Objectives

We aim to assess patient satisfaction using the autologous fat grafting technique (using the patient-reported Breast-Q questionnaire), and fat graft volume (using radiological techniques).

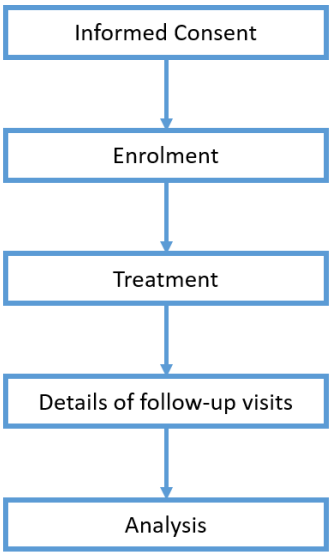
Secondary Objectives

We will assess fat survival and complications (eg, fat necrosis, cysts) using clinical and radiological techniques, and local recurrence using oncological methods. The process will be assessed to determine the number of sessions needed for a satisfactory outcome.

Study Design

This study will be a case series and will aim to recruit 100 patients over a period of one year. All procedures will be performed through St. Vincent's Public Hospital, and will follow the process outlined in Figure 1. No formal statistical calculations were used to arrive at a sample size of 100.

Figure 1. Study flow chart.



Inclusion and Exclusion Criteria

Female patients aged 18-75 who have early stage breast cancer amenable to breast conservative surgery will be included. Confirmation of breast cancer or *in situ* carcinoma must be determined via ultrasound and/or positron emission tomography-computed tomography and cytology, and patients must give written informed consent to participate and comply with follow-up. Patients must also be at least 2 years post-completion of breast conservative surgery and adjuvant radiotherapy, hormone treatments, and/or chemotherapy. Exclusion criteria include patients with more advanced stages of breast cancer necessitating total mastectomy, or those unsuitable for surgical excision. Patients with small breasts, in whom lumpectomy is not feasible, will not be included in the study.

Investigation Plan

Following consent, baseline characteristics will be recorded in an online database. Details will include age, smoking, co-morbidities, unilateral versus bilateral disease, histopathological factors (location of lesion, benign vs malignant tumor, size of lesion, size of total resection, minimum clearance margin, and time since resection), and any chemotherapy, hormone treatment, or radiotherapy.

The procedure of autologous fat grafting involves several steps. The liposuction site is initially infiltrated with combined saline

solution and diluted adrenaline solution, and the adipose tissue is subsequently suctioned using a standard cannula with a conventional liposuction machine. The amount of fat tissue to be grafted is determined by the surgeon at the time of the procedure. The fat graft is subsequently centrifuged to separate out adipose tissue, which is then inserted into the breast. The amount of fat grafted will be recorded in the patient's notes.

Patients will be followed-up in the outpatient clinic to assess graft survival and potential complications at 6 months, 12 months, 24 months, and 5 years. Follow-up visits will entail a physical examination and an ultrasound. In addition, a physical examination will also be undertaken post-operatively at 1 week to detect early complications. Details for each visit are presented in Table 1.

Table 1. The list of interventions at the enrollment visit and at subsequent follow up intervals.

List of Interventions	Enrolment Visit	6 Months	12 Months	5 years
Informed Consent	✓			
Inclusion / exclusion criteria	✓			
Physical examination		✓	✓	✓
Ultrasound		✓	✓	✓
Adverse Event & Serious Adverse Event Assessment		✓	✓	✓

The follow-up protocol for this study differs from the standard of care only in that ultrasound will be used to assess for potential complications relating to fat grafting. The additional costs associated with ultrasounds will be undertaken by the Plastics and Reconstructive Surgery Department. All other aspects of the follow-up (ie, physical examination and adverse event assessment at the specified time periods) are considered standard follow-up for both Plastic and Reconstructive Surgery and Surgical Oncology.

Study Procedure Risks

Important risks associated with this study relate primarily to the autologous fat graft. At the time of operation there will be discomfort and pain at the donor site. The main complications of the graft include fat necrosis, cyst formation, and calcification. These issues will be monitored via the use of an ultrasound at the specified time periods.

Furthermore, the role of autologous fat grafting in local cancer recurrence in lumpectomy patients is not known, as no long-term trials have been conducted. Earlier studies examining this issue have suggested no increased risk one year after the procedure [1].

Recruitment and Screening

Following review in the breast cancer multidisciplinary clinic at St. Vincent's Public Hospital, and having being deemed suitable for this study, patients will be offered autologous fat grafting for repair of their lumpectomy defects.

Informed Consent Process

After the patient is identified as suitable, informed consent will be obtained to enroll the individual in the study. The patient will be informed about how the procedure is conducted, the expected post-operative recovery time, and the follow-up time periods. The risks and benefits of the procedure will also be explained. Finally, the patient will be made aware of suitable alternatives to autologous fat grafting for repair of lumpectomy defects, which will predominately be conservative treatment [5].

Enrolment Procedure

Individuals will be enrolled in the study after the informed consent process has been completed, and the participant has satisfied all inclusion and exclusion criteria. Participants will receive study enrolment numbers which will be documented in each participant's medical record and on all study documents. Patient data will be stored in a de-identified format, and will be kept on a secure server in the Department of Plastics and Reconstructive Surgery.

Adverse Event Reporting

An adverse event is any untoward medical occurrence that results in the following: death, a life-threatening situation, requirement of inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, congenital or birth defect, or a condition requiring medical or surgical intervention. An adverse event can therefore be any unfavorable or unintended sign, symptom, or condition, or an observation that may or may not be related to the study treatment.

Confidentiality, Storage, and Archiving of Study Documents

All participants will be issued a study code and all information will be stored in a de-identified format during the study. Following publication of the results, research data will be non-identifiable, and will be stored in a secure computer server for 15 years in the Department of Plastics and Reconstructive Surgery.

Results

This study will begin enrolment in January, 2017. We anticipate that there will be good patient satisfaction with fat grafting. The risk for long-term breast cancer recurrence has not been evaluated extensively in the literature, however some clinical studies have shown no increased risk of breast cancer in appropriately selected patients after one year. Although some patients may develop complications from fat grafting (eg, necrosis or cysts), these issues should not confuse the radiological detection of breast cancer recurrence.

Discussion

Fat grafting is proving to be a viable option for reconstruction of lumpectomy defects, with good patient satisfaction. The heterogeneous methods of reporting the harvesting of fat in the literature may account for the variable outcomes described, and makes it difficult to compare results with similar studies.

The risk of breast cancer recurrence is cited as the major risk factor with fat grafting. Furthermore, there is ongoing disparity between *in vivo* and *in vitro* studies. Currently, clinical studies do not demonstrate any increased risk of recurrence with fat grafting of lumpectomy defects, but recent laboratory studies have suggested that fat-derived stem cells can make human breast cancer cells more aggressive in animal models [6]. This finding highlights the need for ongoing research in this area.

Acknowledgments

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Conflicts of Interest

None declared.

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Protocol

ActiviTeen: A Protocol for Deployment of a Consumer Wearable Device in an Academic Setting

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Abstract

Background: Regular physical activity (PA) can be an important indicator of health across an individual's life span. Consumer wearables, such as Fitbit or Jawbone, are becoming increasingly popular to track PA. With the increased adoption of activity trackers comes the increased generation of valuable individual-based data. Generated data has the potential to provide detailed insights into the user's behavior and lifestyle.

Objective: The primary objective of the described study is to evaluate the feasibility of individual data collection from the selected consumer wearable device (the Fitbit Zip). The rate of user attrition and barriers preventing the use of consumer wearable devices will also be evaluated as secondary objectives.

Methods: The pilot study will occur in two stages and employs a long-term review and analysis with a convenience sample of 30 students attending Research Triangle High School. For the first stage, students will initially be asked to wear the Fitbit Zip over the course of 4 weeks. During which time, their activity data and step count will be collected. Students will also be asked to complete a self-administered survey at the beginning and conclusion of the first stage. The second stage will continue to collect students' activity data and step count over an additional 3-month period.

Results: We are anticipating results for this study by the end of 2016.

Conclusion: This study will provide insight into the data collection procedures surrounding consumer wearable devices and could serve as the future foundation for other studies deploying consumer wearable devices in educational settings.

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KEYWORDS

mHealth; clinical research protocol; Fitbit; physical activity tracker; survival analaysis; technology deployment; education

Introduction

Regular physical activity (PA) is an important predictor of physical health across the life span [1]. Nonetheless, the frequency of inactivity continues to be problematic for a large number of children and adolescents [2-4]. Although methods for objectively measuring PA in children and adults in naturalistic settings are well established (ie, accelerometry), they are nearly exclusively used in research contexts due to cost and technical requirements that impede their wide-scale use. There does not yet exist low cost, low burden, scalable approaches for the objective measurement of PA. Ultimately, this undermines surveillance efforts by governmental or regulatory agencies, efforts to evaluate PA-related changes in public policy, and schools' abilities to evaluate the effectiveness of their PA-related interventions.

Wearable devices available to consumers offer a wide range of features and can be used to monitor an individual's sleep, diet, or PA. A 2014 national survey indicated that out of 1000 US consumers, one in five individuals own a wearable and one in ten individuals use their wearable on a daily basis [5]. Additionally, given that 64% of Americans own a mobile phone with app capabilities (smartphone) [6], more and more users now own the necessary technology to connect their mobile

phone directly to their wearable. Consequently, the increased adoption of consumer wearable devices has led to a concomitant rise in the quantity of individual-based generated data. Collection of this data could potentially provide valuable insight into an individual's daily routines, lifestyle, and behaviors.

Despite the boom in adoption of consumer wearables, the devices also appear to have a high rate of user abandonment. Research has shown that more than half of activity tracker owners no longer use their device and a third of owners stop using their activity tracker within six months after receiving the device [7]. Moreover, there might be a wide range of factors preventing long-term use of consumer wearables. Not providing new information to the user, inaccurate tracking results, discomfort, or an unpleasing aesthetic design are all barriers that may prevent continued use of consumer wearable devices [7-10].

To assess the practicality of data collection employing consumer wearables with a sample of high school students, the ActiviTeen study was developed. ActiviTeen is a pilot study with a long-term approach to data collection employing a single type consumer wearable device (the Fitbit Zip). This tracking approach offers the benefit of passively collecting data using devices that people typically purchase for their own use to achieve quantitative and unobtrusive data collection for an important component of their health outcomes: PA. The primary aim of ActiviTeen is to demonstrate the feasibility of data collection from the designated consumer wearable devices. Secondary outcomes consist of assessing the rate of attrition study participants experience with wearable devices and identifying barriers preventing participants from routinely using their wearable devices. For the purpose of this paper, the term "Fitbit Zip" and "Fitbit" will be used interchangeably.

Methods

Device Description

The Fitbit Zip was selected due its good reliability and validity and it has shown a significant correlation as an indicator of PA when compared to the Actigraph accelerometer and the Yamax mechanical pedometer [11,12]. The Fitbit Zip will provide data related to the user's step count and level of activity. The participant's step count will consist of the number of steps taken per day. Activity data is calculated by utilizing metabolic equivalents (METs) [13]. The Fitbit will estimate the user's MET value based on the intensity of their activity [13], this will then be broken down into daily minutes sedentary, daily minutes lightly active, daily minutes fairly active, and daily minutes very active.

Participant Eligibility Criteria

ActiviTeen will use a convenience sample of students recruited from Research Triangle High School, located in Durham, North Carolina. Each of the following criteria must be met in order for students to be considered eligible for participation: students must be between 13 and 17 years of age, able to speak and read English, and students must be agreeable to having their step count and activity level monitored throughout the entirety of their study participation. In addition, eligible students must maintain ownership of an Apple or Android mobile phone with app capabilities (smartphone) throughout the study. The mobile phones (smartphones) should be capable of connecting to a wireless network and downloading the free Fitbit mobile app from either iTunes or Google Play. Mobile phone ownership among teenagers is 78%, and of those, 47% own a mobile phone with app capabilities (smartphone) [14]. Therefore, mandating mobile phone (smartphone) ownership as an eligibility requirement is not anticipated to be problematic.

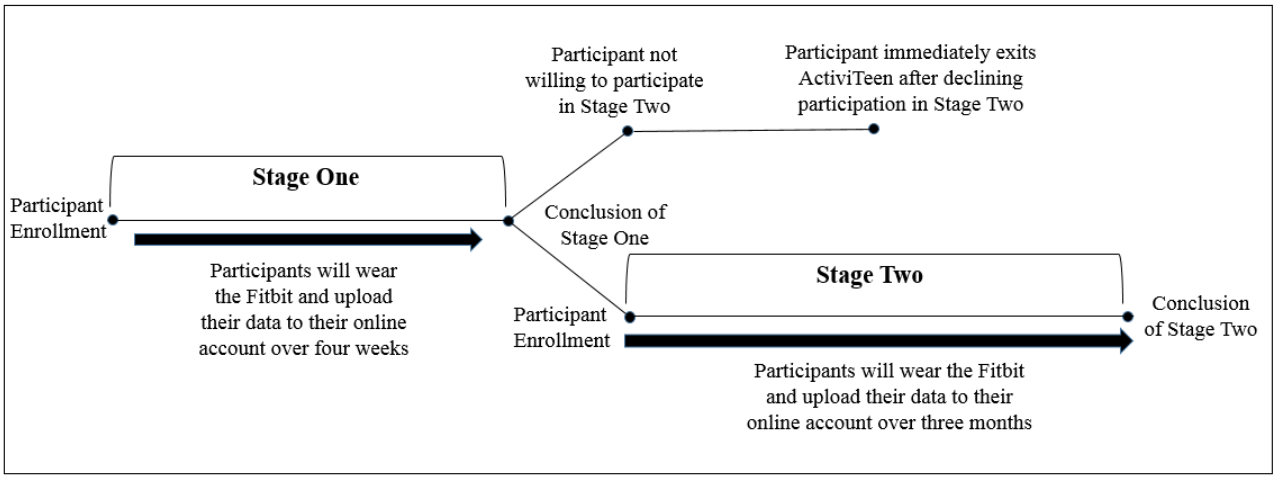
Recruitment Procedure

ActiviTeen's population will consist of up to 30 student participants. The recruitment of 30 students is feasibly managed by the research team, but still allows for sufficient data to be collected regarding Fitbit usage. For recruitment, the research team will run a brief description of the study within the school's student/parent newsletter to identify participants. The description of ActiviTeen will review the following key points: (1) the purpose of ActiviTeen, (2) student eligibility criteria,(3) emphasis that participation in ActiviTeen is voluntary, (4) emphasis that participation will not impact students' academic standing or be a source of extra credit, and (5) that study recruitment is on a first-come, first-serve basis. The newsletter will also state that students will be permitted to maintain ownership over their assigned Fitbit Zip once the study concludes, provide the email contact for a member of the research team and the date when ActiviTeen recruitment will end. Students will be instructed through the student/parent newsletter to email a member of research team if interested in study participation.

Trial Design

ActiviTeen is an exploratory, pilot study occurring over two stages, as outlined in Figure 1. Since a third of US consumers who own an activity tracker stop using their device in six months [7], the original study design took place over a 6-month period. However, the length of the study later had to be tailored to 4 months to align with the school's academic calendar, allowing the study to conclude before students were dismissed for summer break. It was also hypothesized that the most significant decline in use would be observed in the first month, leading to the creation of a 1-month check-in. Although a formal exit point is outlined upon the conclusion of Stage 1, participation is voluntary and students are permitted to leave the study at any point during the two stages outlined below.

Figure 1. ActiviTeen design.



Intervention

Enrollment Preparation

Prior to distribution of the Fitbits, the research team will assign each study participant a unique ID. Each ID will be associated with a separate online account created through the Fitbit website. To simplify the device set-up process, the 30 individual Fitbit accounts will all be associated with one email address: "ActiviTeenRTI@gmail.com". This will be completed by adding a "+" and the student's participant ID to the original email address above, creating 30 individual addresses with the following format: "ActiviTeenRTI+101@gmail.com". While the Fitbit site will view all email addresses separately, Google will not recognize the "+" or the numbers following the "+" as part of the email. Consequently, this allows for the 30 Fitbit accounts to simultaneously link back to a single email address.

Thirty individual packets will then be compiled containing the student assent, an ActiviTeen information sheet, an ActiviTeen frequently asked questions document, the Fitbit Zip product manual, the pre-data collection survey, and a check-off list for the research team member to review when enrolling the student. Each participant ID will be associated with one packet, one online Fitbit account, and one Fitbit Zip.

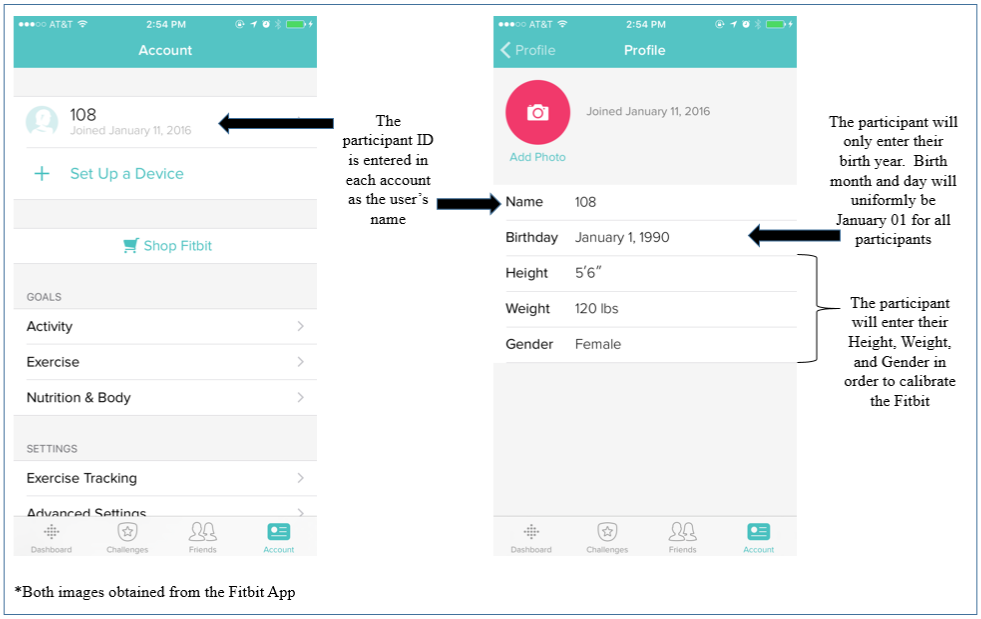
The first 30 students who respond to the newsletter and meet all eligibility requirements will receive a recruitment email stating when the research team will arrive at Research Triangle High School to enroll students and distribute the Fitbits. Those students who respond to the newsletter, but do not meet eligibility requirements, will be sent an email thanking them for their interest and stating they are unable to participate. Students who contact the research team once 30 participants have been successfully recruited will be sent an email thanking them for their interest and stating no further students can be recruited since ActiviTeen has reached the max capacity of participants.

Participant Enrollment

To begin participant enrollment, a member of the research team will individually review each document within the compiled packet and have the participant sign the student assent. Afterward, the student will download the Fitbit app onto their mobile phone and log into one of the previously created Fitbit accounts. To initially calibrate the Fitbit Zip each student will enter their gender, height, and weight. Birth year will be collected by Fitbit, but participants will be instructed not to enter the month or day they were born. To ensure anonymity, January 1st will be uniformly entered as the birth month and day for all participants. The view of how the app will appear on an iPhone is provided in Figure 2. While there are some formatting differences between iPhones and Androids within the Fitbit app, the majority of data elements in Figure 2 are similar across the two device types. Additional features, such as logging calories consumed and creating a food plan, are offered by the Fitbit app and will not be disabled for the study. Students will be instructed not to record any additional information beyond the activity data and step count automatically recorded by their Fitbit device. However, if students do choose to utilize the supplementary features during the study, the additional data will not be reviewed or downloaded by project staff. If unnecessary data beyond the students' activity data and step count is downloaded, it will be immediately deleted. Upon receiving the Fitbit Zip devices, students will also be instructed they are not financially responsible for the device if lost, stolen, or damaged throughout the study. A second device will not be provided if the first becomes lost or unusable due to actions on the part of the student; however, the research team will replace Fitbit batteries and faulty devices as needed.

Students that are absent during enrollment for ActiviTeen will be permitted to enroll at a later date upon notification of the project staff. Although the student might enroll a few days after their peers, they will continue to follow the pre-designated study timeline and will not be given additional days of data collection. However, it will be the student's responsibility to notify project staff via email of their absence and continued desire to participate in the study. Students who do not show up during the enrollment period for stage one or stage two of ActiviTeen will not be re-contacted regarding participation.

Figure 2. Fitbit mobile app appearance.



ActiviTeen Stage One

At the beginning and end of ActiviTeen's first stage, student participants will also be asked to participate in a 10-minute self-administered paper-based survey. The pre-data collection survey will be provided to students as part of their enrollment and will ask the participant if they plan to change their behavior knowing they are being monitored, is it likely they will forget to wear their Fitbit, and do they foresee any problems attaching the Fitbit to their clothes? The post-data collection survey will be administered after the first stage of ActiviTeen has completed and will ask the participant if they were able to wear the Fitbit for the entire 4-week period, how often they forgot to wear their Fitbit, was the Fitbit lost or damaged, were there any problems attaching the Fitbit to their clothes, and if they would be interested in participating stage two of ActiviTeen? Both the pre- and post-data collection surveys will ask the participant their grade level and gender.

For the first stage of ActiviTeen, each Fitbit Zip will be worn by one student participant on their right hip over 4 weeks. The hip was chosen for placement due to the device's enhanced accuracy for counting steps [15]. Students will be instructed during enrollment to wirelessly sync their Fitbit Zip with the downloaded Fitbit app every 3-4 days, transmitting their activity data to their online Fitbit account. To avoid excessive cellular data usage, students will be given the option during recruitment to disable the "All-Day Sync" function offered in the Fitbit app. It will not be mandatory for students to use or disable this feature. In addition, while the students' Fitbit will sync with their online account when the Fitbit app is open and within range of the device, the students will not be reminded by project staff to sync their device at any point throughout the study. The research team will monitor each student's account over the 4-week data collection period and collect the student's activity data and step count by downloading the recorded activity data directly from the online Fitbit portal on a weekly basis.

ActiviTeen Stage Two

Once the initial 4 weeks has concluded, each student will receive an email stating when the ActiviTeen research team will return to campus. During the second visit to Research Triangle High School, student participants will be asked to complete the second paper-based post-data collection survey. Students will then be given the option to continue wearing the Fitbit Zip and allow the research team continued access to their activity data for an additional 3-month period (the second stage of ActiviTeen) or decide to decline continued participation. If they decide not to continue in the study, the student will exit the study and their Fitbit will be removed from the research team's previously created account. For those students who elect to remain in the study, they will be asked to sign a second student assent document and be reminded to continue wearing the device on their right hip and continue syncing their activity data every 3-4 days. The research team will continue downloading the participant's activity data and step count on a weekly basis. When the second stage of ActiviTeen concludes, the remaining student participants will receive an email stating the study has concluded and their Fitbit Zip has been disconnected from any previously made account. ActiviTeen will not utilize strategies to improve participant adherence. However, upon exit of the study, all students will be given their assigned Fitbit Zip and will be allowed to create and personalize their own Fitbit account. No survey will be given to student participants upon the conclusion of the second stage. Deploying a survey in the second stage would likely yield very few respondents given the potential loss to participant attrition. Consequently, it was decided the focus should be active data collection in the first stage to optimize response rates.

Informed Assent

Due the ActiviTeen's minimal risk, a waiver of signed parental consent was received from the RTI International Institutional Review Board (IRB). However, an ActiviTeen information sheet providing a general overview of the study will be emailed to the parents/guardians of all student participants. Before

distributing the Fitbit Zip for the first stage of data collection, students will be asked to review and sign an assent form. Once the student's assent is signed, a verbal confirmation will be obtained to conduct a brief pre-data collection survey. After the initial 4 weeks of data collection has concluded, the research team staff will obtain verbal confirmation from the student to conduct a brief post-data collection survey. If the student is willing to participate in the second stage of data collection, a second assent form will be reviewed and signed.

The assent documentation for both stages of the ActiviTeen study provides an overview of the study as well as how data collection will occur. In addition, the assent addresses the student survey, reminds the student that their participation is voluntary, and reviews benefits as well as risks of participation. The documents also explain how the student's privacy will be protected and who they or their parent/guardian can contact for any follow-up questions or concerns.

Outcome Measures

ActiviTeen's primary outcome is to establish the feasibility of data acquisition from the designated consumer wearable device, the Fitbit Zip. Ease of downloading and collecting participant's activity data and step count throughout the study will be a vital determinant. The secondary outcomes will be an assessment of the rate of attrition study participants experience throughout the course of the study and the identification of barriers preventing users from wearing their device. The step count and activity data will be reviewed to determine if users are continuing to wear their devices on a regular basis. In addition, the pre- and post- data collection surveys will collect user's impressions regarding Fitbit use and will address questions such as why users stop wearing their devices, how long users wear their devices, and how many devices are lost, destroyed, or not worn.

Analysis

Cessation of tracker use over 4 months will be analyzed using survival analyses. Kaplan-Meier life table estimates will be used to characterize and visualize drop-offs in tracker use. This will show how the probability of drop-off in tracker use changes over time. Analyses will be done using the survival package and visualized using the survminer package in R [16-18]. The Kaplan-Meier plot will show cumulative survival probability, and the life table will show the number of participants at risk for dropping off of tracker use at multiple equally-spaced time intervals. The individual student surveys will also be reviewed to evaluate barriers hindering the student's continued Fitbit usage.

Ethics and Confidentiality

The IRB, through RTI International, was utilized to review and provide approval for the ActiviTeen study. Any further changes or modifications to the ActiviTeen study will be submitted as an amendment for IRB review. If any data breeches or adverse events occur throughout the study, the research team will ensure adequate documentation and notification of the IRB.

Confidentiality for the ActiviTeen study is through an RTI International guarantee only. Participating students were made aware within the assent document that the Fitbit app is not secure or encrypted. Anyone who has access to the student participant's personal mobile phone may also have access to their collected activity data. Neither RTI International nor any member of ActiviTeen research team will retain the emails of student participants or their parents/guardians. No personally identifiable information will be connected to any collected data.

Results

We are anticipating results for ActiviTeen by the end of 2016.

Discussion

Study Strengths

ActiviTeen provides a novel methodology for performing data collection utilizing a consumer wearable device. The Fitbit Zip is commercially available, inexpensive, and easily acquired by researchers. In addition, the study provides an overview for the steps required to collect participant's PA data within an academic setting. This protocol is not meant to compare the Fitbit Zip to other devices (ie, accelerometer). The ActiviTeen protocol provides researchers with the necessary background to employ non-traditional devices for the collection of participant's PA data (ie, Fitbit Zip).

Limitations

ActiviTeen may have limited generalizability outside of Fitbit devices since the only consumer wearable device being utilized is the Fitbit Zip. However, the study should have generalizability to the wide range of products offered by Fitbit, since all appear to use the same online account interface. Furthermore, Research Triangle High School may be more accepting of technology-based studies when compared to other schools given it has been identified as a Science, Technology, Engineering, and Math focused institution. Since Research Triangle High School has also been classified as a charter school, the ActiviTeen staff did not have to receive approval from a pre-designated school board.

While creating, managing, and downloading data from 30 Fitbit accounts for the ActiviTeen pilot study is feasible, expanding the study to include a large population might prove problematic. The Fitbit account initiation process as well as downloading activity data and step count from more than 30 participants might likely prove time consuming and error prone. Expansion of the study in future work will require an alternative means of device set-up and data extraction.

Conclusion

This research protocol has provided a detailed description of the steps that will be utilized to deploy the Fitbit Zip within an educational setting. This innovative method will be used to evaluate the feasibility of data collection with consumer wearable devices, the rate of attrition among users of consumer wearable devices, and the barriers preventing users from wearing their devices. We hope this protocol serves as a foundation for the implementation of other consumer wearable device driven studies.

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Conflicts of Interest

None declared.

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Abbreviations

IRB: institutional review board
METs: metabolic equivalents
PA: physical activity

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Protocol

Impact of Elimination or Reduction of Dietary Animal Proteins on Cancer Progression and Survival: Protocol of an Online Pilot Cohort Study

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Abstract

Background: Current evidence suggests that the incidence of cancer is low in vegan populations, and experimental studies have revealed a significant role of dietary proteins in cancer development and progression. However, little data currently exists regarding the effect of a plant-based diet on the progression of diagnosed cancer.

Objective: The main objective of this study is to determine if a reduction or total elimination of animal protein from the diet can positively influence the outcome of an existing cancer and, in addition to standard oncological therapies, increase remission rates.

Methods: The primary aim of this online study is to test the effect on remission rates in cancer patients (primary outcome) with distinct self-selected dietary patterns (omnivore, lacto-ovo-vegetarian, vegan), and allow for an estimation of the effect size. Secondary outcomes are tumor behavior, relapse-free interval, therapies, therapy tolerability and side-effects, comorbidities, medication, quality of life, acceptance, and feasibility of the selected diet. Safety concerns exist for vegan diets (especially in cancer patients) and the study will carefully monitor for deterioration of health, tumor progression, or malnutrition. Furthermore, the study will evaluate the online portal as a study platform (technical and safety aspects, and sequence of displayed questionnaires) as well as the validity of self-reported and online-generated data.

Results: The study was performed between April, 2015 and June, 2016, and a preliminary evaluation of safety aspects was undertaken after June, 2016. Primary and secondary outcomes will be evaluated when the final patients complete the study in December, 2016.

Conclusions: This study will reveal information about the effects of dietary patterns on cancer disease and progression. The methodology of the study addresses several aspects and limitations of nutrition studies in cancer patients, such as precision of nutrition data, acceptance criteria, online methodology, and safety aspects.

ClinicalTrial: Clinicaltrials.gov NCT02437474; https://clinicaltrials.gov/ct2/show/NCT02437474 (Archived by WebCite at http://www.webcitation.org/6jL7UUCVq)

(JMIR Res Protoc 2016;5(3):e157) doi:10.2196/resprot.5804

KEYWORDS

cancer; neoplasms; diet; vegans; vegetarians; omnivore; remission; disease outcome

Introduction

Every year, cancer is diagnosed in 14.1 million people worldwide, and 8.2 million people die from this disease. These figures represent 13% of all deaths around the world, and malignant tumors are one of the main causes of death in industrialized countries [1]. The prognosis for the future is even worse, with a 70% increase in cancer incidence expected, meaning 22 million new cases will be diagnosed every year

over the next twenty years [1]. The most common types of cancer for men are lung, prostate, and colorectal cancer (CRC), while women mostly suffer from breast, colorectal, and lung cancer [1].

Cancer is known to be a multifactorial disease with many external risk factors that need to be considered, especially lifestyle factors. In recent years, nutrition has been highlighted as a key risk factor, and is now considered to be responsible for 30% of all cancer cases in industrialized countries [2]. Different nutritional aspects have been implicated in the stimulation of a large number of cancers. Alcohol is known for its connection to liver cancer, but high body mass index (BMI) and obesity also play a major role in cancer development [3-5]. While these factors primarily affect industrialized countries, cancer in developing countries is often linked to micronutrient deficiencies [6].

Other cancer risk factors include food that has been prepared at high temperatures, high fat consumption, and the excessive usage of salt. Current World Health Organization (WHO) reports also support the hypothesis that above all, red and processed meats are important carcinogens, partly due to nitrites contained in these foods, along with the smoking process. In contrast to this finding, other nutrition aspects (ie, high intake of fiber, and fruit and vegetables) have a cancer protective effect [7-10].

Studies indicate that cancer is low in vegan populations [11,12], but little data exists regarding the effect of a plant-based diet on the progression of diagnosed cancer. However, evidence suggests that a vegetarian or vegan diet provides many other health benefits, such as lower incidence of high BMIs, obesity, and cardiovascular disease [11,12]. The Second World Cancer Research Fund/American Institute of Cancer recommends a mostly plant-based diet and a reduction of red and processed meat in its Research Export Report of 2008 [13], which is also supported by current reports issued by the WHO in 2015 [14]. However, data referring to the therapeutic setting (ie, patients diagnosed with cancer) are still missing. It is of great scientific interest to test the influence of different dietary patterns on the progression of cancer and cancer survival.

Current treatment options for cancer include surgery, radiotherapy, and chemotherapy [1]. Although international research has made progress in the development of new and more specific therapies, treatment options are still limited [15]. Cancer treatments represent a major financial burden on health care systems, patients themselves, and social systems. The main objective of this study is to determine if a reduction or total elimination of animal protein from the diet can positively influence the outcome of an existing cancer and, in addition to standard oncological therapies, increase remission rates.

Furthermore, we aim to estimate the effect size, and enable sample size calculations for future studies. A small number of studies have concentrated on the effect of specific foods, food groups, or food ingredients, such as the effect of soy product consumption in breast cancer patients [16-19], or the effect of reduced red meat intake in patients with colon cancer [20] and prostate cancer [21]. These results are still inconclusive and often show relatively minor effects, likely due to the fact that these studies investigated isolated foods or food groups and not dietary patterns; this study aims to address this limitation.

Cancer patients receive advice from clinicians and their families and friends with respect to nutrition, but studies indicate that patients do not follow this advice over a significant period of time, and improvements based on dietary advice are limited [22,23]. Therefore, it is necessary to test the acceptance and feasibility of different diets, particularly a plant-based diet, in cancer patients. This study hopes to determine if patients who eat a typical omnivore diet can adjust to an alternative diet, and maintain this lifestyle over a period of 6 months or longer. Concerns exist that suggest a vegan or vegetarian diet could lead to a deterioration of health, to tumor progression, or to malnutrition. To address this issue, this study will carefully monitor any deterioration of the patients' health status.

Previous nutrition and oncological studies have required many professional staff and enormous financial resources. Such studies are often time-consuming for the patients (therefore limiting compliance), necessitating the development of new tools to simplify the process of data collection. To this end, new technologies have been developed and intensively tested [24]. This study will examine the usage of a new online portal as a study platform, in addition to standard medical practices. If this platform proves to be useful, it could be adapted for future studies in the field of nutritional health care.

The validity and significance of self-reported and online-generated data has been questioned [25,26]. Therefore, it is necessary to test these parameters, along with the usability of online data with regard to future applications of research results.

This study aims to address the following issues: (1) to test the hypothesis that the elimination or reduction of dietary animal protein leads to an improved prognosis in tumor patients, as defined by the remission rates, tumor behavior, and relapse-free interval; (2) to estimate the effect size and enable sample size calculations for future studies; (3) to test the feasibility and tolerance of different diets (particularly a vegan diet) in cancer patients, and to assess the effect of a vegan diet on deterioration of health, tumor progression, and malnutrition; (4) to test the online platform as a study platform; and (5) to test the validity of self-reported and online-generated data.

Methods

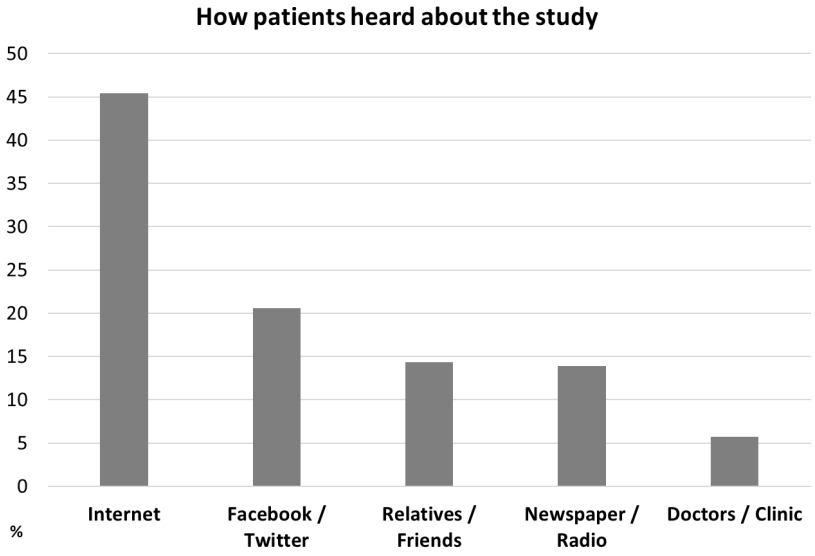
Study Design

This is a prospective, longitudinal, and observational cohort study of cancer patients with four cohorts: (1) omnivore diet, (2) lacto-ovo-vegetarian diet, (3) vegan diet, and (4) other diets (see Table 1). All four cohorts will complete online questionnaires including a baseline assessment and follow-up assessments at 3 and 6 months (Figure 2). At the 12 and 24 month time points, participants will be contacted via email to complete a truncated study questionnaire.

Table 1. Definition of dietary patterns.

Cohort	Meat & fish	Milk & dairy products	Eggs	Honey	Plant products
Omnivore diet	+	+	+	+	+
Lacto-ovo-vegetarian diet	-	+	+	+	+
Vegan diet	-	-	-	-	+
Other diets	Those that do not correspond to any of the above				

Figure 1. How patients heard about the study (n=209).



Eligibility and Recruitment

Patients were eligible for this study if they were diagnosed with cancer, >18 years of age, and were included in a tumor treatment regime or a follow-up program. Exclusion criteria included psychiatric treatment during the previous 3 months, pregnancy, breastfeeding, BMI below 18 kg/m^2, major difficulties with food intake (eg, swallowing, lack of appetite), and participation in other studies requiring the use of a special diet.

Potential participants were recruited online (via the study website, Facebook, online reports, and television and media reports) and offline (via clinical practices, oncological departments, and associations supporting cancer patients). Recruitment took place between April, 2015 and June, 2016.

Study Population and Setting

Whenever possible, participants selected one of three defined diets (omnivore, lacto-ovo-vegetarian, or vegan) at baseline. If none of these diets was applicable, participants were classified as having *other diets* (Table 1). Participants were instructed to maintain the chosen diet for 6 months. In addition, respondents were encouraged to continue their prescribed cancer treatment during the study period, and to undergo all recommended follow-up investigations.

Calculation of the required sample size for this study is not possible, as the effect size of the dietary patterns is unknown. Therefore, this study is classified as a pilot study.

The study is being conducted online via a bilingual study website [27]. Registration processes, eligibility assessments, and questionnaires at baseline and follow-ups are all completed online between April, 2015 and December, 2016. Prior to study participation, potential participants performed an online eligibility check (Multimedia Appendix 1), and were asked to provide contact information and a signed patient information and consent form. After registration, participants received an email including their personal login information for the study website, their study identification number, and a link to their baseline questionnaire. Invitations for assessments at 3, 6, 12, and 24 months are delivered by email (Figure 2). If participants do not fill in their questionnaires at the respected time, they are sent reminder emails. In addition to the three main study questionnaires, study participants are asked to report any severe deterioration, unplanned change of their selected diet, or withdrawal from study participation, via online forms (Multimedia Appendix 2).

Ethical approval was obtained from the Ethics Committee of the City of Vienna on February 2nd, 2015 (EK 15-021-VK_NZ).

Study Groups

At baseline, participants chose one of three defined diet forms for the study period or *other diet* (Table 1). Definitions and nutritional information regarding the diet forms were compiled by a nutritionist, and are available on the study website. All groups were given clear information regarding the avoidance of nutrient deficiencies, and participants were encouraged to continue their prescribed cancer treatment and follow-up

investigations. Participants were also advised to have their serum levels of albumin, iron, vitamin D3, and vitamin B12 checked regularly.

Measures and Evaluation Procedures

The primary outcome of this study is defined as complete tumor remission, and calculated as the rate of complete remissions at 6 months by intention-to-treat (ITT) analysis.

Secondary outcomes include tumor history, further classifications of tumor behavior (complete remission, partial remission, no change, or progression), relapse-free time (in months), survival rates for end stages, previous and current tumor therapies (including tolerance and side effects), comorbidities (eg, high blood pressure, stroke), as well as medications unrelated to the tumor (including dosage and intake plan). The determination of tumor behavior during the study period will be evaluated by two investigators, each using independent radiological and laboratory reports.

Data regarding previous nutritional history, the chosen diet during study participation, acceptance and feasibility of the chosen diet, frequency of dietary pattern change, extent and duration of nutritional changes, and the type and strength of support for nutritional changes will also be assessed. In addition, during baseline and follow-up surveys, adherence to dietary patterns will be cross-referenced by food frequency questionnaires (FFQs), which were specifically adopted for discrimination of plant- and animal-derived foods. Participants were also asked to self-report any unplanned change in diet during study participation. Nutritional status of participants will be evaluated using body weight (kg), BMI (kg/m^2), laboratory test results (eg, albumin), and questions referring to eating problems. Results referring to nutrition and dietary patterns will be evaluated in terms of change and duration of change in dietary patterns (in months).

Study questionnaires also contain questions referring to quality of life covering the Karnofsky Index, as well as additional dimensions (ie, psychosocial wellbeing, psychosocial support). Online questionnaires were designed to be self-instructive and self-evident (Multimedia Appendix 3). In order to evaluate these parameters, questions pertaining to the study platform and interaction with the study team were also included in the questionnaires. The list of parameters included in the study questionnaire was designed to examine all study objectives, and is detailed in Multimedia Appendix 4.

Confounders and Bias

Possible confounders include gender [28] and BMI [29]. Moreover, it is likely that tumor stage and type may influence the results of this study. Therefore, we will examine these factors and adjust our interpretations accordingly. Furthermore, the nature of our website (which highlights the benefits of vegetarian and vegan diets) might attract a population that actively seeks healthy lifestyle habits [27]. Conversely, this group might prefer alternative therapies, and be less compliant to conventional oncological therapies. Therefore, we plan to undertake a subanalysis for treatment groups (oncological treatment followed, oncological treatment rejected, or oncological treatment completed).

Nutrition Safety

To ensure timely detection of the deterioration of nutritional and/or health status of the patients in this study, an intermediate data evaluation is planned, and will include all participants registered before January, 2016. This evaluation will examine tumor staging and the nutritional status of all participants. If this evaluation demonstrates a significantly increased risk of health deterioration in one diet group compared to the omnivorous group, the study will be stopped preterm.

Feasibility, Physical Tolerance, and Acceptance of Chosen Diet

Feasibility of the protocol will be examined by (1) assessing compliance with the chosen diets at the 3 and 6-month time points, (2) asking the study participants to report any intermediate changes of the planned diet, and (3) specific questions contained in the questionnaire regarding the ease or difficulties of the diet, and support from family members and medical staff (Multimedia Appendix 4).

Physical tolerance will be examined via questions regarding physical symptoms. Acceptance will be examined via questions regarding ease, difficulties, and willingness to continue their diet until the study is completed and thereafter (Multimedia Appendix 4).

Online Platform Performance

Prior to the recruitment phase, the study platform (checklist, registration) and surveys were tested by four patients, and adaptations were made according to their feedback. As shown in Multimedia Appendix 4, the performance of the online platforms (webpage platform, survey platform) was assessed via questions regarding users' experience with the platforms, and with the questionnaires (eg, technical performance, ease of understanding the questionnaires, significance of content). Moreover, it was possible to evaluate time spent filling in the questionnaires, dropout rates between and within the questionnaires (incomplete questionnaires), webpage user statistics, and user characteristics such as time spent reading web content, favorite web content, and user interactions.

Nutrition Data Validity

As shown in Multimedia Appendix 4, self-selected dietary patterns will be cross-referenced via FFQ. Moreover, laboratory parameters will include albumin, urinary pH, blood urea nitrogen, and hematocrit. It was not possible to control for additional vitamins, such as vitamin C. Questions regarding motivation and intention to choose a certain dietary pattern will serve as data to further support the validity of the trial, or reveal potential inconsistencies.

Data Safety

Online data safety was a priority in the development of this study, and we strictly separated participants' personal data (used for communication) from anonymous health/disease related data. To ensure anonymity, each participant received a personal login and study identification number. Administrative (personal) data were collected and stored on servers with enhanced security features. Password-restricted logins and Secure Sockets Layer-encrypted data transmission were used, and host server

providers were required to sign a contract according to the German Bundesdatenschutzgesetz [30] to guarantee state-of-the-art handling, storage, and deletion of personal data. Health-related data were collected and hosted at Survey Monkey [31], using anonymous study questionnaires on a server compatible with the Health Insurance Portability and Accountability Act.

Statistical Analyses

Statistics regarding safety issues will be performed in July, 2016 and a complete evaluation will be performed in January, 2017. Comparison of dietary groups in regard to primary and secondary end points will be performed as ITT. Data will be analyzed and adjusted for possible confounders (eg, gender, age, tumor type, tumor stage, weight status, accompanying treatment) and stratified by sex, age, type of tumor, tumor staging, and oncological therapy. Changes over time (eg, weight changes) will be analyzed by paired sample tests. Unpaired tests will be used when making comparisons between cohorts. Descriptive statistics will be used to summarize parameters such as comorbidities, oncological therapies, and additional therapies. *P*-values of <0.05 will be considered significant.

Results

Data collection commenced in April, 2015 and recruitment ended in June, 2016. After completion of the study in December, 2016, data will be analyzed and prepared for publication.

Recruitment and Dropout Rates – Preliminary Experiences

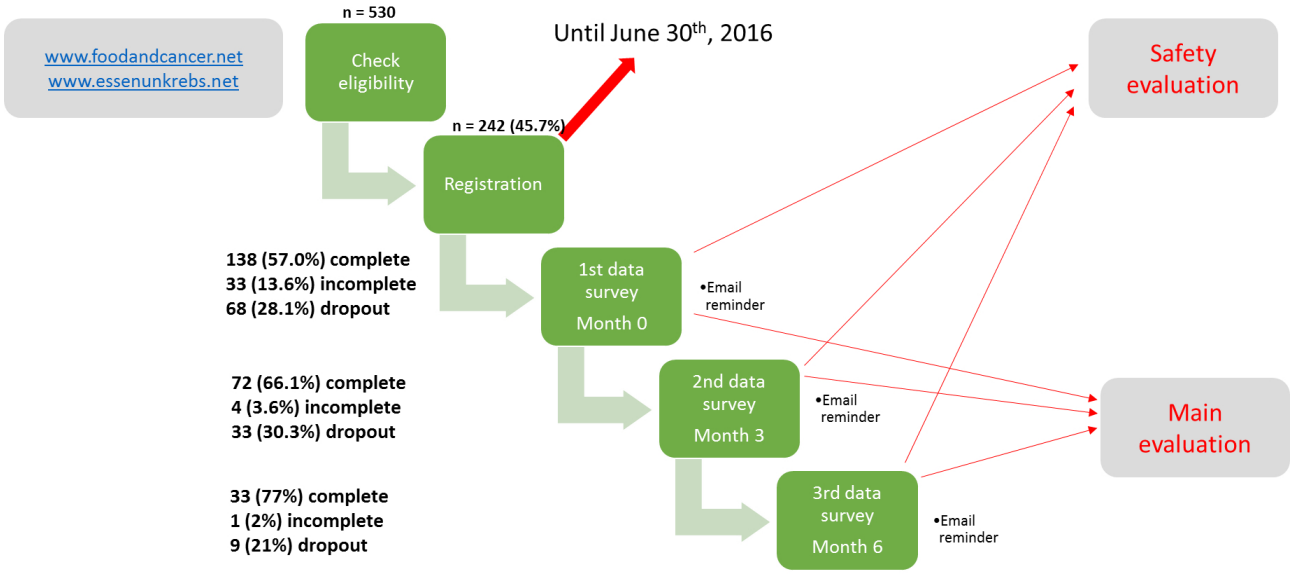
As of May, 2016, 530 participants filled out the checklist and 242 (45.7%) have registered for the study. Most respondents were female (174/242, 71.9%), while 68 were male (28.1%). Mean age was 54.7 years (standard deviation 11.7). Most participants were recruited in German speaking countries (Germany, Austria, and Switzerland). As shown in Figure 1, most participants found the website via the Internet or social media (eg, Facebook and Twitter).

Dropouts occurred at each stage of the study, from the checklist for eligibility to the third data survey, as shown in Figure 2. After filling out the registration forms, 242 participants received the invitation for their first data survey, which was completed by 138 respondents (57.0%). Some respondents (33/242, 13.6%) sent an incomplete survey, and 68 of the original participants (28.1%) did not send a survey. Dropout rates consider participants who withdrew study participation, died, or did not answer after being reminded by email. Four patients have been reported to have died as of May, 2016.

Three months after completing the first survey, participants received an invitation for the second survey (n=109 as of May, 2016), which was completed by 72 respondents (66.1%). Four participants (4/109, 3.6%) sent an incomplete survey and 33 (30.3%) dropped out of the study at this point. The study is still underway, and participants who did not receive the second and/or third surveys have been excluded from these calculations.

The 6-month data survey was sent to 43 participants who completed the first and second surveys. As of May, 2016, this survey was completed by 33 participants (77%); 2% (1/33) sent an incomplete survey, and 21% (9/33) dropped out of the study at this point. Given the number of participants who enrolled in the study at least 6 months before May, 2016 (n=101), this gives a completers rate of 32.7%.

Figure 2. The study protocol showing the 5 steps for each participant, the planned evaluations, and the number of participants and dropouts.

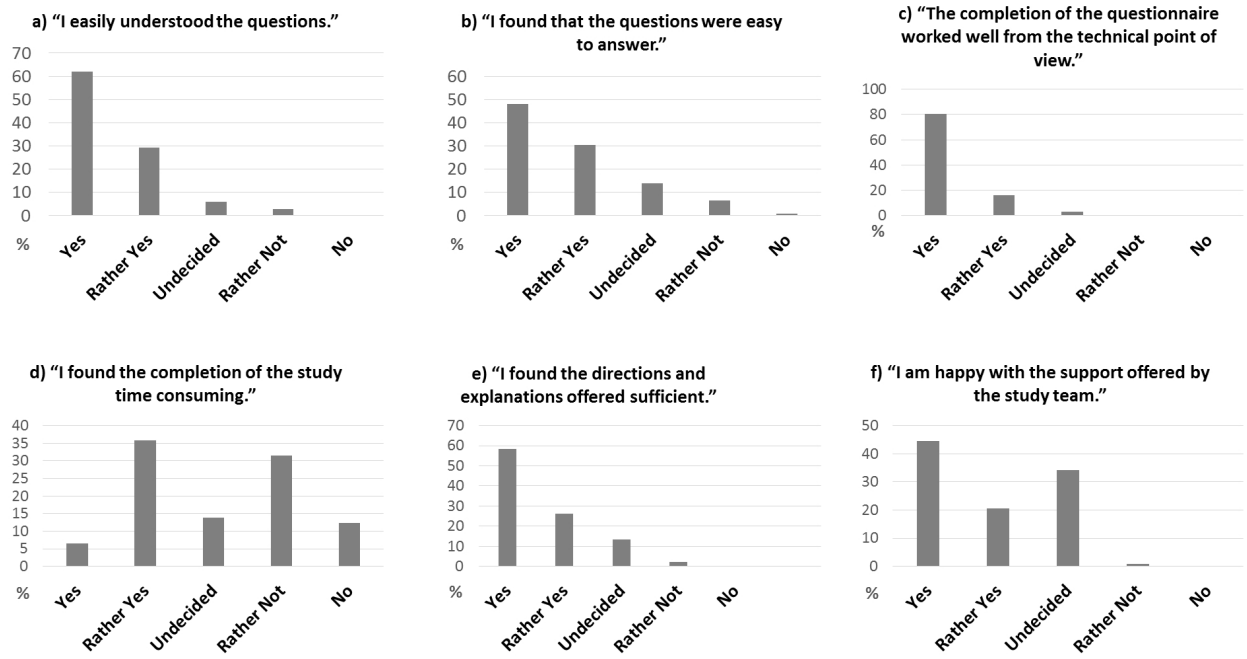


Preliminary Experiences with Online Questionnaires and Study Platform

The questionnaires in this study are very comprehensive (more than 100 items) and contain questions referring to medical data. Participants are also asked about the experience, acceptance, and usability of the study platform. The data collected from the first study survey (n=138) are displayed in Figure 3. The overall acceptance of the questionnaires was good, and most (62% *yes* and 29% *rather yes*) of the participants found the questions easy to understand (Figure 3 a), while 78% (48% *yes* and 30% *rather yes*) found them easy to answer (Figure 3 b). Almost all

participants (80% *yes* and 16% *rather yes*) had no problems with the technical aspects of the study (Figure 3 c). When asked if the questionnaire was too time consuming, an equal number of participants (43%) answered with *yes* or *rather yes*, compared to participants who answered with *no* or *rather not* (Figure 3 d). Most (58% *yes* and 26% *rather yes*) of the participants felt that the directions and explanations were satisfactory (Figure 3 e), and the support of the study team was adequate for most (44% *yes* and 21% *rather yes*) of the participants (Figure 3 f). Many participants never contacted the study team (apart from study registration), resulting in 34% of the participants rating this aspect as *undecided*.

Figure 3. The participants' opinions about data surveys (n=138).



Discussion

The purpose of this study is to assess whether a reduction or elimination of animal proteins from the diet influences the course of existing cancer, and if this tactic can increase remission rates while following standard oncological therapy. Data is being collected using online data surveys.

Study Aims and Approach

To date, only a small number of studies have investigated the effect of nutrition on established cancer. Among these studies, research on CRC, prostate cancer, and breast cancer have given insights regarding the impact of animal proteins on cancer [16,18,20,21]. McCullough et al found higher CRC-specific mortality in patients with consistently high intake of red and processed meat pre- and post-diagnosis, in comparison to those who did not [20]. Interestingly, the difference was not significant if red and processed meat intake were calculated separately. This result could indicate the significance of the total amount of animal proteins and the importance of defining food patterns. This study did not examine a group without meat consumption, possibly reducing the effect size on CRC-related mortality [20].

Richman et al reported that the post-diagnostic consumption of processed and unprocessed red meat, fish, or skinless poultry was not associated with prostate cancer recurrence, whereas consumption of eggs and poultry with skin may increase the risk of recurrence [21]. The FFQ used in this study included 137 food and beverage items and supplements, from which the research team selected five food groups (processed red meat, unprocessed red meat, fish, poultry, and eggs) but did not include dairy products in their analysis. Current research suggests that the intake of dairy products is linked to prostate cancer [32,33], and this finding may have affected patient cancer recurrence rates in the Richman et al study. In another study, researchers observed that men with a high post-diagnostic cruciferous vegetable intake had a statistically significant (59%) decreased risk of prostate cancer progression compared to men in the lowest quartile [34].

It has been demonstrated that breast cancer patients who consumed high levels of soy products had cancer recurrence rates equal to (and in some cases even less than) patients with low consumption [16,18], but it was not reported whether the patients consumed meat, fish, eggs, or milk, and in what quantities. Similarly, Pierce et al reported that breast cancer patients who continued consuming meat, but increased their intake of fruits and vegetables to five portions per day and physical activity to six times per week, had increased survival rates by as much as four fold, in comparison to the lowest intake and physical activity cohort [35].

Animal proteins have been reported to play a significant role in certain cancer types, such as hepatocellular carcinoma of hepatitis-induced carcinoma [36], and may also be a factor in many other cancer types [37-40]. This study aims to approach all cancer types in the pilot study. In addition, we will not examine single foods or food groups, but instead investigate whole dietary patterns. As we divide our study collective into four cohorts (omnivore, lacto-ovo-vegetarian, vegan, or other),

we hope to draw correlations between the amount of consumed animal proteins and cancer progression and survival.

This study will make it possible, for the first time, to estimate the effect size of animal protein consumption in cancer patients, and to stratify for age, body weight, tumor stage, and tumor type. These findings may be of high importance for the selection of certain patient groups for future studies with more detailed questioning.

It is known that dietary advice is difficult to follow for many patients, making it challenging to achieve improved prognoses by dietary advice alone [22,23]. Therefore, it is crucial to examine the acceptance and feasibility of the recommended diet. To this end, tools are needed that can increase motivation and compliance, and reduce attrition rates. Online tools like ours appear to be particularly suitable for this issue, based on a study that used a similar procedure [24].

Changing one's diet to a more plant-based diet has not only been shown to decrease the negative side effects of chemotherapy in cancer patients [6] (such as the severity of vasomotor symptoms [41] and events of hot flush (HF) in HF-positive women recently treated for breast cancer [42]) but also to regulate weight [12], which plays an important role in the outcome of cancer treatments [43,44]. Suggestions that a vegan diet might lead to deterioration have not be empirically proven [45], and intermediate fasting did not have detrimental effects on patients receiving chemotherapy for hematological diseases [46,47].

Self-reported measures have been frequently used and analyzed in psychological studies in recent years [48], but not as extensively in clinical studies. In the context of this study, we developed and tested an Internet study platform, which enabled us to reach a wider population by decreasing the threshold of participation for patients. In addition, the expenditures for both the study team and the patients are clearly decreased. We hope to use the current study to adapt and optimize the portal for future investigations, including study questionnaires and data-collecting processes. The current study platform may allow for more economical and more precise studies regarding the effects of nutrition on existing cancer.

In contrast to statements that self-reported and online-collected data show less validity, publications exist that demonstrate the opposite [25,49,50]. These new technologies have the potential to increase data precision, quality, and quantity [25,49,50], particularly if the technology of this study platform is integrated with tools for precise dietary monitoring in the future.

Preliminary Experiences

The preliminary dropout rate of 67.3% (67/101) appears to be quite high. However, this rate is comparable with other studies performed online, in which dropout rates range from 33% [49] and 34% [51], up to 82% [52] and 88% [53], depending largely on the type of study and if participation was associated with clinical contact and intervention. Dropout rates are also influenced by the disease and stage being investigated.

The questionnaires in this study are very comprehensive (more than 100 items) and contain not only personal questions about symptoms and habits, but also questions referring to medical data. It was important to evaluate whether or not participants were able to complete the surveys. The answers regarding experience and usability of the study platform and questionnaires were encouraging, and the majority of participants did not experience difficulties. This notion is supported by the fact that many more registered participants dropped out between the three study surveys than those who left an incomplete questionnaire. Dropout rate was highest after the first data survey and decreased significantly with each subsequent survey. We therefore conclude that anonymity and lack of contact with the study team caused the attrition rates.

Bias

This study was performed under free-living conditions, and it was not blinded (open-label design). Study participants chose their dietary pattern by themselves, resulting in participants and study team members being aware of the participants' dietary pattern. This factor could introduce performance bias (systematic differences between groups in the care that is provided, or due to exposure to factors other than the factor of interest). When choosing their dietary pattern, participants were not manipulated in any way to choose a certain group, and we did not declare the vegan diet as a sufficient treatment for cancer, which might have led to exaggerated expectations.

As of July, 2016, 10 participants with cancer diagnosis and treatment were recruited via a clinical practice, and agreed to participate in the control group (unchanged omnivore diet). These participants have personal contact with study team members, unlike the rest of the included participants. However, all four groups (omnivore, lacto-ovo-vegetarian, vegan, or other) received the same neutral recommendations for avoiding malnutrition.

We did not exclude certain cancer types or stages, and cannot exclude a bias towards certain cancer types prior to the onset of the study. The distribution of these factors (frequency of certain types and stages of cancer) will be analyzed in the complete study evaluation.

Participants were recruited from various countries, and we considered socioeconomic and gender aspects in our study websites, newsletters, questionnaires, and dietary recommendations. Finally, a possible limitation of a web-based study is the attrition phenomenon, which leads to attrition bias. We aimed to minimize this effect using email reminders, and by offering frequent newsletters, blogposts, articles, and a Facebook site for the study.

Conclusions

To date, most studies addressing the topic of nutrition and cancer have only considered the preventive aspect, while our study focusses on the influence of a plant-based diet on an existing cancer. The results of our study will add useful information to currently existing experimental data, and will indicate whether it is possible to influence the course of an existing cancer by changing dietary patterns, such as animal protein consumption.

With our innovative study design that includes online questionnaires, an Internet platform, dietary recommendations

and motivating newsletters, we aim to demonstrate a cost-effective technique that can be used to carryout future studies on this topic.

Conflicts of Interest

None declared.

Multimedia Appendix 1

The checklist, which serves for potential participants to check their eligibility.

[PDF File (Adobe PDF File), 93KB - resprot_v5i3e157_app1.pdf]

Multimedia Appendix 2

The login area, which can be accessed by the participant via a username and password. Participants can check their study status, fill out forms for unplanned changes in diet or health status, withdraw from the study, or upload new medical reports.

[PDF File (Adobe PDF File), 67KB - resprot_v5i3e157_app2.pdf]

Multimedia Appendix 3

Example page from study questionnaire one demonstrating guidance of users with predefined answer options.

[PDF File (Adobe PDF File), 28KB - resprot_v5i3e157_app3.pdf]

Multimedia Appendix 4

Data obtained at baseline and follow-ups (months 3 and 6).

[PDF File (Adobe PDF File), 33KB - resprot_v5i3e157_app4.pdf]

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Abbreviations

BMI: body mass index
CRC: colorectal cancer
FFQ: food frequency questionnaire
HF: hot flush

ITT: intention-to-treat
WHO: World Health Organization

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Protocol

An Online Learning Module to Increase Self-Efficacy and Involvement in Care for Patients With Advanced Lung Cancer: Research Protocol

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Abstract

Background: Improving patient care for individuals with lung cancer is a priority due to the increasing burden of the disease globally. One way this can be done is by improving patient self-management capabilities through increasing their self-efficacy. This can improve positive outcomes for patients with chronic conditions and increase their ability to manage the challenges of such illnesses. Unfortunately, patients with chronic conditions often struggle to travel far from home to engage with patient education events, a common means of improving self-efficacy. The development of more accessible tools for improving patient self-efficacy is required to increase quality of life for patients with chronic conditions.

Objective: To evaluate the feasibility of delivering symptom identification and management information to patients with advanced lung cancer using an online program.

Methods: This article describes a pre-post test study to evaluate a Qstream online learning platform to improve patient self-efficacy for managing advanced lung cancer symptoms. Undertaking this program should increase participant knowledge about the side-effects they may experience as a result of their treatment and in turn increase help-seeking behavior and self-efficacy for the participant cohort. Quantitative data collected by the Qstream platform on the completion rates of participants will be used as a tool to evaluate the intervention. Additionally, validated scales will be used to collect data on patient self-efficacy. Qualitative data will also be collected via an exit survey and thematic content analysis of semi-structured interviews.

Results: The research is in the preliminary stages but thus far a protocol has been approved in support of the project. Additionally, advisory committee members have been identified and initial meetings have been undertaken.

Conclusions: Development of new approaches for increasing patient understanding of their care is important to ensure high quality care continues to be delivered in the clinical setting.

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KEYWORDS

patient education; eHealth; online learning; lung cancer; palliative care; side-effect management; patient safety and quality; patient self-efficacy

Introduction

In 2012, 1.82 million people globally were diagnosed with lung cancer, making it the most commonly diagnosed cancer [1]. The World Health Organization predicts that by 2020 that number will increase to 2.2 million [2]. In Australia, nearly 80% of lung cancers are diagnosed at an advanced stage when prognosis is poor, and the overall survival rate is only 15% [3]. These patients often experience multiple symptoms as a result of their disease and/or treatment, including unrelieved pain, breathlessness, distress, and nausea and vomiting [4-5]. Appropriate management of these symptoms is important due to the negative impact on patients, which may include hospitalization if these symptoms are poorly controlled [6].

Managing symptoms in the community requires patients and their caregivers to have good self-management capabilities to ensure they are capable of optimally handling both pharmacological and nonpharmacological interventions. Factors that reduce patient self-efficacy include low health literacy and lack of involvement in treatment decision making. This is particularly concerning considering the literature has shown that both health literacy and involvement in shared decision making significantly impact patient satisfaction and treatment outcomes [7]. There is also evidence that patients with lung cancer may have a diminished understanding of their illness and prognosis and less support in facing end-of-life issues [3]. As a result, these patients are less likely to be proactive in symptom management or demonstrate help-seeking behaviors that could improve their quality of life.

The ability of patients to self-manage aspects of treatment is important because it has been shown to improve outcomes for patients. Doing so can also increase the likelihood patients will successfully manage the challenges of chronic illness [8-9]. One approach to doing this is through the delivery of face-to-face patient education programs. However, these programs could also be delivered online, increasing accessibility for patients unwilling or unable to attend patient education events as a result of their condition. Additionally, there is evidence to suggest an online self-management program can impact self-care and health behaviors in patients [10].

This protocol describes a methodology designed to develop and evaluate a new approach to increasing disease literacy and help-seeking behavior in patients, a high priority for clinicians and patients alike [11]. In addition to the potential benefit of reducing hospital use costs, earlier treatment of side-effects resulting from better patient education may lead to patients receiving more of their planned therapy. A phase I feasibility study design is being used to evaluate the impact of an online learning program on self-efficacy and help-seeking behavior in patients with advanced lung cancer. The project aims to improve the quality of life for these patients by increasing their ability to identify and manage symptoms of their treatment.

Methods

Aims

The proposed study evaluates the feasibility of delivering an online self-efficacy program to patients with advanced lung cancer using an online education platform. This program will provide patients with relevant information to identify symptoms resulting from their treatment and provide them with strategies to manage these symptoms when they occur. Additionally, the study aims to assess the impact of the intervention on patient self-efficacy and help-seeking behavior.

In the context of this study, feasibility, including whether the patient population will complete a self-efficacy program delivered online, is being evaluated from the perspective of the patient and not the clinical organization. Additionally, the study will look at whether participants found the program beneficial for identifying and managing their treatment symptoms. This will be evaluated using semistructured interviews.

Design

A pre-post test design is being used to evaluate an online learning program for improving patient self-efficacy in managing symptoms of treatment for advanced lung cancer. Use of the program should increase participant knowledge about side-effects they may experience and in turn increase help-seeking behavior and self-efficacy for the patient cohort. The online module in this study will be delivered on the Qstream spaced education platform.

Qstream is an evidence-based form of online education that has been shown to improve knowledge acquisition, enhance knowledge retention, and change behavior [12]. Participants in Qstream courses receive repeating, short, case-based questions as well as expert feedback via email in a reinforcing pattern over a number of weeks. The methodology is based on two core psychological research findings: the spacing and testing effects. The *spacing effect* refers to the finding that educational encounters repeated over time increase the acquisition and retention of knowledge. The *testing effect* refers to the finding that the process of testing not only measures knowledge but also improves retention [13-14].

The Qstream spaced learning platform has repeatedly been shown in medical professional development to impact learner knowledge, resulting in behavior change [15]. However, its utility as a tool for engaging with patients has yet to be explored. Existing research on health literacy has shown that improving patients' knowledge about their treatment can positively impact on quality of life by reducing anxiety and mood disturbances [16]. However, current interventions aimed at improving patient knowledge about treatment side-effects are often either health provider–focused applications or passive dissemination of information in written or Web-based materials [17]. In this study, the Qstream platform will be used for dissemination of key information in a dynamic, personalized, and active manner.

Based on the current research into Qstream as a tool for knowledge dissemination and reinforcement, there is reason to believe it has potential as a means of improving self-efficacy for cancer patients [12]. In addition, the platform has been shown to be easily accessible to learners due to its ability to deliver short, focused pieces of key information at times that suit the learner [18], making the platform adaptable to individual patient information needs.

Quantitative data collected by the Qstream platform on the completion rates of participants will be used as a tool to evaluate the intervention. Additionally, validated scales will be used to collect data on patient self-efficacy. Qualitative data will also be collected via a survey at the conclusion of the module and thematic content analysis of semistructured interviews.

Setting

This study will be undertaken within the Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, Australia, which runs a dedicated clinic to support patients with a new diagnosis of lung cancer.

Study Inclusion and Exclusion Criteria

Eligible participants will be age 18 years or older with a new diagnosis of stage II to stage IV lung cancer and a life expectancy greater than three months. Additionally, participants will need access to an Internet connection and a level of spoken and written English adequate to understand the Qstream cases. Patients who are considered too physically or mentally unwell to participate in the study, do not have adequate English skills, or do not have access to the Internet will be excluded from this study.

A clinical nurse consultant experienced in supporting patients with advanced lung cancer will meet with potential participants to assess their eligibility. This identification process is being used instead of alternative methods such as the Eastern Cooperative Oncology Group (ECOG) status or treatment algorithm due to the difficulty of determining whether patients are physically well enough to participate in the study.

Study Recruitment

The research team aims to recruit 60 patients from the new lung cancer clinic between January and June 2016. Given that approximately 40 new patients are referred every month, we estimate it will take six months to recruitment 60 patients. This cohort size accounts for an attrition rate of 30%, consistent with other online programs [19].

Developing the Side-Effect Management Online Learning Module

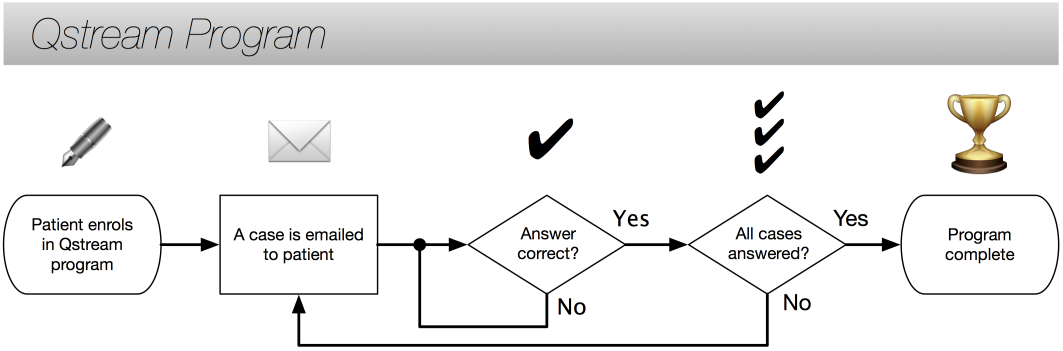
A brief review of the literature will be undertaken to identify which key symptoms, such as pain management or constipation, are identified as having significant quality-of-life impact for patients with advanced lung cancer. The identified symptoms will inform the focus of the side-effect management program. In addition to a literature review, a local retrospective record audit of between 40 and 60 patients who attended the new lung cancer patient clinic at Westmead Hospital will be undertaken. The local audit will review the symptom burden in the local population to ensure it aligns with the literature.

To oversee the development of the side-effect management program, an expert advisory committee will be convened with representatives from a range of clinical disciplines including at least one representative from the medical oncology, nursing, and palliative care services. This advisory group will have a central role in determining the key messages of the online program, which will be used to develop cases for the Qstream platform. Additionally, the advisory committee will review and prioritize the key domains that the side-effect management program will address.

The Qstream program will consist of approximately one dozen cases in order to convey necessary information. Cases will be developed in two different categories: symptom identification and symptom management, including when to seek medical assistance. Cases will have a consistent format and include an example of a common event encountered as part of lung cancer treatment along with advice on how to address this scenario. In each key symptom domain, there will be a case example guiding participants through identification of a symptom and when and how to seek help if a symptom is unmanageable.

For each case, participants will be given a choice of options for how to respond to the situation, of which they will select one. Once participants have selected an option they will be shown how their response compares to other participants undertaking the program. All participants will be given aliases to use in the Qstream platform to ensure patient confidentiality is maintained. In addition to presenting responses of other participants, each case will contain video feedback from a member of the lung cancer team at Westmead Hospital to reinforce the correct approach in a friendly, accessible, and personalized manner. Finally, written feedback will be provided along with links to further resources for participants to explore if they wish. See Figure 1 for a flow chart of patient movement through the Qstream program.

Figure 1. A flow chart showing how patients work through the Qstream program.



Implementing the Side-Effect Management Online Learning Module

Once the side-effect management module has been completed it will be made available to study participants. All participants will be automatically enrolled in the Qstream program and receive cases via email or smartphone in the following manner:

1. Each participant will be sent an email every 2 days containing at least 2 questions.

2. If they answer a question incorrectly, it will be re-sent 5 days later.

3. If they answer a question correctly, the question will be re-sent 8 days later.

4. If a question is answered correctly twice in a row, the question will be retired.

5. The course will be completed once all questions have been retired.

We anticipate that most participants will take between 4 and 6 weeks to complete the Qstream program.

Evaluating the Side-Effect Management Online Learning Module

Baseline Data Collection

Baseline data will be collected for the study prior to the dissemination of the Qstream intervention. The research team will use validated surveys to collect information on participant self-efficacy, technical literacy, and involvement in care.

Six weeks after completion of the course, participants will be asked to repeat the survey and answer a number of questions evaluating the Qstream program. Additionally, patients will be invited to participate in an endpoint semistructured interview to evaluate their perception of the impact of the course on their self-efficacy and quality of life. See Table 1 for the tools being used to collect data throughout the study and the time points at which they are being used.

Finally, metrics collected routinely by the Qstream platform will be reviewed to determine usage of the program. A particular focus will be on the number of participants who complete the program and how many cases were completed by participants who do not.

Table 1. Overview of measurements used in the study and timing of data collection.

Measures	Pre-intervention	Intervention	Post-intervention
Self-Efficacy for Managing Chronic Disease 6-Item Scale	X		X
Online Technologies Self-Efficacy Scale (OTSES)	X		
Lerman Perceived Involvement in Care Scale (PICS)	X		
Eastern Cooperative Oncology Group (ECOG) score	X		X
Symptom diary		X	
Exit survey			X
Semistructured interviews			X

Self-Efficacy for Managing Chronic Disease 6-Item Scale

The Self-Efficacy for Managing Chronic Disease 6-Item Scale [20], developed by the Stanford Patient Education Research Center, will be used to rate participants across several domains common in chronic disease including emotional functioning and symptom control. The scale is based on a larger self-efficacy scale developed for the Chronic Disease Self-Management Study [21].

The scale requires respondents to rate 6 items on a scale of 1 to 10, where 1 indicates “not at all confident” and 10 indicates “totally confident.” The scale was tested on a cohort of 244 individuals with chronic disease: the mean score was 30.24, with a standard deviation of 6.28 and internal consistency reliability (Cronbach alpha) of .93 [20]. Although the tool has not been used with lung cancer patients, it has been used to measure self-efficacy in breast cancer patients [22].

Online Technologies Self-Efficacy Scale

To evaluate the technical literacy of participants, the Online Technologies Self-Efficacy Scale will be used. The validated scale was developed in 2000 to assess respondent confidence across a range of domains including use of email, use of Web browsers, and navigation of websites [23]. The scale was tested on a cohort of 330 tertiary level students. The Cronbach alpha is .95.

Lerman Perceived Involvement in Care Scale

The final validated scale being used is the Lerman Perceived Involvement in Care Scale (PICS). This tool will be used to collect baseline data on participant perception of involvement in their care. The PICS has 13 items that were validated using a test cohort of 131 individuals. The Cronbach alpha is .73. An alpha coefficient of .60 was determined using an independent sample of 81 patients [24]. This tool has been used effectively with a number of patient populations including a group of 1081 early stage breast cancer patients [25].

Eastern Cooperative Oncology Group Score

The ECOG score will used to collect baseline data regarding disease progression and other treatment information. Information for this ranking, along with basic demographic data such as gender, age, and postal code, will be obtained from the patient medical record.

Symptom Diary

To minimize recall error, participants will be asked to keep a diary to capture incidences of symptoms that occur during the intervention [26]. Study participants will be provided with a prestructured diary booklet to use as a guideline that includes instructions on what to include in entries and an example of an entry. The booklet will be accompanied by a cover letter reenforcing the outline and the disease-specific information to be included. Contact information will be provided for participants who have questions. At the conclusion of the study period, the diary will be evaluated for feasibility as a measurement tool and influence of the intervention on symptom management. The diary entries may be discussed with patients in a later interview.

Data Analysis

The primary goal of this study is to assess the feasibility of delivering treatment self-management information to patients using the Qstream platform. Quantitative data collected by the platform will be analyzed to gain insight into the uptake and completion rates of the program by the study participants. Additionally, qualitative data will be analyzed to measure the impact of the program on symptom management knowledge, self-efficacy, and help-seeking behaviour.

Quantitative data on patient self-efficacy is being collected via a validated survey administered at two time points: two weeks prior to intervention and two weeks postintervention. All data analysis will be performed using SPSS statistical analysis software (IBM Corp). The after minus before difference will be measured for each patient who completes both the pre- and postsurvey. The average of the before/after difference will be determined to test the hypothesis that the difference is not zero. A matched *t* test will be used at a level of significance set at 0.05. The difference (as a 95% confidence interval) and the *P* value will be presented.

Qualitative data is being collected through semistructured interviews with participants. This data will be thematically analyzed to identify emergent and overarching themes with characteristic quotes used to exemplify each theme. Two researchers will read each transcript and independently create a draft coding scheme. This will be discussed, and any differences will be resolved in consultation with the wider research team. Additional transcripts will be read with iterative refinement of the draft coding scheme. An appropriate software program will be used to organize the data and allow development of themes, subthemes, and higher order themes, with characteristic quotes. The final thematic summary will be sent to a subset of participants who will be phoned for feedback on the accuracy of this summary.

Ethical and Legal Considerations

As of January 2016, the protocol has been granted ethical approval by the Western Sydney Local Health District Human Ethics Committee. To obtain ethical approval this study was evaluated for compliance with the National Statement on Ethical Conduct in Human Research 2007 and the National Health and Medical Research Council guidelines under Section 95 of the Privacy Act 1988.

Data Storage Procedure

All data collected from participants will be deidentified and coded with a participant identification code on a master log sheet by a member of the research team. Participant codes will be kept in a password-protected Excel spreadsheet on a password-protected electronic database. Only deidentified information will be used by members of the research team when data analysis is being undertaken.

Information collected for, used in, or generated by this project will remain securely stored in the offices of the principle investigator. For digital information, this will involve storage password-protected personal computers. Paper copies will have identifiers removed and will be stored in a locked filing cabinet.

Potential Risks

There is a risk that some participants may experience distress during this study. Participants will be provided access to a counseling service if they are experiencing distress. Information on how to contact the counseling service will be provided to participants when they register for the study. Loss of confidentiality is an additional risk of this study. Researchers are minimizing this risk by following the data storage procedure outlined earlier in this protocol.

Results

This protocol describes a research study in its preliminary stages and, as such, only modest results can be reported. One significant outcome is the development of a comprehensive method for evaluating the impact of a online program for delivering symptom identification and management information to patients.

An expert advisory committee including medical oncologists, palliative care specialists, and clinical nurse consultants has been identified and convened to guide the direction of this project. Initial consultation with the advisory committee has identified symptoms that will be targeted by the Qstream program. The advisory committee has decided pain management, breathlessness, constipation, nausea, and lethargy would be the most relevant areas to address for the patient population in this study. All of these symptoms are identified in the literature as being challenging for patients to self-manage.

Discussion

Prinicipal Findings

The development of tools to support patient self-efficacy in managing advanced lung cancer is important due to the significant burden cancer represents globally [1]. Although interventions exist to improve patient health literacy and increase patient involvement in their care, these interventions largely focus on passive dissemination of information [17]. This research protocol explores an online knowledge dissemination module that has been demonstrated to impact both knowledge and behavior [12]. The Qstream platform has not previously been used for patient education but has been used extensively for delivering health education to other groups [15]. As a result, the findings of this study contribute to addressing a clear gap in the current literature.

Although the program is being evaluated in the context of lung cancer, it has potential to be used across a range of other cancers and chronic conditions. The literature on symptom prevalence for patients with advanced lung cancers shows that patients with this condition experience nausea and vomiting, and symptoms resulting in patient hospital admission include pain and dyspnea [6]. These symptoms are not unique to lung cancer and are prevalent across chronic conditions including heart disease, AIDS, and renal disease [27]. If the intervention is effective with patients with lung cancer it may be applicable across a much broader patient population.

Finally, in order to ensure a high quality of care continues to be delivered to patients, the evaluation of new techniques for dissemination of patient information is a priority. Unfortunately the literature to date suggests that there is a gap in knowledge relating to the identification and uptake of appropriate behavior change techniques to promote such behaviors in patients [28]. By evaluating the impact of Qstream on patient self-efficacy and help-seeking behavior we anticipate that a significant contribution will be made to address this gap in the literature.

Conclusions

Developing and evaluating new techniques for dissemination of patient information to enhance patient self-efficacy and understanding of their care is integral for ensuring high quality care continues to be delivered in the clinical setting. This is particularly important for treatment of chronic conditions such as advanced lung cancer, because optimal delivery of such information can improve patient self-efficacy and ensure a high quality of life is maintained during end-of-life care.

Conflicts of Interest

None declared.

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Abbreviations

ECOG: Eastern Cooperative Oncology Group
PICS: Perceived Involvement in Care Scale

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Protocol

Large-Scale Wearable Sensor Deployment in Parkinson's Patients: The Parkinson@Home Study Protocol

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Abstract

Background: Long-term management of Parkinson's disease does not reach its full potential because we lack knowledge about individual variations in clinical presentation and disease progression. Continuous and longitudinal assessments in real-life (ie, within the patients' own home environment) might fill this knowledge gap.

Objective: The primary aim of the Parkinson@Home study is to evaluate the feasibility and compliance of using multiple wearable sensors to collect clinically relevant data. Our second aim is to address the usability of these data for answering clinical research questions. Finally, we aim to build a database for future validation of novel algorithms applied to sensor-derived data from Parkinson's patients during daily functioning.

Methods: The Parkinson@Home study is a two-phase observational study involving 1000 Parkinson's patients and 250 physiotherapists. Disease status is assessed using a short version of the Parkinson's Progression Markers Initiative protocol, performed by certified physiotherapists. Additionally, participants will wear a set of sensors (smartwatch, smartphone, and fall detector), and use these together with a customized smartphone app (Fox Insight), 24/7 for 3 months. The sensors embedded within the smartwatch and fall detector may be used to estimate physical activity, tremor, sleep quality, and falls. Medication intake and fall incidents will be measured via patients' self-reports in the smartphone app. Phase one will address the feasibility of the study protocol. In phase two, mathematicians will distill relevant summary statistics from the raw sensor signals, which will be compared against the clinical outcomes.

Results: Recruitment of 300 participants for phase one was concluded in March, 2016, and the follow-up period will end in June, 2016. Phase two will include the remaining participants, and will commence in September, 2016.

Conclusions: The Parkinson@Home study is expected to generate new insights into the feasibility of integrating self-collected information from wearable sensors into both daily routines and clinical practices for Parkinson's patients. This study represents an important step towards building a reliable system that translates and integrates real-life information into clinical decisions, with the long-term aim of delivering personalized disease management support.

ClinicalTrial: ClinicalTrials.gov NCT02474329; https://clinicaltrials.gov/ct2/show/NCT02474329 (Archived at http://www.webcitation.org/6joEc5P1v)

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KEYWORDS

Parkinson's disease; ambulatory monitoring; signal processing; computer-assisted; wearable sensors

Introduction

Parkinson's disease (PD) is a progressive and complex neurological disorder. Patients can experience a wide range of motor symptoms and signs, including bradykinesia, tremor, rigidity, and postural instability. Non-motor symptoms include executive dysfunctions, memory disturbances, attention difficulties, and reduced ability to smell [1-3].

The cornerstone of current therapy is based on the replacement of dopamine, but can also include other drugs that play a role in the activation of dopamine receptors [4]. Although these medications initially have good results in disease management, the effects remain successful for a limited period of time. Most patients eventually develop motor complications, such as the wearing-off effect or dyskinesias [5,6]. Some disease symptoms, such as postural instability and voice/speech impairment, are insufficiently (or sometimes not at all) responsive to dopaminergic therapy.

Two major problems hamper the delivery of optimal individual treatment. First, evaluation of day-to-day variations in a complex disease such as PD is difficult when relying solely upon periodic consultations with experts working in a clinical setting [7]. Even when health professionals use specific and validated instruments, such as the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [8], the results represent a subjective and episodic *snapshot* taken under well-controlled conditions, which are usually not representative of the patient's functioning in daily life. More detailed, objective, and reliable knowledge about real-life functioning would greatly improve the quality of individual medical management. Second, virtually all scientific evidence that is presently available to inform PD management stems from biased clinical studies with short follow-up periods in highly selected sub-populations, who were studied under carefully controlled trial conditions [9,10]. As such, this evidence does not reflect the clinical presentation, treatment response, or disease progression in actual daily life.

To overcome these limitations, wearable sensors are emerging as new tools to continuously and longitudinally obtain information from patients in real-life. The accuracy of sensor data for everyday activity recognition (eg, walking, running) in real-life ranges from 58% to 97% [11]. These sensors, typically consisting of embedded accelerometers, have been used successfully to determine PD-related symptoms [12-16]. However, to date these studies have relied upon small sample sizes (n=5 to 43 participants) and short follow-up periods (3 days to 6 months; see Multimedia Appendix 1).

The primary aim of the Parkinson@Home study is to evaluate the feasibility and patient compliance of using wearable sensors to collect data for at least 3 months in a large patient group. A secondary aim of this study is to address the usability of these data for answering clinically relevant research questions (eg, to determine the relationship between sensor-derived measures and clinical measures). Finally, the study aims to build a database for future development and testing of novel algorithms applied to sensor-derived data from PD patients during daily functioning.

Methods

Study Design

The Parkinson@Home study is an observational study involving 1000 patients (from whom data will be recorded) and 250 physiotherapists (who will assist in performing the clinical assessments, and who may act as personal coaches during follow-up). Both patients and therapists will be recruited throughout the Netherlands. The study consists of two phases. Phase one aims to assess the feasibility of deploying wearable sensors in a large PD population (n=300). For this purpose, patients will use a number of wearable devices (Pebble smartwatch, Android smartphone, and fall detector) in combination with a customized app (Fox Insight). Follow-up will occur after 3 months (13 weeks), starting from the moment the first data are streamed to the server. In addition to using wearable devices, participants will attend a one-time consultation, during which a detailed clinical assessment will be performed by an experienced physiotherapist or a research team member. This clinical assessment will take place in week 7, or later during the follow-up period. Phase two, which will include an additional 700 participants, aims to collect raw sensor data in order to investigate the usability of these data for answering clinical research questions. This phase will also be used to build a database for future validation of novel algorithms applied to sensor-derived data from PD patients during daily functioning. Patients involved in phase one can also be included in phase two if they wish. Data collection for clinical results and device-based outcomes, as well as the follow-up period, will be identical to phase one. To ensure the success of the raw data collection during phase two, devices and raw data collection strategies used in this phase will be chosen after the evaluation of data collected during phase one.

The study protocol was successfully piloted prior to full study implementation to ensure methodological feasibility. In total 20 Dutch PD patients participated in this pilot, using a set of wearable devices (one smartphone and one smartwatch) and the Fox Insight app. The patients were asked to use these devices for 24 hours, seven days a week, and were followed for four weeks. In total, 58% of patients that were approached agreed to participate. Some patients were reluctant to manage technology and to deal with possible technical problems, which caused them to refrain from participation. All participants

(except for two) needed at least one support call for device troubleshooting. Streaming compliance for the sensor data was 88%.

Inclusion and Exclusion Criteria

Patients

The inclusion and exclusion criteria for patients will be kept purposefully broad, in order to represent the full diversity of real-life PD experiences. Inclusion criteria specify that patients must be 30 years of age or older, and be diagnosed with PD by a physician. No exclusion criteria will be applied.

Physiotherapists

Physiotherapists who are members of the Dutch ParkinsonNet [17,18] are eligible to participate. ParkinsonNet physiotherapists have received several PD-specific educational training programs, and treat a high number of PD patients each year. Physiotherapists who want to participate should take the official MDS-UPDRS course (provided online by MDS [19], and further in person training provided by the research team) and be able to include and/or assess an average of four PD patients for the study.

Patient Recruitment Process

We will apply an incremental recruitment strategy. Initially, we will only include patients that already possess a compatible Android/iPhone smartphone. Subsequently, and only if needed, we will include patients that do not possess a smartphone; these patients will be provided with a loaned smartphone device. The reason for this incremental approach is that patients with their own device will likely require less technical support from the research team, as was the case in our pilot study. This strategy will increase the feasibility of complete data collection in a total of 1000 patients.

Patients will be recruited both in the community and through their treating physiotherapists. To reach potential participants in the community, we will use a number of communication channels: (1) the ParkinsonConnect community, an online community for Parkinson's patients and healthcare professionals involved in their care [18]; (2) the webpage of the Dutch Parkinson Patient Association; (3) an article in the magazine of the Dutch Parkinson Patient Association; (4) presentations about the study to local patient support groups (*Parkinson Cafés*); (5) promotional material for patients will be sent to all ParkinsonNet physiotherapists (approximately 990 individuals), regardless of whether they participate in the study or not, and we will ask them to recruit patients within their practice; and (6) via a study website [20] which provides information about the study. The study website offers both patients and physiotherapists the possibility to sign up for the study online.

After signing up for the study, potential participants will be contacted by phone by a member of the research team, who will provide additional information about the study and check eligibility. If respondents are eligible and willing to participate, they will receive an informed consent form. After the informed consent form has been signed digitally, the research team will provide the participant with all necessary devices and user manuals.

Recruitment and Training of Physiotherapists

All ParkinsonNet physiotherapists will be contacted by email to inquire about study participation. Should this email not result in adequate numbers of participating physiotherapists, we will personally contact ParkinsonNet physiotherapists by telephone. As with the recruitment process for patients, after signing up via the study website, physiotherapists will be contacted by email or phone to check eligibility.

Once included, physiotherapists must pass the online MDS-UPDRS training successfully [19], as required by the International Parkinson and Movement Disorder Society, which allows them to perform the MDS-UPDRS [8]. After successful completion of the training, physiotherapists will participate in one face-to-face training session, in which they will assess one patient, in order to practice the MDS-UPDRS assessment and consolidate their understanding of the assessment process and study procedures.

Ethical Aspects and Trial Registration

This study will be conducted in compliance with the Ethical Principles for Medical Research Involving Human Subjects, as defined in the Declaration of Helsinki. The study protocol and communication materials have been approved by the local ethics committee (Commissie Mensgebonden Onderzoek, Arnhem-Nijmegen; NL53034.091.15).

Consent will be obtained by the research team through an innovative online procedure, which includes a compulsory cooling-off period in a digital environment. When the patient is deemed eligible (eg, meets the inclusion criteria specified in the online sign-up form), an information letter and consent form will be send by email. The research team and an independent physician can be approached for questions and verbal explanation. Next, the potential participant has the possibility to confirm participation digitally, via a new URL sent to him/her by email after 48 hours. The URL redirects the patient to the study webpage, where he/she can confirm that they have read all information and that they agree to participate. As recommended by the ethics committee, this final step is blocked for 48 hours after the first email has been sent, to ensure that potential participants take time to consider participation. After the agreement to participate, the participant will see a confirmation message on the study webpage. No signature or scanning of documents will be necessary at this point. The Parkinson@Home study is registered in the ClinicalTrials.gov registry (NCT02474329) [21].

Wearable Sensors Phase One

Pebble Smartwatch

The Pebble is a commercially available smartwatch, with a variety of embedded sensors, such as tri-axial accelerometer, light sensor, and magnetometer. Accelerometers are able to record acceleration along three orthogonal spatial axes, producing acceleration vectors as single data points, and up to 100 acceleration data vectors can be recorded per second. The Pebble smartwatch operating software allows access to the unprocessed *raw* accelerometer data vectors, creating the opportunity for subsequent analyses of this sensor data. In order

to obtain continuous accelerometer data, the Fox Insight app will be installed on each smartwatch. The app enables streaming of the accelerometer data to the smartphone, with a sampling frequency of 50 data vectors per second, using the built-in Bluetooth radios of both the smartwatch and smartphone.

Fox Insight App

The Fox Insight app is an Android/iPhone app created and developed by Intel Corporation (Tel Aviv, Israel). This app receives 50 accelerometer data points per second from the Pebble smartwatch, and estimates levels of activity, tremor, and sleep movement analyses using dedicated algorithms running within the app. The app presents these estimated quantities to the user by means of graphs and summary reports of the data collected.

Activity graphs show the level of activity throughout the day (Figure 1). The calculation is performed by aggregations (30 second intervals) of the raw data previously collected. The graph also highlights the moments in time when medication was taken.

Daily tremor graphs show how many minutes the patient has experienced tremor during a certain day (a tremor is defined as any movement in the range of 3.5-12Hz). Sleep analysis graphs (Figure 2) show the amount of time that the patient has been active during the sleep time. These graphs provide an impression of the intensity and duration of movements.

These estimated quantities are sent every 10 minutes to a cloud-based data platform through an Internet connection on the smartphone. Different mechanisms allow the participants to know whether the data are recorded correctly. First, participants can check the metric graphs (eg, activity graph, sleep analysis, and tremor); these graphs are plotted using the data recorded in the servers, and will only appear if the data were collected. Second, the main app screen (Figure 3) displays how many hours of data the participant has contributed to the study; if this metric does not increase it means the data are not being collected. Finally, participants can view the white *pill* icon in the smartphone task bar; if the icon has a crossing line over it, data are not being actively recorded.

Figure 1. Fox Insight Mobile App activity graph.

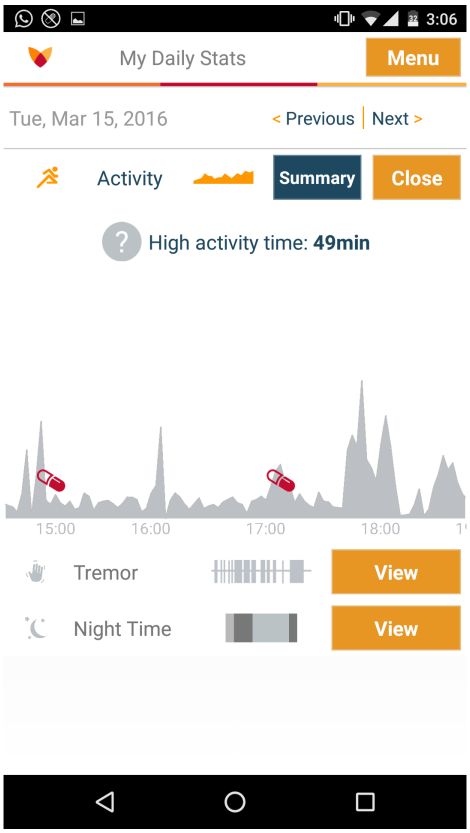


Figure 2. Fox Insight Mobile App sleep analysis graph.

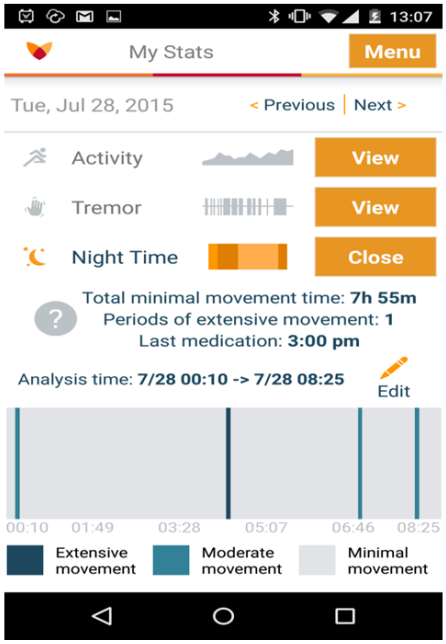
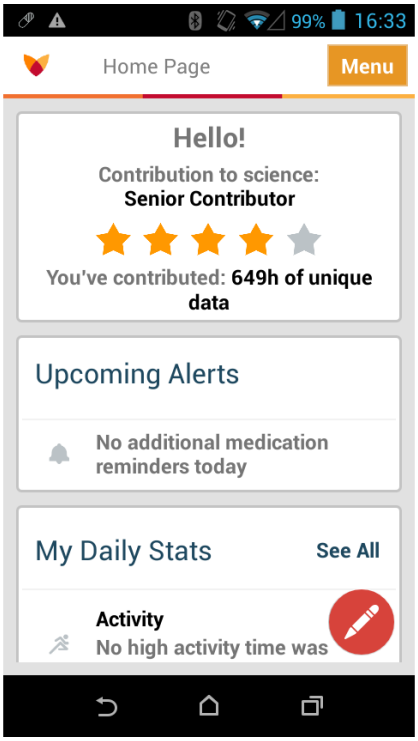


Figure 3. Fox Insight Mobile app main screen.



Fall Detector

Falls and movement patterns are measured with a pendant device. Patients are given the choice to wear either a fall detector (FD), or the Philips Mobility Monitor (PMM) [22,23]. Both sensors are CE-marked non-medical devices; the PMM is developed by Philips Research. The FD device used in this study is an adapted fall detection device, originally intended for seniors living in their own homes, that was designed to detect falls from stance. The FD device can be worn 24/7, while the PMM is recharged overnight and thus only worn during the day. The FD device uses multiple sensors and a proprietary analytical algorithm to detect some types of fall events, which are stored in the device. The PMM contains a 3-axial accelerometer and a barometric pressure sensor, with a sampling frequency of 50Hz and 25Hz, respectively. Data are continuously recorded and stored on a micro SD card within the device. Based on these data, information about the daily movements, as well as falls detected, are calculated after read-out at the end of each patient's trial period.

Wearable Sensors Phase Two

Devices will be chosen after analysis of the study procedure, and data collection is complete in phase one.

Technical Support

Patients will have access to extended support, including an installation guide, user manual, and information on the study's webpage. For the duration of the study, a helpline will be available during working hours to support the installation and device usage, and for troubleshooting.

Clinical and Feasibility Assessment

Certified physiotherapists will perform the short version of the Parkinson Progression Marker Initiative (PPMI) in order to assess disease status [24]. This assessment includes: the MDS-UPDRS (parts I, III, and IV) for disease rating [8]; the Montreal Cognitive Assessment for cognition [25]; and the Modified Schwab and England Activities of Daily Living Scale for activities of daily living [26].

Additional questionnaires will be completed by the patients: MDS-UPDRS part II for motor experiences of daily living; the Scales for Outcomes in Parkinson's Disease - Autonomic System (SCOPA-AUT) for autonomic dysfunction [27]; the Geriatric Depression Scale for depressive symptoms [28]; and the Epworth Sleepiness Scale for day sleepiness [29].

To assess feasibility, patients will also complete the System Usability Scale [30] and a satisfaction survey created by the research team, to address patients' impressions on how well particular features of the app are functioning, and the burden associated with the methodology. An overview of outcomes is provided in Multimedia Appendix 2.

Data Collection and Management

Due to privacy issues, patients will receive a personal identification code that does not contain any information that relates to the individual. The key-file, connecting personal identification codes to personal information, will be stored on a Radboudumc data server, and only the research team has access to the key-file. The key-file will be stored on a different server from the study data for five years, allowing the research team to contact patients after they have finished the study. We anticipate that our efforts to obtain additional research funding will allow for additional follow-up assessments. The key-file will be destroyed after five years.

Data for the study will be collected in the following ways:

Data from smartwatch and smartphone: data will be collected continuously in a coded manner, and will be transferred to Intel's cloud data storage environment using an Internet connection. The cloud environment is based on Amazon Web Services, and developed and managed by Intel's Advanced Analytics team. Data from the watch and Fox Insight app will be transferred to the Intel platform using a personal identification code for each patient. Moreover, no personally identifiable data will be entered into the app or sent to this data storage platform.

Data from the PMM and FD: data will be collected during the time that patients are not lying in bed. Each FD has a unique identifier, and Philips Research will only receive coded data. No personal information is required to use these devices, and no personal data from patients will be shared with Philips.

Data from the clinical assessments: data will be collected by means of paper-based forms, and will be entered manually into an online certified data management system. Forms will only contain personal identification codes.

Data from support and logistics: ZenDesk software will be used to support the logistics of the recruitment process, and provide technical support during the follow-up phase. ZenDesk is Internet-based, and data access is authenticated by username and password. All communications with ZenDesk servers use industry-standard Secure Sockets Layer encryption by default, and the ZenDesk servers are located at a different site than the Amazon servers. Therefore, research data is never stored on the same server as patients' identifying codes.

Patients that complete the clinical assessment and stream data for more than seven days will have their data included in further analyses.

Data Analyses

Phase One

Feasibility and compliance will be addressed using descriptive analyses. For feasibility, the primary outcomes will include the total support time per participant, the number and rate of drop-outs, usability of the system, bias within recruitment strategies, and the type of problems faced by patients. Regarding compliance, the outcome measures include the total hours of sensor data collected per participant, the number of compliant days, and the percentage of time that sensor data were streamed during the follow-up period.

Phase Two

The potential for the data to answer clinically relevant research questions will be explored. First, we aim to extract a limited set of outcomes, including: the number, diversity, and performance of physical activities; specific activities (eg, standing, walking, sitting); response fluctuations in relation to drug treatment; and specific motor symptoms (eg, tremor, gait freezing, shuffling, falls).

Additionally, we aim to explore how these outcomes are related to clinical assessments, and to self-monitoring during follow-up (including timing of medication intake and fall incidents). Finally, we aim to extract patterns of disease progression, assess the recognition of disease profiles based on reported symptoms and progression patterns, and address the effect of medication intake on symptoms. In both phases, analyses will be performed using specialized algorithms (when necessary) developed within the Matlab platform, with additional statistical analyses using the R software package.

Results

Patient Recruitment Process

Within eight months of recruitment (August, 2015 to March, 2016) the Parkinson@home study received 1164 applications. Among those invited for phase one (n=342), the participation rate was 87.7%, resulting in 300 inclusions. Recruitment

strategies through the network of the Dutch Parkinson Association, and a personal approach by the research team or health care providers, have been very successful (Table 1). *Applicants* include all respondents that demonstrated interest in the study, while *participants* include all respondents that were actually included in the study (which excludes dropouts and those who refused to participate). Phase two will begin in September, 2016, and participants will be recruited from the 734 participants placed in the study waiting list.

Table 1. Number of applications obtained from each recruitment strategy.

Recruitment Strategy	Applicants n=1164 (%)	Participants n=258 (%)
Online community for patients (ParkinsonConnect)	12 (1.03)	8 (3.10)
Website of the Dutch Parkinson Association	142 (12.19)	20 (7.75)
Article in the magazine of the Dutch Parkinson Association	451 (38.74)	100 (38.75)
Informative presentation at Parkinson Cafés by research team	112 (9.62)	36 (13.95)
Personal invitation by Physiotherapist or Neurologist	198 (17.04)	31 (12.02)
Others	224 (19.24)	51 (19.77)
Not specified	25 (2.14)	12 (4.65)

Discussion

In this paper we present the rationale and design of the Parkinson@Home study, a large (n=1000) observational cohort study that aims to explore the feasibility and usability of collecting raw sensor data from wearable sensors in patients with PD. There is a pressing need for collection of reliable medical information from PD patients while they perform activities of daily living, due to gaps in knowledge as to why different patients have variable rates of PD progression and different patterns of symptoms [31,32]. It has proven to be extremely difficult to understand such variations, and to capture objective data about the patient's actual functioning in current clinical practice, which typically consists of episodic and brief clinical evaluations in hospitals.

Gathering data from wearable sensors has high scientific potential and offers several advantages compared to more traditional methods of data collection. Wearable sensors offer the possibility to collect data by self-administered tests, and to objectively monitor PD symptoms and day-to-day variation both remotely and at home [33-35]. The raw sensor data can be analyzed later by specialized algorithms or by algorithms embedded in apps themselves, providing scientific insights for researchers and clinicians. Moreover, data can be collected continuously over a prolonged period of time. For individual PD patients, those data can be used for long-term health monitoring. When applied in a group context, the data may offer a better understanding of PD (eg, by revealing the presence of specific phenotypic subtypes, or by predicting disease progression) [36].

Using wearable sensors also brings about challenges. First, data from sensors are a potential target for invasions of privacy [37]. For example, Global Positioning System-based sensor data can be used to identify the physical location of an individual, and their homes [38]. As a remedy, approaches such as restricting access to the data and anonymizing files have been suggested [39]. To allow for the collection of sensitive data, and to address security issues, the Parkinson@Home project will adopt several precautions, including: coding the data; storing the data on secure servers, separately from personal data; and restricting data use, by only allowing access to authorized researchers within the research team. When making information available to the wider research community, data will be anonymized and access will be granted only through a secure research database. These actions decrease the risk of identification of the patient and inappropriate use of the data.

A second challenge faced in the Parkinson@Home study is the lack of experience that elderly people have with technical devices. This lack of experience affects the acceptance of, and compliance with, the technology [40]. Overcoming this lack of experience in our target population, without introducing a selection bias, will be a challenge. However, we believe that the best approach for this issue is to rely on the willingness of patients to learn and be engaged in the management of their disease, combined with an efficient support model.

In conclusion, this study will generate new insights into the use of wearable sensors in daily living by PD patients, and if the data collection shows potential, it will make a contribution to the integration of self-collected information into clinical practice for PD patients. This study represents the first steps towards building a reliable system that integrates real-life information into clinical decisions.

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Authors' Contributions

Ana Lígia Silva de Lima made substantial contributions to the conception and design of the study, and was involved in drafting the manuscript, and revising it critically for important intellectual content. Tim Hahn was involved in drafting the manuscript and revising it critically for important intellectual content. Nienke M de Vries, Eli Cohen, Lauren Bataille, Max Little, and Heribert Baldus were involved in revising the manuscript critically for important intellectual content, and agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. Bastiaan R Bloem and Marjan J Faber made substantial contributions to conception and design of the study, were involved in revising the manuscript critically for important intellectual content, agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved, and gave final approval of the version to be published.

Conflicts of Interest

Ana Lígia Silva de Lima is supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES Foundation; grant number 0428-140). Bastiaan R Bloem received grant support from the Michael J Fox Foundation and the Stichting Parkinson Foundation. Eli Cohen is supported by Intel Corporation. Lauren Bataille is supported by the Michael J. Fox Foundation. Max Little is managing director of NumericAnalysis Ltd. and received research funding support from the Michael J Fox Foundation. Heribert Baldus is supported by Philips Research. Tim Hahn, Nienke M de Vries, and Marjan J Faber declare no competing interests.

Multimedia Appendix 1

Overview of studies applying wearable sensors and their use in Parkinson’s disease.

[PDF File (Adobe PDF File), 89KB - resprot_v5i3e172_app1.pdf]

Multimedia Appendix 2

Parkinson@Home study data.

[PDF File (Adobe PDF File), 34KB - resprot_v5i3e172_app2.pdf]

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Abbreviations

FD: fall detector
MDS-UPDRS: Movement Disorder Society - Unified Parkinson's Disease Rating Scale
PD: Parkinson’s disease
PMM: Philips Mobility Monitor
PPMI: Parkinson Progression Marker Initiative
SCOPA-AUT: Scales for Outcomes in Parkinson’s Disease – Autonomic System

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Original Paper

The Development and Piloting of a Mobile Data Collection Protocol to Assess Compliance With a National Tobacco Advertising, Promotion, and Product Display Ban at Retail Venues in the Russian Federation

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Abstract

Background: Tobacco control policies that lead to a significant reduction in tobacco industry marketing can improve public health by reducing consumption of tobacco and preventing initiation of tobacco use. Laws that ban or restrict advertising and promotion in point-of-sale (POS) environments, in the moment when consumers decide whether or not to purchase a tobacco product, must be correctly implemented to achieve the desired public health benefits. POS policy compliance assessments can support implementation; however, there are challenges to conducting evaluations that are rigorous, cost-effective, and timely. Data collection must be discreet, accurate, and systematic, and ideally collected both before and after policies take effect. The use of mobile phones and other mobile technology provide opportunities to efficiently collect data and support effective tobacco control policies. The Russian Federation (Russia) passed a comprehensive national tobacco control law that included a ban on most forms of tobacco advertising and promotion, effective November 15, 2013. The legislation further prohibited the display of tobacco products at retail trade sites and eliminated kiosks as a legal trade site, effective June 1, 2014.

Objective: The objective of the study was to develop and test a mobile data collection protocol including: (1) retailer sampling, (2) adaptation of survey instruments for mobile phones, and (3) data management protocols.

Methods: Two waves of observations were conducted; wave 1 took place during April-May 2014, after the advertising and promotion bans were effective, and again in August-September 2014, after the product display ban and elimination of tobacco sales in kiosks came into effect. Sampling took place in 5 Russian cities: Moscow, St. Petersburg, Novosibirsk, Yekaterinburg, and Kazan. Lack of access to a comprehensive list of licensed tobacco retailers necessitated a sampling approach that included the development of a walking protocol to identify tobacco retailers to observe. Observation instruments were optimized for use on mobile devices and included the collection of images/photos and the geographic location of retailers. Data were uploaded in real-time to a remote (“cloud-based”) server accessible via Internet and verified with the use of a data management protocol that included submission of daily field notes from the research team for review by project managers.

Results: The walking protocol was a practical means of identifying 780 relevant retail venues in Russia, in the absence of reliable sampling resources. Mobile phones were convenient tools for completing observation checklists discretely and accurately. Daily field notes and meticulous oversight of collected data were critical to ensuring data quality.

Conclusions: Mobile technology can support timely and accurate data collection and also help monitor data quality through the use of real-time uploads. These protocols can be adapted to assess compliance with other types of public health policies.

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KEYWORDS

tobacco; tobacco marketing; retail environments; compliance assessment; policy implementation; point-of-sale; Russia; mobile data collection; mobile devices

Introduction

Tobacco Control Policy

Tobacco use is the leading preventable cause of premature death and disease in the world, killing approximately 6 million people annually and costing more than half a trillion US dollars in health care costs [1]. The health burden of tobacco use is heavier in certain countries and regions of the world due to higher prevalence of use. One of the highest burdened countries in the world is the Russian Federation (Russia). The World Health Organization (WHO) estimates that over 60% of men and 22% of women in Russia smoke cigarettes (approximately 43.9 million adults) [2]. The tobacco industry strives to increase tobacco consumption among current users, attract new consumers, and encourage former customers to resume tobacco use through the use of tobacco advertising, promotion, and sponsorship (TAPS) strategies [3]. The tobacco industry spends tens of billions of US dollars worldwide each year to develop TAPS strategies, produce marketing media, and advertise their brands [1,4]. Exposure to tobacco advertising and the availability of promotions in the retail environment are known to increase the likelihood of smoking uptake among youth [5]. Article 13 of WHO's Framework Convention on Tobacco Control recommends the adoption and implementation of comprehensive laws that ban all forms of TAPS [6]. Complete bans on TAPS activities that prohibit the display of products (in addition to signage and other promotions) at the point-of-sale (POS) are essential policies that reduce people's exposure to tobacco marketing [7]. Although TAPS bans that eliminate POS marketing are a crucial element of comprehensive tobacco control strategies, even jurisdictions with strong community support face significant barriers to successful implementation. These policies can be challenged by tobacco companies on the basis of laws that govern freedom of expression and free enterprise [8].

In Russia, the federal law N 15-FZ "On Protecting the Health of Citizens from the Effects of Second Hand Tobacco Smoke and the Consequences of Tobacco Consumption" [9] (2013), addresses such tobacco control measures as smoke-free places, TAPS bans, packaging and labeling, price, tax, and sale. On June 1, 2013, the sale of tobacco products was prohibited in the premises and within 100 meters of locations that provide educational services. The law later banned all forms of advertising, promotion, and sponsorship effective November 15, 2013 including signage, distribution of free products, use of price discounts, brand stretching, use or imitation of tobacco products, organization and performance of events (such as concerts), and the use of tobacco trade names in charitable activities. The law prohibited the display of tobacco products at "retail trade sites" [9], effective June 1, 2014. Retail venues are permitted to provide customers with an alphabetized list of products and prices in plain black font on a white background, with no graphics or images. Further regulations took effect on June 1, 2014, prohibiting the sale of tobacco at kiosks (street stalls) [9].

Monitoring Tobacco Advertising

Rigorous and well-timed tobacco control policy compliance assessments can determine whether the new laws are being followed and can be used to expose loopholes in weak regulations, or to strengthen enforcement [10]. Ideally, assessments of new policies, such as POS advertising, promotion, and display restrictions should be conducted both before and after the law takes effect, within a reasonable implementation period [11]. Sampling should include relevant tobacco retailers and observers should revisit the same retail location in each wave of data collection. A representative sample of tobacco retailers provides the most reliable evidence to inform policymakers and enforcement authorities; however, many jurisdictions do not have complete lists of retailers or such information is not available to nongovernmental organizations (NGOs) or academics interested in policy evaluation. Furthermore, assessments collecting repeat measures from the same locations can be challenging when addresses are poorly labeled or, in the case of Russia, when retail venues are clustered kiosks which may not have an address at all.

City neighborhoods may also differ across relevant dimensions, such as retail offerings and enforcement activities. Retailers tend to cluster and venues will stratify, for example, some parts of a city will have a higher concentration of expensive or high-end retailers, while other neighborhoods will have a higher proportion of low-end or less expensive retail offerings, which must be addressed when selecting a sample of venues. Previous studies have developed retail venue sampling protocols that use a walking pattern to traverse a city while collecting littered tobacco packs for later coding and analysis [12]. Similar work relied on census data to identify and select the neighborhoods within a city from which to collect littered packs [13].

Policy compliance measures should be collected by staff that are knowledgeable about the law in order to ensure the accuracy of observations. Data collectors also need to be suitably discreet to avoid retailer interference, which can be difficult when entering a POS with a clipboard, camera, and global positioning system (GPS) device. Further, the oversight of data collection and data management/validation can be challenging when the sample is geographically dispersed in multiple time zones with thousands of potential retail locations. As with any research study, procedures for communicating with the study team and managing collected data should be in place to verify that the protocol is followed faithfully and that data are collected accurately.

The increasing ubiquity of mobile phones and access to wireless networks makes these devices a realistic option for data collection. Mobile phones and mobile software applications

(apps) allow users to collect and record observational data, images, and metadata (such as timestamp, GPS-based location coordinates, device identification number, etc) in the field, using specific or customized survey instruments. Photos are a useful source of data that can be utilized for quality control and validation purposes, for the practical purpose of revisiting certain locations, for research involving secondary analysis of the photos, and as visual representations of the data to assist with dissemination of findings. Additionally, devices that are connected to a network service through cellular data or wireless local area network (WiFi) can upload data immediately, allowing for real-time data validation and project management. Metadata can be cross-referenced to ensure that all technology is functioning properly (device, software, and network) and that data collectors are following the study protocol and schedule.

Mobile technology has been used extensively in public health research and practice, and has proven effective in the collection of data in various settings and locales [14-18]. Mobile phones specifically have been used for data collection whether via SMS/texting or via a mobile Internet connection [19,20]. Interest in using mobile devices in the field of tobacco control is growing, with more work focusing on smoke-free environments, retail environments, health communication, detection of illicit trade products, and support of alternative livelihood options for tobacco farmers and workers [21-23]. One study developed protocols to use mobile phones to collect photos and geospatial data to examine POS marketing characteristics and their effect on craving to smoke; this work relied on sophisticated software platforms and required significant time and human resources to process and code data [24].

Recent work has aimed to mitigate the bottleneck created by the mobile collection of observation data, geospatial data, and photographs and the time required to properly link, code, and annotate these data with the use of crowdsourcing methodology [25]. Crowdsourcing is a convenient option when potential workers are readily available and can be easily dispatched to a clearly defined sampling area to complete a simple task, but may not be conducive to rapid policy assessment and reporting. Procedures or observations that are more complex require significant oversight to ensure adherence to the study protocol, to validate observations, and to troubleshoot technical or logistical issues that arise in the field, which can be difficult to manage among a group of crowdsourced data collectors. Such protocols that also necessitate discretion on the part of the study team in order to avoid interference from the industry are better suited for a group of trained data collectors. Studies show that mobile devices are useful tools for conducting public health research, although the use of such technology entails an additional layer of complexities and limitations that researchers must account for. There remains a need for additional guidance on adapting these tools and literature on the utility of mobile technology for broader public health based research, such as policy implementation.

This manuscript outlines a research protocol utilizing mobile technology to collect observational data before and after the implementation of sales restrictions and a product display ban at tobacco retail venues in Russia. Although the protocol was developed specifically for Russia, the methods are adaptable to other jurisdictions. The protocol includes three components: (1) a rigorous sampling protocol, (2) data collection instruments including capture of images/photos and geographic coordinates, and (3) data management protocols.

Methods

Groups Involved in the Study

This work was conducted by the US Institute for Global Tobacco-based Control (IGTC) at Johns Hopkins Bloomberg School of Public Health. IGTC partnered with the Campaign for Tobacco Free Kids (CTFK), an international public health NGO, and a team of Russian tobacco control experts based in Moscow, Russia. Local experts provided guidance and context about the sampling framework, instrument development, and data collection logistics. The in-country team conducted the fieldwork and submitted daily reports for review by the project management team in Baltimore, Maryland.

Sampling Approach

Sampling Protocol Objectives

The sampling protocol first identified which Russian cities would be included in the study. The study team wanted to conduct sampling in socioeconomically diverse areas, so it was necessary to identify zones of the city that met different criteria. The team also needed to identify where observations would occur within those zones (ie, sampling areas) to evaluate implementation and compliance with the law. The sampling strategy considered which tobacco-retailer types (kinds of stores) would be sampled and how to identify those retailers in a manner that was both systematic and sufficiently random, while allowing for timely collection of data with a preference for walking between retailers. Finally, the sampling protocol needed to support a multi-wave design to ensure revisiting retail venue locations would be possible.

The goals of the sampling protocol, the criteria or process used to achieve the sampling goals, and the decisions made are outlined in Table 1. Further details about each step are discussed later.

Table 1. Sampling decisions.

Goals		Criteria or process used	Decision
Identify cities where sampling will take place.		Include cities that have a large population; include cities that are geographically dispersed throughout the country.	The following five cities were identified: Moscow, St. Petersburg, Novosibirsk, Yekaterinburg, and Kazan.
Identify diverse socioeconomic zones in each city.			
	Identify and map zones in city based on socioeconomic status.	Include areas of different socioeconomic status; without available census data on resident education and income, a proxy value of property value is used.	Study mapped 3 types PVZ[a]. PVZ[a] was classified as being: •High property value (>1.25x average property value) •Average property value (>0.85-1.25 x the average property value), or •Low property value (<0.85x the average property value).
Identify sampling areas.			
	In each property-value-zone, identify areas of the city with significant retail activity (retail centers). Create a catchment area around the retail center, this area is known as the sampling area.	Identify three different types of retail centers in each PVZ[a]: 1. Shopping mall, 2. Major intersection, and 3. Transit station.	From each retail center, a 3 km radius was drawn, creating 3 different sampling areas in each of the 3 property-value-zones. [9 sampling areas in each city]
Identify retail venues to be sampled in each sampling area.			
	Identify which types of tobacco retail venues (POS) to be included.	Chain supermarkets [both up market (luxury) and mid-low market]; independent markets/convenience stores; Kiosks (street stalls).	Sampling goals included an equal number of: 1. Chain supermarkets, 2. Independent markets/convenience stores, and 3. Kiosks. Chain supermarkets included equal number of luxury/high market stores, and mid-low market stores when possible. Independent markets include both convenience stores and gas stations. [6 chain supermarkets, 6 independent markets, and 6 kiosks per sampling area-18 total retail venues per sampling area]
	Identify locations of specific retailers within the sampling areas.	Use available databases that list and include the location of chain supermarkets (both high end, and mid and low end) in each study city. Map locations of chain supermarkets to identify which stores are in the physical sampling areas. If there are more than 9 chain supermarkets in the sampling area, number stores and use a number generator to randomly identify stores to be included in the sample.	In each sampling area, 6 chain supermarkets were identified and mapped in each of the cities' 9 sampling areas. An additional 3 “back-up” chain super markets were also included in the sampling areas. [54 chain supermarkets per city, and 27 back-up chain supermarkets]
	Identify other retailers nearby supermarkets.	There are no available lists of licensed retailers, so a walking protocol is used to identify near-by independent markets (convenience stores and gas stations) and kiosks.	After data are collected at a chain supermarket, data collectors will exit the supermarket and, using the walking protocol, identify a nearby independent market and kiosk. [54 independent markets and 54 kiosks per city]

[a]PVZ: property-value-zones

Cities Included in the Sample

The cities of Moscow, St. Petersburg, Novosibirsk, Yekaterinburg, and Kazan were selected for data collection based on their relative population (Table 2), and geographical dispersion (Figure 1 shows this). Each of the five cities are located in separate and distinct federal subjects (or

municipalities) and are among the top ten most populous cities in Russia.

Table 2. Cities included in the sample and their relative rank by population within Russia [26].

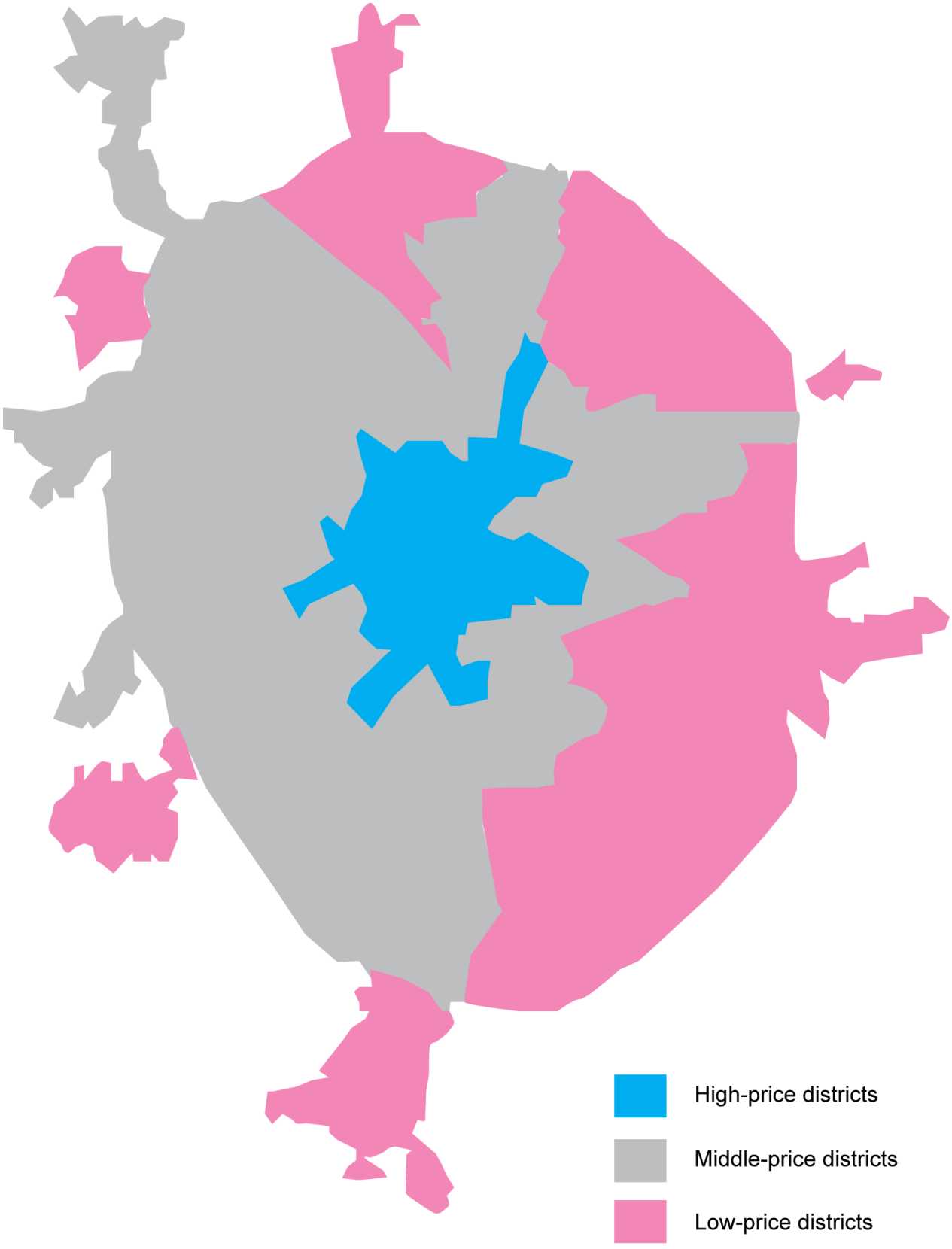
City	2012 population size (millions)	Rank (within Russia)
Moscow	11.92	1
St. Petersburg	4.99	2
Novosibirsk	1.51	3
Yekaterinburg	1.39	4
Kazan	1.17	8

Figure 1. Map of five cities included in the sample.

Property-Value-Zones Identified

Ideally, census data would be used to identify areas or zones within a city representing a range of socioeconomic statuses (SES). This approach ensures that the evaluation is not conducted in homogenous areas, thereby possibly missing compliance or enforcement trends. Local-level SES data were not available to the research team so a proxy measure, relative real-estate value (rubles per square meter), was used to classify property-value-zones (PVZ). Local experts gathered information about residential property values from reputable sources [27-32]. For each of the 5 cities, maps were created with polygons identifying PVZ's as "high" (more than 125% of the average real estate price), "average" (85%-125% of the average price), or "low" (less than 85% of the average price). These zones were mapped using Adobe Illustrator (Figure 2 shows this).

Figure 2. Moscow property-value-zones.



Identification of Retail Centers and Surrounding Sampling Areas

In each high, medium, and low PVZ, 3 different retail centers were identified including a large shopping mall, a major intersection, and a transit station (subway, bus, or train) for a total of 9 unique retail centers per city. Local experts suggested these types of retail centers based on knowledge of venue dispersion and walkability. Researchers applying this protocol in other settings should consider the retail venue density and

local transit options in the jurisdiction of interest when selecting retail centers. A radius of 3 km was drawn around each retail center using 2GIS [33], to identify the catchment area, referred to as the study "sampling area". The study included sampling areas containing educational facilities (where tobacco sale are prohibited). Effort was made to ensure that sampling areas did not overlap with each other or include areas across PVZs. The shopping mall, intersection, and transit station in each PVZ were identified using an Internet business database (2GIS), and mapping software (Google Maps and Yandex Maps) [34,35]. Using local knowledge, retail centers were selected in areas of the city that had a concentration of tobacco retailers to support expedient data collection by data collectors walking or taking mass transit, or a taxi between venues.

Tobacco Retailer-Types Identified

There were three different kinds of retailers that were included in the sample: (1) chain supermarkets (roughly equal number of up market, and mid-low market stores), (2) independently owned markets/convenience stores (including gas stations), and (3) kiosks. Kiosks were explicitly included in the sample because the legislation required these retailers to stop selling tobacco after June 1, 2014.

Ideally, retail venues included in a policy evaluation would be randomly selected from a list of all licensed tobacco retailers. Such lists were not available to the study team, so a walking protocol was developed. The study team set the goal of collecting data from 54 unique retail venues (18 chain super markets, 18 independent markets/convenience stores/gas stations, 18 kiosks) per PVZ (high, average, low), in each of the five cities. This sampling design resulted in 162 tobacco retailers and 270 different retailers per POS type, for a total of 810 tobacco retail locations across the country (Table 3).

Table 3. Tobacco retailer sampling goals by city, PVZ, and retailer type.

		Retailer (POS) type			
City	PVZ	Chain supermarket	Independent market/convenience store	Kiosk	Total per city
Moscow	Low	18	18	18	162
	Average	18	18	18	
	High	18	18	18	
St. Petersburg	Low	18	18	18	162
	Average	18	18	18	
	High	18	18	18	
Novosibirsk	Low	18	18	18	162
	Average	18	18	18	
	High	18	18	18	
Yekaterinburg	Low	18	18	18	162
	Average	18	18	18	
	High	18	18	18	
Kazan	Low	18	18	18	162
	Average	18	18	18	
	High	18	18	18	
Total per venue type		270	270	270	Total: 810

Point-of-Sale Selection

Identification of Chain Supermarkets

Using 2GIS, Google Maps, and Yandex Maps, it was possible to identify and map a comprehensive list of supermarkets and their locations within each of the 9 sampling areas in each city. A list of all chain supermarkets and their classification (up-market, and mid-low market) was created for each sampling area using 2GIS. In all cases, this list was more than the desired 6 supermarkets per sampling area. A random number generator was used to select a total of 6 supermarkets from the lists in each sampling area. When possible, the 6 chain supermarkets included 3 up-market and 3 mid-low market venues. If fewer than 3 high-end supermarkets were located in a sampling area, additional mid- to low-end chain supermarkets were randomly selected to achieve a total of 6 chain supermarket locations per sampling area. Within each sampling area, 3 additional chain supermarkets were randomly selected as back-up retail venues in case any of the primary locations were closed or could not be observed. Data collectors were provided with the lists of randomly selected chain supermarket locations for the 9 sampling areas (3 in each PVZ) in the 5 cities.

Identification of Independent Markets/Convenience Stores and Kiosks

After visiting the chain supermarket and collecting relevant observations, data collectors exited the store to identify independent markets (including convenience stores and gas stations), and kiosks (street stalls, often located in underground crossing areas). Researchers identified these venues by following a walking protocol (see Multimedia Appendix 1). First, data collectors exited the supermarket via the main exit/entry point, and would look for an independent market, or kiosk (or underground crossing where kiosks are often located) within eyesight. If there were tobacco retailers located on each side of a street or underground crossing, the POS on the left was selected. If retail venues were only located on the right side of a street or underground crossing, the location on the right was observed. If there was more than one retail venue located on the side of the street or underground crossing being observed (kiosks are often placed in clusters or banks), the closest POS on that side was observed. If data collectors could identify and observe one of each POS type immediately after exiting the supermarket, they would do so and then proceed to the next supermarket location on the list.

If data collectors could not identify an independent market or kiosk immediately after exiting the supermarket, they were instructed to turn left (from the supermarket) and walk, looking for either an independent market or kiosk. Data collectors were instructed to walk in the same direction (walking trajectory) for approximately 5 minutes. If data collectors were able to collect data at both an independent market and kiosk at any point during the 5 minute walking protocol, they could proceed to the next supermarket on the list. If data collectors still needed to observe one or more retail locations after 5 minutes of walking, they were to turn left again (onto a street with vehicle traffic, not a side-street or back-alley), and walk for another 5 minutes, to identify a POS to observe on their path. If data collectors still needed to observe one or more retail locations, they were to turn left again (onto a street with vehicle traffic, not a side-street or back-alley), and this time walk for 10 minutes, to identify a POS to observe on their path. If data collectors still needed to observe one or more retail locations after 10 minutes, they were to turn left again (onto a street with vehicle traffic, not a side-street or back-alley), and walk for another 10 minutes, to identify a POS to observe on their path. Data collectors may have ventured outside of the original 3 km neighborhood radius while following this walking protocol, if observing from a supermarket that was located near the perimeter of the sampling area radius.

After 30 minutes of total walking time (5 minutes, 5 minutes, 10 minutes, and 10 minutes), if data collectors still could not identify an independent market and kiosk or kiosk, they could proceed to the next supermarket on their list. If en route they identified a suitable venue, they could stop there to conduct observations/data collection.

Data collectors were instructed not to observe more than one of the same POS type on the same street. If data collectors could not follow the walking protocol due to the layout of the streets, they were to use their best judgment and document any deviation from the protocol in their daily reports.

Revisiting Point-of-Sale Locations

Wave 2 data collection required data collectors to revisit the locations from wave 1. Daily routes were identified using the street location of each POS venue. In the event of no (or unclear) street addresses, reports from wave 1 and photos collected during the initial visit were used to verify the POS and ensure the same location was visited.

Data Collection Protocol

Instrument Content

The survey instrument (observation checklist that contained the items to measure for compliance including product sale, advertisement, promotion, and display) was first developed by thoroughly reviewing the Federal Tobacco Control Law N 15-FZ, focusing on Articles 16 and 19 which regulate TAPS and the retail trade of tobacco products and goods. The instrument was reviewed by CTFK staff and local tobacco control experts including an in-house lawyer in order to ensure that survey questions addressed the specific provisions of the law, as well deficiencies of the law which were known to be exploited with the use of such promotional tactics as light boxes or enlarged packages that advertise a tobacco brand by enhancing the product display (Figure 3 shows this).

Questions that further characterize POS environments, such as availability and display of electronic cigarettes and alcohol, were incorporated in order to measure additional changes in the marketing of these products that may result from the implementation of this policy. Data collected by category and wave are outlined in Table 4.

Table 4. Data collected by category and wave.

Category	Wave 1	Added to wave 2
Metadata	•Device identification number •Time data recorded (on device) •Latitude/longitude •GPS accuracy •Record # •Time data uploaded (to cloud database)	
General	•Data collector name •City •PVZ •Sampling area center type (shopping mall, intersection, or transit station) •POS type •Street address	•POS ID# •POS status (open, closed, combined with other POS, or changed POS type) •Does POS still sell tobacco? (yes/no)
TAPS	Presence and offending brand of: •Light boxes •Enlarged packaging •Signage •Imitation tobacco products •Brand stretching •Discounts •Gifts (free or with purchase) •Free distribution of tobacco products •Other advertisement or promotion (open response)	
Product display	Display of tobacco products visible from: •Window on street or underground crossing •Cashier zone •On a power wall •Other display area (open response)	•Compliance with product listing requirements
Image/photograph	•Front/entrance of the POS •Inside POS near display area (optional) •Close-up of product display/advertisement/promotion (optional) •Other POS product display (optional)	
Retail environment	Presence or sale of: •A door for customers to enter/exit •Candies/sweets/snacks in the cashier zone •Alcohol •Gasoline •Electronic cigarettes	

Figure 3. Light-box used for tobacco product "display".

Instrument Adaptation for Mobile Data Collection

The survey instrument were inputted into the "Mobile Data Collection" [36] (MDC) software app, using the "Mobile Data Collection Portal" [37]. The MDC software was installed on Blue Dash 4.0 mobile phone devices which were selected for their ability to: function globally (by inserting a subscriber identification module or SIM card from a local network); capture high quality photos; geo-locate; support the MDC app; and for affordability in price. The devices ran on the Android operating system and were configured to display only the MDC app, camera, and toolbar (to control network connection and screen brightness) on the home screen. The MDC software was selected for its ability to capture metadata (specifically the GPS-location feature), collect observations using customized questions and response options including photographs, and upload data in real-time to the cloud-based (Internet-accessible) database, "GIS Cloud" [38]. If the device could not establish network access for real-time upload, data were saved in a queue within the MDC app for automatic uploading once a connection was restored. Fields for capturing photographs of POS entrances (for reference during wave 2 of data collection), product displays, and advertising or promotional activities were added to the survey within the MDC app. Photos of POS entrances were a required field within the survey, while the others were optional. Although mobile phones are a practical tool for discretely collecting data, it may be difficult to capture quality photos of the retail environment in venues that are small and narrow, and in a culture where taking photos in public places may be viewed with suspicion and hostility. While field-testing the protocol during the training period, data collectors were occasionally reprimanded by store clerks or security guards for taking photos. The study team decided to format questions asking for photos of tobacco product displays, advertisements, or promotions as optional fields in order to prioritize the safety of data collectors. The sequence of questions (including photo fields) within the MDC app was designed to match data collectors' paths as they approached, observed, and departed from the POS in order to minimize observation time and allow for discrete collection of data.

Mobile Data Collection

Before setting out to observe tobacco retailers, data collectors were to ensure their devices were fully charged, and that SIM cards were loaded and functioning in their mobile phones (to confirm network connectivity). Data collectors were instructed to carry a copy of the protocol, the mobile phone charger, and paper copies of the survey instrument (in case of device or software failure) during each observation day. Before initiating a new record (venue), data collectors were to verify that the GPS and WiFi functions were activated on the mobile phones (in order to optimize geo-location), and to verify their location on the mapping function within the MDC app. Data collectors began by making observations from outside of the POS, before entering the location (if applicable). Data collectors were instructed to behave as customers (using a shopping basket, making small purchases) and to appear as if they were using their mobile phones in a normal manner (texting, looking at a shopping list, playing a game) in order to ensure discretion while extending observation time. If electronic cigarettes were not on display at a particular POS, data collectors were required to ask a salesperson or cashier if they were available for sale as they exited the location. If needed, data collectors were able to use the mobile phone's default mapping software (Google Maps) to navigate to the supermarkets on their lists, but were encouraged to disconnect the GPS and WiFi functions and reduce screen brightness when possible, in order to conserve battery power. Figures 4 and 5 show the MDC app interface for collecting observational data at a POS.

Figure 4. Mobile data collection app interface from mobile phone (general questions).

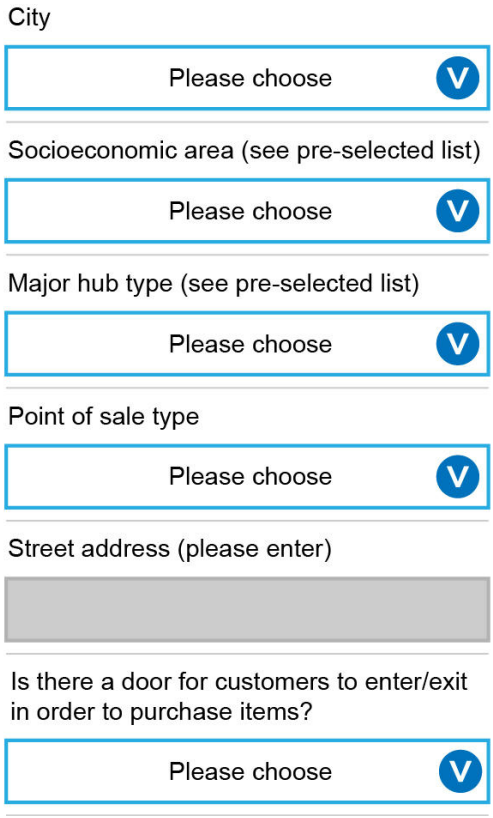
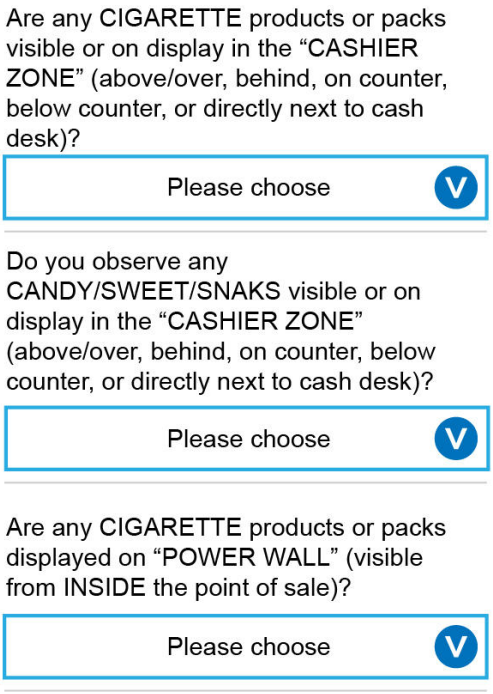


Figure 5. Mobile data collection app interface from mobile phone (product display questions).



Training and Pilot Testing

Data collectors attended a three-day, in-person training in Moscow given by the research team and were trained in all aspects of the study, including the legal/policy background, data analysis objectives, and intended use of results. Training materials included content on the nature and function of TAPS activities at retail venues and relevant components of the tobacco control law before outlining the sampling framework for each city. Data collectors studied the venue inclusion protocol for identifying and selecting independent markets and kiosks surrounding the selected supermarket locations. A thorough explanation of the survey instrument included definitions and photos of key terms and observation items.

As part of the training, data collectors practiced using the mobile phones provided for data collection in order to familiarize themselves with the device operating system and the electronic

version of the survey instrument and response options within the MDC app. The group reviewed strategies for discretely collecting data and taking photos. Training allowed two full days to pilot-test the data collection protocol and instrument, in order to optimize the walking instructions and survey format, and prepare data collectors to record observations.

Data Management Protocol

In order to verify that data were being correctly recorded (by data collectors) and uploaded (by the MDC app and mobile phone device), data collectors in Russia prepared and submitted daily field reports to the study team in Baltimore, USA. The reports showed the city, PVZ, sampling area type, POS type, POS address, and data collector name for each POS location observed that day, as well as comments addressing any deviations in the walking protocol or observations that may not have been captured within the form. The study team was also able to review data daily by accessing the Geographic Information System (GIS) Cloud database and validate observations by cross-referencing the uploaded data with the daily reports. Cross-referencing the uploaded data with the photos that were captured from retail locations also validated observations.

Results

Sampling Approach

Wave 1 Sample

Observations were recorded from 780 unique tobacco retail venues in five cities from April 17-May 30, 2014 (Table 5). Researchers found differences in the dispersion/density of retail locations and urban layout/design between cities. During collection, the study team discovered that some sampling areas contained educational or health care facilities, where the sale of tobacco was prohibited (on the premises and within 100 meters). Retail venues located adjacent to these facilities could not be observed if they did not sell tobacco products, which required data collectors to spend additional time and cover a greater distance using the walking protocol. Data collectors also found that kiosks were sometimes located in clusters near sampling area centers rather than dispersed within the 3 km radius of the retail center, and were not identified using the walking protocol. The protocol was adjusted during the collection period to allow data collectors to observe more than one of the same POS type on the same street. There were two additional transit-station sampling areas that were identified for each PVZ in each city, except Novosibirsk, where data collectors were easily able to identify the required POS types and locations. Data collectors visited the additional sampling areas in each city to identify and observe the remaining independent market/convenience stores and kiosks needed that could not be identified by following the walking protocol in the primary sampling areas. Sampling area centers (instead of supermarkets) served as the starting point for data collectors to follow the walking instructions. These minor adjustments were necessary in order to account for the nonuniform distribution of retail venues within the cities. Researchers applying this protocol in other locations should be familiar with the dispersion of retailers in the jurisdiction of interest, and be mindful of adjustments that may confound the stratification of venues, such as between PVZ's or SES. The use of extra sampling areas to identify retail venues resulted in only 1 location being observed twice, by different data collectors, likely an effect of passing through bordering sampling areas while following the walking protocol. Once identified, the duplicate observation was dropped from the dataset. In the city of Kazan, which is the smallest city by population included in the sample, data collectors were only able to identify 30 of the target 54 kiosks using the walking protocol and extra sampling areas. We expect that the lower number of kiosks observed in Kazan is due to the size of the city and overall availability of retail venues.

Wave 2 Sample

The sampling objective for the second wave of data collection was to revisit and observe the same 780 retail locations observed during wave 1. Data collectors were provided with a list of retail venues visited in wave 1, organized by sampling area, that included a POS identification number, retailer type, address, and photo. Data collectors returned to these same locations to collect observations during wave 2 of this study. Of the 780 retail venues observed during wave 1, 779 were revisited during wave 2 of data collection (Table 6); only one POS could not be located (Table 7).

Table 5. Retail venues observed in wave 1 of data collection.

Wave 1 locations observed					
		POS type			
City	PVZ	Chain supermarket	Independent market/convenience store	Kiosk	Total per city
Moscow	Low	18	19	19	167
	Average	18	18	18	
	High	23	17	17	
St. Petersburg	Low	17	17	15	156
	Average	18	18	18	
	High	18	19	16	
Novosibirsk	Low	18	18	18	162
	Average	18	18	18	
	High	19	17	18	
Yekaterinburg	Low	18	18	18	162
	Average	19	17	19	
	High	16	19	18	
Kazan	Low	17	18	9	133
	Average	16	17	13	
	High	18	17	8	
Total per venue type		271	267	242	780

Table 6. Retail venues observed in wave 2 of data collection.

Wave 2 locations observed					
		POS type			
City	PVZ	Chain supermarket	Independent market/convenience store	Kiosk	Total per city
Moscow	Low	18	18	16	150
	Average	15	15	15	
	High	21	17	15	
St. Petersburg	Low	17	17	11	148
	Average	18	16	18	
	High	17	18	16	
Novosibirsk	Low	18	16	16	148
	Average	18	17	15	
	High	18	16	14	
Yekaterinburg	Low	18	17	18	152
	Average	19	15	15	
	High	16	18	16	
Kazan	Low	17	18	6	122
	Average	15	14	9	
	High	18	17	8	
Total per venue type		263	249	208	720

Table 7. Status of retail venues revisited in wave 2 of data collection.

Wave 2 POS status	
Open and still sell tobacco	589
Open and no longer sell tobacco	131
Closed	52
Not observed (failed upload)	7
Not observed (location not found)	1
Total	780

Data Collection Protocol

Wave 1 Data Collection

At the onset of data collection, the research team identified that the use of radio buttons within the survey caused data collectors to accidentally select or change a response option when scrolling down the page to subsequent questions. This issue was resolved by adjusting the response format of the survey questions to provide a drop-down list rather than radio buttons to enter observations. Although four people attended the training, only three of those data collectors were deemed competent enough in the protocol during the pilot test to participate in actual data collection. No further adjustments were required for the data collection protocol during wave 1. Data collectors captured a total of 1815 images during wave 1 of the study, 780 of which were required photos of the venue entrance, and 1035 of which were optional photos of tobacco product displays, advertisements, or promotions.

Wave 2 Data Collection

During wave 2 of this study, the survey instrument was duplicated from wave 1 and inputted to the MDC software app following the same mobile adaptation procedure used in wave 1. Only three questions were added to the observation checklist in order to record whether a POS location was still in business, selling tobacco, and whether the newly required product listings were compatible with the law. As a walking protocol was not required during wave 2, data collectors simply navigated to each POS location on their assigned lists and followed the same data collection protocol utilized during wave 1.

Wave 2 data collectors underwent the same training and pilot testing as in wave 1. The data collectors in wave 2 of this study included two staff members who participated in wave 1 and two staff members who were new to the study. Although the walking protocol was not needed for wave 2, the instructions were thoroughly reviewed with the data collection team to support ease of identifying POS locations to revisit. Data collectors also reviewed the newly implemented requirements for product listings that took effect following the June 1st display ban, and this information was provided for reference within the study protocol. During wave 2, the team collected 1277 images from retail venues, 720 of which were required photos of the venue entrance, and 557 of which were optional photos of the newly implemented tobacco product cases, or violations of the law showing display, advertisement, or promotion of tobacco products.

Data Management Protocol

The research team monitored data collection by reviewing the data as they were uploaded to the cloud database and cross-referencing the uploaded data with the collection schedule and daily reports submitted by each data collector. This detailed oversight allowed the study team to quickly identify and troubleshoot the feature within the layout of the survey that caused data collectors to select incorrect response options. The use of daily reports to validate POS characteristics also helped to identify and correct a glitch in capturing geographic coordinates for each location observed. Due to varying network coverage between the cities, one mobile phone during wave 1 data collection device became “stuck” on a particular set of coordinates in Novosibirsk and continued to record these coordinates for dozens of retail venues in St. Petersburg. The use of reference information allowed us to verify in which city the retailers were actually located and to correct this information within the dataset. A review of POS photos and data also revealed duplicate uploads of five retail locations, which were deleted from the dataset.

During wave 2, the data collection team submitted daily reports in the same format as wave 1, using Google Sheets to update one unique report per city rather than reconciling multiple Microsoft Excel files from each data collector. The daily reports were amended to include fields for recording whether a retail location was still open and selling cigarettes. The study team identified a problem within the MDC software app/GIS Cloud, wherein observations recorded within the mobile survey instrument were not properly uploaded and those fields were left blank. The team made efforts to resolve this issue during the data collection period, but the software development team was unable to address the issue until data collection was nearly completed, resulting in missing data for several observation items during wave 2.

Discussion

Principal Findings

The sampling approach, data collection, and data management protocols worked well and only minor revisions were needed during fieldwork to improve the protocols workability. Aspects of this study can be adapted and operationalized for rapid evaluation of POS marketing regulations or other policy assessments in a variety of jurisdictions by NGO’s, local government, or academic researchers. Tailored design of the sampling approach and walking protocol to the local context in

Russia was essential to the collection of quality data. A detailed review of the tobacco control law and customization of the survey instrument with the help of local legal experts and advocates resulted in a checklist that captured valuable data for assessing compliance, identifying loopholes in the law, and detecting possible changes in the retail environment that result from policy implementation. Pilot testing of the walking protocol most importantly, as well as the survey instrument, mobile phone technology, and data collection protocol, were essential to optimizing the procedures and survey format for collecting observations quickly and discretely. Future adaptations of these protocols may need to pilot test the walking protocol in each city depending on the scale of the jurisdiction and variation in urban or rural layout and dispersion of local retail venues. Pilot testing in multiple cities would also further inform time required to collect data, and other logistical considerations. Comprehensive training of data collectors, not only in protocols, tools, and technology, but also in the law, purpose of study, remote data management process, intended analysis, and use of study results, prepared data collectors in Russia to execute the protocol, and proactively communicate with the study team in Baltimore to troubleshoot issues in the field.

Vigilance in data management and validation, and close communication between the study coordinators and the field team, were essential to ensuring the success of all protocol components. The use of metadata, photos, and daily reports allowed the study team to identify and solve several problems in real-time during pilot testing and data collection periods, which would have otherwise resulted in the collection of invalid observations and inaccurate geospatial data. If possible, additional pilot testing of this process including a simulation of potential problems that may arise during the influx of data-upload would more thoroughly prepare the study coordinators and field team to address these issues while working remotely and across multiple time zones. Further pilot testing of the data management protocol and MDC software would also inform which metadata and other validation measures to have in place (such as daily reports or daily tests of software and network functioning) to anticipate and circumvent problems that may occur in the field, and allow coordinators to allocate the human resources needed to review uploaded data. The study coordinators should be mindful to anticipate complications and schedule sufficient time to communicate with the field team on a regular basis in order to address and solve issues that may arise with the technology or data collection in general. Coordinators may also want to establish a connection to representatives of the mobile software app selected for data collection, before data collection begins. Even free software programs generally offer basic support for bugs, glitches, and troubleshooting that may be useful when working within a short timeline before a policy is implemented, or another key change takes place in the retail environment. Detailed measures for data management and validation help ensure the integrity of data and study protocols.

Limitations

The protocols used in this study were limited by lack of availability of comprehensive lists of tobacco retail venues, including the databases we referenced to identify chain supermarkets, which may have been missing some locations. The study also needed to use proxy values for SES; using property values is an adequate proxy for income, but may not overlap with dimensions of education or other predictors of tobacco use. Although the study team may have ventured outside of the defined 3 km sampling radius while collecting observations, the walking protocol kept data collectors within the sampling areas' corresponding PVZ's, and did not result in any POS locations being misclassified by PVZ type. Relying on digital technology to collect data can be risky, as the data can be lost or compromised if an error occurs within the mobile phone hardware, app software, or communication network. During wave 1, the study team experienced a problem with the network that recorded inaccurate geographic coordinates for some locations, while 5 duplicate records and 7 failed uploads were identified during the second wave of data collection. When using mobile and cloud-based technology, vigilant monitoring of the dataset and close communication with the field team are imperative to ensuring collection of comprehensive, high quality data. Given the high prevalence of Internet use in Russia, these issues are probably of less concern than they might be on other jurisdictions.

Conclusions

The use of a walking protocol and mobile technology was helpful for conducting a tobacco control policy evaluation of retail venues and can be adapted for use in other jurisdictions or policy settings. Successful operationalization of a walking protocol requires familiarity with cities and retail environments, and can be useful for evaluations where reliable sampling information, such as lists of retail venues, are not available. The introduction of new technology to these protocols also adds a requirement for thorough training, testing, and very close oversight of data collection. The protocols outlined in this manuscript offer relatively low cost, accessible methods for conducting an expedient evaluation of POS marketing restrictions, retail environments, and policy implementation in general.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Walking protocol animation.

[GIF File, 215KB - resprot_v5i3e120_app1.gif]

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Abbreviations

apps: applications
CTFK: Campaign for Tobacco Free Kids
GIS: geographic information system
GPS: global positioning system
IGTC: Institute for Global Tobacco Control
MDC: mobile data collection (software application)
NGOs: nongovernmental organizations
POS: point-of-sale (of tobacco products)
PVZ: property-value-zone
Russia: Russian Federation
SES: socioeconomic status
TAPS: tobacco advertising, promotion, and sponsorship
WiFi: wireless local area network
WHO: World Health Organization

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Original Paper

EXpanding Treatment for Existing Neurological Disease (EXTEND): An Open-Label Phase II Clinical Trial of Hydroxyurea Treatment in Sickle Cell Anemia

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Abstract

Background: Cerebral vasculopathy in sickle cell anemia (SCA) begins in childhood and features intracranial arterial stenosis with high risk of ischemic stroke. Stroke risk can be reduced by transcranial doppler (TCD) screening and chronic transfusion therapy; however, this approach is impractical in many developing countries. Accumulating evidence supports the use of hydroxyurea for the prevention and treatment of cerebrovascular disease in children with SCA. Recently we reported that hydroxyurea significantly reduced the conversion from conditional TCD velocities to abnormal velocities; whether hydroxyurea can be used for children with newly diagnosed severe cerebrovascular disease in place of starting transfusion therapy remains unknown.

Objective: The primary objective of the EXpanding Treatment for Existing Neurological Disease (EXTEND) trial is to investigate the effect of open label hydroxyurea on the maximum time-averaged mean velocity (TAMV) after 18 months of treatment compared to the pre-treatment value. Secondary objectives include the effects of hydroxyurea on serial TCD velocities, the incidence of neurological and non-neurological events, quality of life (QOL), body composition and metabolism, toxicity and treatment response, changes to brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), genetic and serologic markers of disease severity, and cognitive and pulmonary function.

Methods: This prospective Phase II trial will enroll children with SCA in Jamaica, between the ages of 2 and 17 years, with either conditional (170-199 cm/sec) or abnormal (≥ 200 cm/sec) TCD velocities. Oral hydroxyurea will be administered daily and escalated to the maximum tolerated dose (MTD). Participants will be seen in the Sickle Cell Unit (SCU) in Kingston, Jamaica monthly until achieving MTD, and then every 3 months. TCD will be performed every 6 months.

Results: Currently, 43 participants have been enrolled out of a projected 50. There was one withdrawal due to immigration, with no permanent screen failures. Of the 43 enrolled, 37 participants have initiated study treatment.

Conclusions: This trial investigates the effects of hydroxyurea treatment at MTD in children with conditional or abnormal TCD velocities before transfusion therapy and may represent an important advance towards establishing a suitable non-transfusion protocol for stroke prevention in children with SCA. The trial outcomes will have profound significance in developing countries where the disease burden is highest.

ClinicalTrial: ClinicalTrials.gov NCT02556099; https://clinicaltrials.gov/ct2/show/NCT02556099 (Archived by WebCite at http://www.webcitation.org/6k1yMAa9G)

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KEYWORDS

ultrasonography; Doppler; transcranial; stroke; anemia; sickle cell; child

Introduction

Sickle cell disease (SCD) is an inherited hematological disorder that is appropriately considered a major global public health problem [1]. Although Africa bears the highest burden, SCD occurs worldwide including the United States, the Caribbean, Central and South America, the Mediterranean region, and India [2,3]. The most common and severe genotype of SCD is homozygous sickle cell anemia (HbSS), usually referred to as sickle cell anemia (SCA). Manifestations of SCA include chronic hemolytic anemia, frequent pain and other vaso-occlusive complications including acute chest syndrome, widespread organ damage, and early mortality.

Stroke is a particularly devastating complication of SCA. At the University of the West Indies (UWI), strokes occurred in 17 of 310 children with SCA followed from birth, representing an incidence of 7.8% by 14 years of age [4]. In the US Cooperative Study of Sickle Cell Disease, the cumulative incidence of primary stroke in SCA was 11% by age 20 years [5]. Even with prompt recognition and emergency medical management, the clinical sequelae of strokes are significant with frequent motor and neurocognitive deficits.

Risk factors for ischemic stroke include prior transient ischemic attack, low steady-state hemoglobin concentration, rate of and recent episode of acute chest syndrome, and elevated systolic blood pressure [5]. However, an elevated transcranial Doppler (TCD) velocity is the strongest known risk factor for stroke in SCA; in particular, high blood flow velocities in the middle cerebral artery are strongly associated with an increased risk of primary stroke [6].

Adams et al demonstrated that TCD could effectively be used to screen pediatric patients with SCA to identify those with an increased risk of primary stroke [6,7]. These landmark studies documented that the relative risk of stroke was much higher among children with an abnormal TCD, defined as the maximum time-averaged mean velocity (TAMV) ≥ 200 cm/sec. The stroke risk in children with SCA and abnormal TCD velocities, or those with conditional velocities (170-199 cm/sec), are 9% and 2% to 5% per year, respectively [6]. Age is also an important risk factor: among patients under 10 years of age, the overall risk of converting from a normal or conditional TCD velocity to an abnormal velocity is about 30% [8].

The predictive value of TCD velocities has led to its widespread use in screening children for primary stroke risk, and to guide therapy for stroke prevention. After TCD velocities cross the threshold of 200 cm/sec into the abnormal category, monthly transfusions are recommended to reduce stroke risk. [9,10]. However, this treatment modality is impractical in many developing countries where the blood supply may be inadequate, expensive, or unsafe. Challenges associated locally such as inadequate blood donations and high costs associated with chelation therapy to treat transfusion-acquired iron overload make chronic transfusion programs not feasible. Hence, an alternative therapy is needed for stroke prevention. Particularly for developing countries, the identification of an effective non-transfusion protocol for both primary and secondary stroke prevention in SCA is of critical importance.

Preliminary data have provided evidence that hydroxyurea provides neuroprotection and significantly reduces TCD velocities [11-14], and a small randomized prospective trial documented its efficacy in preventing conversion from the conditional to abnormal range [15]. Recent data also support the use of hydroxyurea as a substitute for chronic transfusion after at least one year of transfusion in children with SCA who have abnormal TCD without severe vasculopathy as defined by magnetic resonance angiography (MRA) in order to maintain TCD velocities and help prevent primary stroke [16]. However, a substantial knowledge gap exists regarding the role of hydroxyurea for newly diagnosed severe cerebrovascular disease, before the use of transfusions. No prospective trials have been conducted in this setting, although a retrospective review in Jamaica concluded that hydroxyurea could effectively prevent secondary stroke compared to observation alone [17]. Within the context of this background, and to address this critical knowledge gap the EXpanding Treatment for Existing Neurological Disease (EXTEND) trial was designed to investigate the effect of open label hydroxyurea on the maximum TAMV after 18 months of treatment compared to the pre-treatment value.

The authors believe that the publication of this protocol allows for an increased awareness of a successful working partnership between countries. The objective of this manuscript is to describe the protocol of this trial and provide a brief summary of results to date.

Methods

Study Design and Aims

The aim of EXTEND is to prospectively treat children with SCA who have either a conditional or abnormal TCD velocity with hydroxyurea in order to determine whether treatment is associated with altered velocity in the intracranial vessels, neurological outcomes, or quality of life (QOL) differences when compared to the pre-treatment state. It is an open-label trial designed to provide data on the safety and benefits of hydroxyurea in Jamaica. This is a Phase II clinical trial because the primary outcome, which is the effect of hydroxyurea on lowering elevated TCD velocities, is without a comparison arm. In this setting, it is neither practical nor ethical to include a

control arm since regular blood transfusions for the treatment of cerebrovascular disease are not available in Jamaica. In addition, a prospective randomized controlled trial demonstrated that hydroxyurea could effectively lower conditional TCD velocities [15], and a retrospective study performed in Jamaica concluded that hydroxyurea could be beneficial for secondary stroke prevention [17]. The overall goal of the trial is to determine prospectively if hydroxyurea can serve as a protective treatment for neurovascular disease in children in a setting where the standard treatment of chronic blood transfusions is not practicable. EXTEND includes children with SCA and conditional TCD velocities, but also those with abnormal velocities and those who have already experienced a stroke, but who still have conditional or abnormal TCD velocities. Children who have experienced a stroke and maintain a conditional or abnormal TCD velocity will be eligible because a broad goal of EXTEND is to determine if hydroxyurea is a feasible treatment for neurovascular disease in children with SCA. Therefore, it is important to include even those on the most severe spectrum of disease, as there is no other treatment available. Only those with abnormal or conditional velocities are included to ensure the primary study endpoint can be evaluated in all participants.

The primary outcome measure is maximum TAMV obtained in the main intracranial arteries, typically the middle cerebral artery or distal internal carotid artery in both hemispheres. TCD velocities will be measured every 6 months, and the primary endpoint is the change in highest TAMV between the pre-hydroxyurea value and after 18 months of treatment. The Sparing Conversion to Abnormal TCD Elevation (SCATE) trial (NCT01531387) demonstrated that hydroxyurea could significantly reduce conditional TCD velocities within this timeframe [15].

Secondary endpoints of the EXTEND trial will include serial TCD velocity changes, incidence of neurological and non-neurological events, magnetic resonance imaging (MRI) and MRA changes of the brain, hydroxyurea-related toxicities and treatment responses, genetic and serological markers of disease severity and changes to QOL, neurodevelopment, body composition, resting metabolic rate, and lung function.

Study Setting

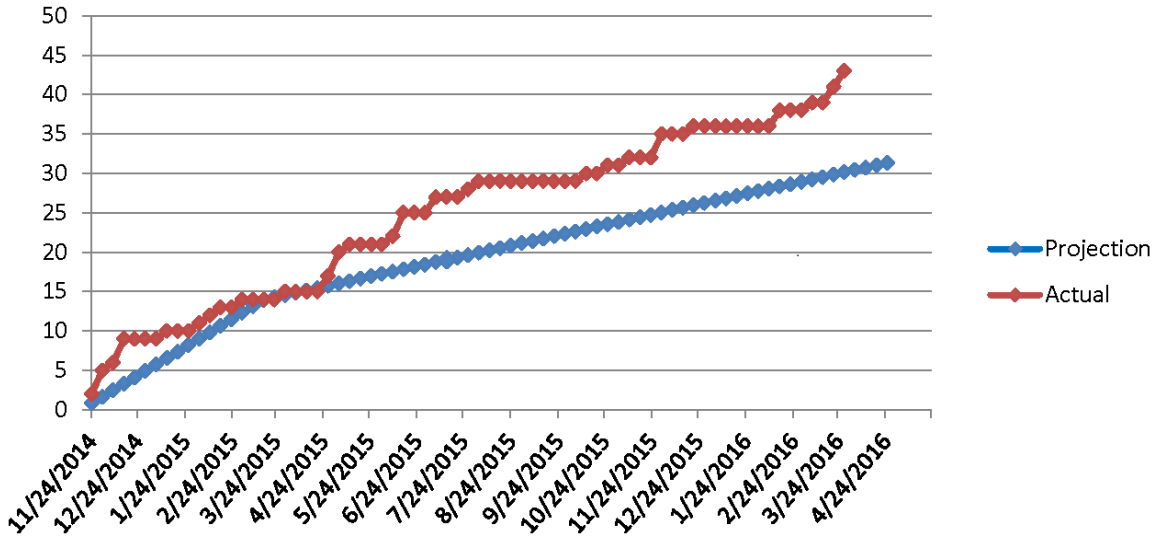
Cincinnati Children's Hospital Medical Center (CCHMC) serves as both the medical coordinating center (MCC) and the data coordinating center (DCC), while the Sickle Cell Unit (SCU) at UWI in Kingston, Jamaica is the clinical site. The SCU sees patients with SCA throughout their lifespan and has recently begun universal TCD screening to identify children at highest risk for stroke. The EXTEND protocol is approved by both the UWI Ethics Committee and the CCHMC institutional review board (IRB).

Recruitment

A maximum of 50 children will be recruited for the study. All children with SCA identified by routine TCD screening to have either conditional or abnormal TCD velocities are eligible for participation. The first enrollment into EXTEND was November 2014 with plans for completion during 2016; current enrollment is illustrated in Figure 1.

Specific inclusion criteria include: patients between ages 2 to 17 years with SCA (defined as genotypes HbSS, HbSβ^0 thalassemia, HbSD, $HbSO_{Arab}$), if their maximum TAMV is in the conditional (170-199 cm/sec) or abnormal (≥ 200 cm/sec) range by TCD ultrasonography within 6 months of enrollment. Key exclusion criteria include (1) participants who received an erythrocyte transfusion within the past 2 months; (2) the use of novel therapeutic agents within 3 months of enrollment; (3) known allergy to hydroxyurea therapy; and (4) positive human immunodeficiency virus (HIV) serology, malignancy, or other serious conditions. To protect against toxicity, patients with abnormal laboratory values on screening, defined by hemoglobin < 6 gm/dL, absolute reticulocyte count (ARC) < 100 x 10^9/L, white cell count < 3.0 x 10^9/L, or elevated serum creatinine will be temporarily excluded until the laboratory parameter improves.

Figure 1. Actual and projected enrollment in the EXTEND study.



Study Treatment

Participants will receive open-label hydroxyurea, available as capsules (200 mg, 300 mg, 400 mg, or 500 mg), or as a liquid formulation (100 mg/mL) as described [18]. Hydroxyurea will be administered once daily by mouth. Participants will be monitored monthly with dose escalation to the maximum tolerated dose (MTD) and thereafter with quarterly clinical evaluations, laboratory tests, and semi-annual TCD examinations. Strategies for monitoring drug adherence include counting or measuring drug supply returned at each study visit, and participant and family report of adherence. During the trial, routine care for each participant will be continued in the regular sickle cell clinic.

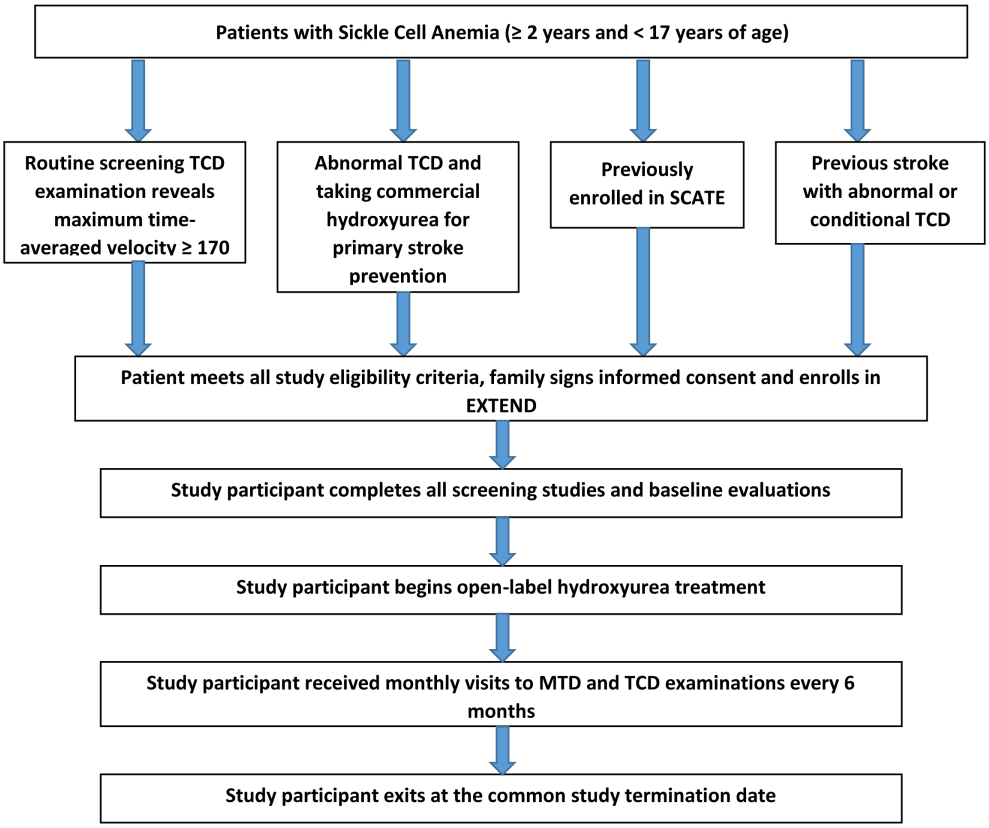
Hydroxyurea dosing and escalation will occur as previously described [19]. Briefly, hydroxyurea treatment will commence at 20 mg/kg/day and be titrated to the MTD as defined by mild marrow suppression, even if the participant has clinical well-being at a lower hydroxyurea dose. The target absolute neutrophil count (ANC) on hydroxyurea therapy will be 1.0 to 3.0 x 10^9/L, but the marrow suppression should also include reduction of the reticulocyte count [20]. Dose escalation will occur until the target suppression (ANC < 3.0 x 10^9/L) is achieved. After reaching MTD, minor hydroxyurea dose adjustments can be made periodically, as necessary based on weight changes and blood counts, to maintain the optimal laboratory response and to prevent dose-related toxicity. Hydroxyurea will be temporarily discontinued for hematological toxicities with dose reductions for repeated or prolonged toxicities.

Study Procedures

The EXTEND recruitment and enrollment procedures, followed by the treatment and monitoring process is illustrated in Figure 2. Once the legal guardian provides informed consent and participants aged 12 to 17 years provide assent, study procedures will commence. Complete blood count (CBC), reticulocyte count, serum chemistries, and hemoglobin electrophoresis will be performed at the screening visit to evaluate eligibility. Additional assessments performed during the screening period include: TCD, comprehensive history and physical examination, vital signs and anthropometric measurements, neurological exam, and a pregnancy test if applicable.

Once the local site confirms eligibility of the participant, the following baseline visit assessments will be performed: (1) blood counts and chemistries as well as hemoglobin electrophoresis, (2) TCD, brain MRI/MRA, pulmonary function tests (PFTs), (3) QOL and neuropsychological assessments, and (4) metabolic studies of body composition, resting energy expenditure and protein metabolism. TCD examinations will be performed every 6 months and participants will remain on study treatment for at least 18 months, until a common study termination date approximately 3 years after the first enrollment.

Figure 2. EXTEND study flow diagram.



Study Evaluations

The TCD procedures in EXTEND will follow the Stroke Prevention in Children with Sickle Cell Anemia (STOP) study protocol [7,21]. All TCD examinations will be performed by a trained examiner using a non-duplex 2-MHz Doppler ultrasound machine (SONARA/tek, Natus Medical Inc., Middleton,

Wisconsin). All TCD studies will be evaluated and scored locally, and the results entered into the EXTEND electronic database. There will be no central review of the TCD examinations, but 10% of scans will be reviewed every 6 months for quality control. The TCD coordinator from the MCC, who has been responsible for training TCD examiners and reading and reviewing research TCDs for over twenty years, will train and certify all EXTEND TCD examiners as well as perform quality control as described.

To more comprehensively evaluate neurovascular disease, brain MRI and MRA will be performed at study entry and after 18 months of study treatment for all children who receive study treatment. Brain MRI/MRA will also be performed to evaluate all acute neurological events experienced by EXTEND participants. Imaging sequences will include sagittal T1, axial T1, fluid attenuated inversion recovery (FLAIR), T2-weighted images coronal FLAIR, and diffusion weighted images on MRI, and MRA using three dimensional time of flight techniques, as described [22].

Additional Study Measurements

The validated Pediatric Quality of Life Inventory (PedsQL) tool will measure QOL. Because the PedsQL 4.0 contains two components of child self-report and parent proxy-report, young patients will have the parent proxy-report data only. QOL will be measured at baseline, after 18 months of study treatment, and exit. Neurodevelopment will be measured at baseline and after 18 months of hydroxyurea treatment, using the standardized Wechsler Abbreviated Scale of Intelligence (WASI) neuropsychological assessment tool. PFTs including pulmonary function spirometry will be performed in age-appropriate children at baseline and after 18 months of study treatment. Lung volume will be measured using a helium gas dilution technique (Morgan TLC Test Mk 11, Morgan Scientific, Haverhill, MA) [23]. Resting energy expenditure will be measured using the indirect calorimetry method, and body composition by deuterium dilution. Protein metabolism will be measured using a prime continuous infusion of ^{13}C-phenylalanine in the fed state. All of these tests will be performed at study entry and again after 18 months of study treatment.

Management of Data

Clinical data will be entered via the secure, Internet-based electronic data capture (EDC) system, OnCore, provided by the DCC. OnCore provides real-time data validation feedback, with an opportunity for real-time or delayed data corrections. The OnCore Protocol Management & Data Capture System provides tools to implement a wide variety of validation rules, such as edit checks, valid value and range checks as well as consistency checks. Validation rules will be applied whenever possible in the data entry and management process. Such reports will be generated at intervals that are useful to study leadership, the operations committee, the study monitor, and other applicable groups.

Queries are issued via the Data Monitor Console in the OnCore system, which is used as the validation and management workspace for online forms. As case report forms (CRFs) are completed, the monitor is able to validate the entered data and either issue a new query or lock the form. Issuing a query will send the form back to the person who entered the data with any questions associated with the query, whereas locking the form will preserve the data and prevent it from being altered once validated. This auditing will occur on an ongoing basis, and on-site monitoring visits will occur at least once per year.

Statistical Analysis

For the primary endpoint, up to 50 children will be enrolled, depending on the screening efforts performed by the clinical site. No formal sample size calculations have been performed since EXTEND enrollment is based on available patients with conditional or abnormal TCD velocities. However, our projected sample size in EXTEND will allow us to detect an effect size of > 15 cm/sec for hydroxyurea treatment with an alpha of .05 and power of > 90%.

For secondary endpoints, the highest TAMV for each time period along with the baseline values will be analyzed using repeated measures analysis of variance (ANOVA) in order to model the potential efficacy of hydroxyurea in reducing elevated TCD velocities in a longitudinal manner. To compare the cumulative incidences of categorical changes of TCD velocity (eg, conditional to abnormal, or abnormal to normal), participants with drug adherence of ≥ 50%, determined by measuring monthly returned medication, will be analyzed to determine the percentage of children with either conversion or reversion of their TCD velocities. Baseline labs will be compared to the exit studies using Wilcoxon signed-rank tests, while clinical efficacy will be assessed by comparing the number of hospitalizations and transfusions during study treatment, compared to data prior to enrollment. The incidence of stroke, non-stroke neurological events, and non-neurological sickle-related events will also be compared.

Changes in QOL scores from baseline to study exit will be compared between treatment groups by the Friedman test. The sub-scores for each domain, including physical, emotional, social and school functioning will be analyzed individually and in aggregate. Finally, a preliminary analysis of the cost-effectiveness and clinical efficacy of hydroxyurea will be performed to evaluate whether treatment can serve as an effective front-line therapeutic alternative to blood transfusions for existing neurological disease among children with SCA living in developing countries where chronic transfusions are not always feasible or available.

Results

A total of 43 participants have been enrolled. One participant withdrew from the study due to emigration outside of Jamaica. There have been no permanent screen failures. Of the participants, 37 have initiated study treatment; 36 participants are currently receiving study treatment, with plans to initiate all participants on treatment by July 2016. All participants will complete at least 18 months of study treatment before exiting the study at the common termination date. The early baseline results of this trial will be reported in early 2018. Final results will be reported in early 2019.

Discussion

Principal Findings

EXTEND is a continuation of the collaboration between CCH and UWI, officially established in 2012, but with beginnings prior because of a common interest in neurological complications of SCD by the lead investigators. The development of the partnership and SCATE protocol (NCT01531387) established a high quality TCD screening program in a large pediatric sickle cell population in Jamaica and provided the very first TCD findings in Jamaican children with SCD. The local health care team gained experience using hydroxyurea, which has improved the likelihood of future utilization in the general clinic population, particularly with regard to dosing and therapeutic monitoring. SCATE evaluated the effect of hydroxyurea compared to observation on conditional TCD velocities.

EXTEND is an innovative prospective trial that will evaluate the utility and efficacy of hydroxyurea in the setting of children with SCA and newly diagnosed cerebrovascular disease identified by conditional or abnormal TCD velocities. Building on a growing body of evidence, EXTEND aims to provide additional data to support the use of hydroxyurea as a treatment alternative to the current standard treatment of blood transfusions for cerebrovascular disease; this alternative is sorely needed in developing countries where access to safe blood transfusions is limited. If children with documented cerebrovascular disease are able to benefit from hydroxyurea without transfusion support, then TCD screening programs in developing countries can be developed without the requirement for safe and affordable blood. In addition, EXTEND will provide data on the benefits of hydroxyurea on other critical factors of health for children afflicted with SCD in Jamaica such as growth and nutrition, neurocognition, pulmonary function, and QOL. Importantly, any off-study treatment decisions should await completion of full data analyses.

Conclusion

The EXTEND trial results will potentially have a large impact on the management of children with SCA on a worldwide scale. The study represents international collaborative research involving developing countries, which is a stated goal of the National Heart, Lung and Blood Institute and the subject of academic advocacy [24,25]. Beyond the specific study objectives, the development of such collaborations between resource-rich countries and the developing world has the potential to be of considerable benefit to the health and well-being of patients with SCA in those developing nations. In the case of EXTEND, it is therefore expected that a successful collaborative research study with Jamaica will advance research expertise and potentially improve clinical care for all children with SCA. Finally, EXTEND represents continued collaboration between an established sickle cell program at CCHMC and a distinguished international SCA program in Jamaica, which may lead the way for future collaborative studies.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

ANC: absolute neutrophil count
ARC: absolute reticulocyte count

CCHMC: Cincinnati Children's Hospital Medical Center
DCC: data coordinating center
EXTEND: EXpanding Treatment for Existing Neurological Disease
FLAIR: fluid attenuated inversion recovery
HbSS: homozygous sickle cell anemia
MCC: medical coordinating center
MCV: mean cell volume
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
MTD: maximum tolerated dose
PedsQL: Pediatric Quality of Life Inventory
PFT: pulmonary function test
QOL: quality of life
SCA: sickle cell anemia
SCD: sickle cell disease
SCU: Sickle Cell Unit
TAMV: time-averaged mean velocity
TCD: transcranial Doppler
UWI: University of West Indies

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Original Paper

Predicting Negative Emotions Based on Mobile Phone Usage Patterns: An Exploratory Study

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Abstract

Background: Prompt recognition and intervention of negative emotions is crucial for patients with depression. Mobile phones and mobile apps are suitable technologies that can be used to recognize negative emotions and intervene if necessary.

Objective: Mobile phone usage patterns can be associated with concurrent emotional states. The objective of this study is to adapt machine-learning methods to analyze such patterns for the prediction of negative emotion.

Methods: We developed an Android-based app to capture emotional states and mobile phone usage patterns, which included call logs (and use of apps). Visual analog scales (VASs) were used to report negative emotions in dimensions of depression, anxiety, and stress. In the system-training phase, participants were requested to tag their emotions for 14 consecutive days. Five feature-selection methods were used to determine individual usage patterns and four machine-learning methods were tested. Finally, rank product scoring was used to select the best combination to construct the prediction model. In the system evaluation phase, participants were then requested to verify the predicted negative emotions for at least 5 days.

Results: Out of 40 enrolled healthy participants, we analyzed data from 28 participants, including 30% (9/28) women with a mean (SD) age of 29.2 (5.1) years with sufficient emotion tags. The combination of time slots of 2 hours, greedy forward selection, and Naïve Bayes method was chosen for the prediction model. We further validated the personalized models in 18 participants who performed at least 5 days of model evaluation. Overall, the predictive accuracy for negative emotions was 86.17%.

Conclusion: We developed a system capable of predicting negative emotions based on mobile phone usage patterns. This system has potential for ecological momentary intervention (EMI) for depressive disorders by automatically recognizing negative emotions and providing people with preventive treatments before it escalates to clinical depression.

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KEYWORDS

mobile phone usage; depression; emotion; machine learning; affective computing

Introduction

According to the World Health Organization, an estimated 350 million people are affected by depression worldwide. Depression is the leading cause of disability, and a major contributor to the global burden of disease, as measured by disability-adjusted life years [1]. Apart from pharmacological treatment and psychotherapy, self-management of negative emotions is of paramount importance because unprocessed negative emotions may escalate to clinical depression, and relapse of depression often results from an inadequate response to negative emotions [2]. In addition to those with clinical depression, the general public has developed an interest in recognizing their negative emotions, a major determinant of quality of life and adoption of health risk behaviors [3,4].

Awareness of negative emotion is crucial because it allows individuals to promptly respond with cognitive and behavioral strategies, avoiding escalation to clinical depression [5]. The concepts of ecological momentary assessment (EMA) and ecological momentary intervention (EMI) are the basis for real-time monitoring and management of context-specific emotional states [6,7]. A common and effective way to improve self-awareness is via regular self-tracking [8]. Several questionnaires pertaining to symptoms of depression have been implemented to mobile devices to help individuals track their emotional states [9-12].

In recent years, a novel and promising way for tracking emotion has emerged: via the mobile phone. The number of mobile phone users worldwide will surpass 2 billion in 2016 [13]. Mobile phone users spend almost an hour per day on their phones and check their phones on an average of 150 times daily [14]. Thus, mobile phones and mobile apps represent an opportunity to monitor and possibly intervene in mental health conditions [15,16]. In previous studies, mobile phones have shown potential for self-tracking of negative emotions [15,17,18].

Automatic Detection of Emotion with Mobile Phone Sensors

Affective computing aims to automatically detect emotions when they arise [19,20]. Prior studies have attempted to infer emotions with various sensors. For example, the collection of voice and speech signals [21-26] has been attempted, but it requires the use of a camera or microphone, which is more invasive and power-consuming. Tracing physiological correlates of emotions, such as heart rate variability [27] and electro-dermal activity [28] via portable sensors is another viable strategy, though these parameters are often interfered by determinants other than emotion itself, including physical exertion and environmental conditions (eg, temperature, humidity [29]). Information retrieved from Global Positioning System (GPS) signals (geospatial activity), multi-axial accelerometers (kinesthetic activity), and light/sound sensors (ambient features, sleep) is frequently used to differentiate emotional statuses [16,18,23-26,30]. Samsung Technology also conducted studies related to emotion detection [31,32], which focused on users' physical signals including hand gestures performed on the touch screen of a mobile phone.

Using Mobile Phone Usage Patterns to Predict Emotional State

Behavioral patterns can either be an antecedent or a consequence of human emotion [33]. Mobile phone usage patterns are a traceable behavioral characteristic potentially associated with concordant emotional states [34]. Apps tracing mobile phone usage are generally lightweight and power efficient, without a need for computationally intensive or power-consuming data processing of video, audio or physiological signals [35]. Faurholt-Jepsen et al [24] demonstrated in patients with bipolar disorder possible correlations between number of calls and depressive symptoms. Saeb et al indicated that high phone usage was associated with depressive scores reported at baseline [30]. Burns et al [36] used mobile phone data, such as call logs, SMS (short message service) text messaging, and GPS to predict mood states, however, results were poor. Microsoft has developed the MoodScope system [37], which predicted users' emotional state based on text messaging, emails, phone calls, application usage, Web browsing, and location and found that a personalized model with sufficient training period (ie, 2 months) would achieve a high predictive accuracy. However, few attempts have been made to compare the predictability of mobile phone usage data collected in different time frames (eg, 1 hour vs 2 hours prior to the reported emotion). In addition, a more sophisticated machine-learning algorithm was seldom applied.

The present study intends to capture user's self-reported negative emotions and mobile phone usage data, and analyze their association in order to predict negative emotion. The specific aims of this study are (1) to develop a mobile phone application for data collection; (2) to use machine-learning methods for system building; and (3) to prospectively evaluate the system predictability.

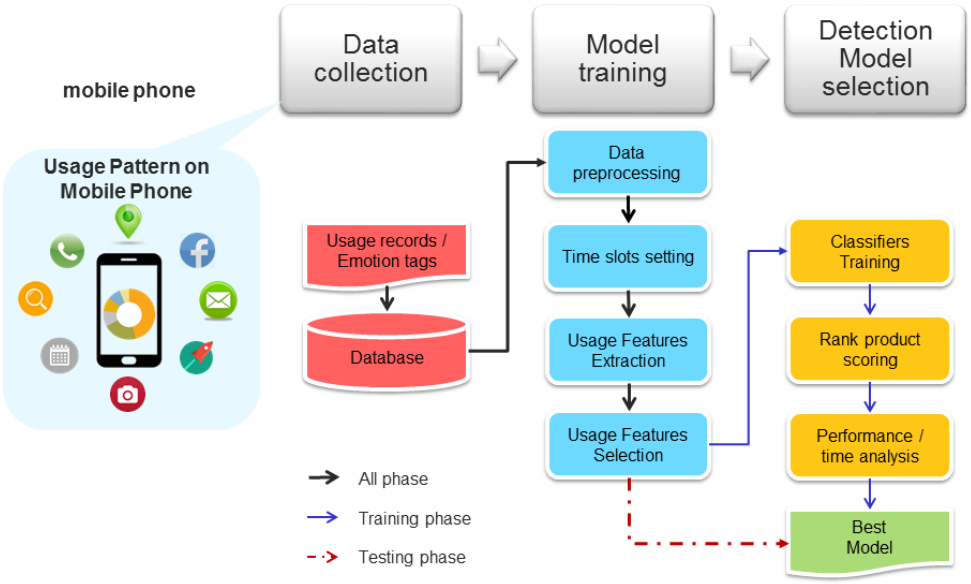
Methods

Design

We developed a mobile app (iHOPE) to capture self-reported negative emotions and automatically collect mobile phone usage patterns in the background.

The study procedure was divided into the following three phases (Figure 1): (1) data collection, which involves collecting negative emotion reports and raw mobile phone usage data, (2) classifier training, which involves quantifying negative emotions, defining usage patterns, feature extraction and selection, and selecting adequate time slots, with each combination being defined as a classifier, and (3) detection classifier selection where we developed a detection classifier selection method based on rank product scoring to reduce the number of combinations. We then evaluated the performance of each classifier and chose the best-performing one.

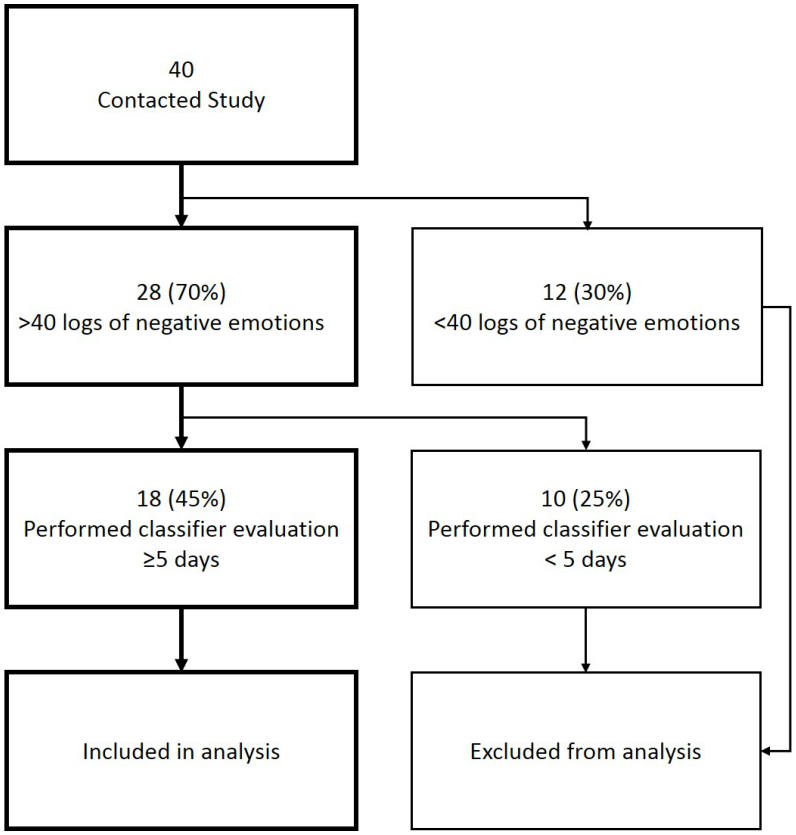
Figure 1. Study procedures.



Recruitment

Participants were graduate students recruited from the Institute of Medical Informatics, National Cheng Kung University, and medical professionals at Taipei City Psychiatric Center. In this exploratory study, we intended to recruit medical professionals with regular mobile phone use, better emotional awareness, and protocol adherence to properly train and validate our system. An invitation letter for participating in the study was sent to potential participants via email. After enrollment, they were requested to download and use the app on their primary mobile phone and tag the momentary state of depression, stress, and anxiety 4 times daily, with an interval of at least 3 hours between 2 consecutive tags, for 14 consecutive days. A notification was sent to the participants each time they were requested to tag emotions. All data were uploaded to a cloud server to train their personalized classifier. At the evaluation phase, we sent the personalized classifier via email for installation and requested the participants to validate the predicted negative emotions for at least 5 days. The study procedure is depicted in Figure 2.

Figure 2. Study flow from recruitment to analysis.



Data Collection

Negative Emotions

In collaboration with a psychiatrist at Taipei City Psychiatric Center (GCH), we built the app with visual analogue scales (VASs) to measure negative emotions in three dimensions: depression, stress, and anxiety (Figure 3). Each VAS contained a slider for the user to drag to a specific point indicating their current level of emotion. For depression, the lowest level indicated normal mood, whereas the highest level reflected the most depressed state. For anxiety and stress, the lowest level represented the usual state, whereas the highest level indicated the most anxious and stressful condition.

Figure 3. Visual analogue scale for anxiety.

Mobile Phone Usage Patterns

Our raw data contains call states and the package name of the app currently on the screen. We define the following three calling states: (1) idle state, the call function is not activated, (2) ringing state, which is a call waiting for the user to answer, with the phone either ringing or vibrating, and (3) off-hook state, that is, at least one call was dialing, active, or on hold. Our application monitored these calling states on the mobile phone every 3 seconds.

The package name of the app is recorded. To avoid duplicate app names, we record the package name of the app, which is unique in the installed-app list on the mobile phone. If there are several apps in the operating system hash, we only consider the app that currently occupies the screen. App categories, top ten apps, and screen usage are then inferred from the app package name records. Call-in, call-out, and missed calls are inferred from the call states.

Timeslot Selection

We set a timeslot for every emotion tag, ranging from 0.5 hour, 1 hour, 1.5 hours, to 2 hours. In a given timeslot, the following mobile phone usage features were extracted: (1) count (the number of occurrences of the usage type within the timeslot), (2) total duration (the sum of the execution times), (3) average duration (the sum of the execution time divided by occurrence of usage), and (4) average interval (the average of the intervals between the start time of a usage and end time of previous usage of the same type). For example, if a time slot of 1 hour is selected, and we are determining the features of phone calls, we would extract the information regarding (during the hour preceding the emotional tag) the number of phone calls, the average and total durations of the phone calls, and the average duration of intervals between the two phone calls.

Machine-Learning Methods Training

We used four conventional classifiers for analyzing mobile phone usage patterns (1) the Naïve Bayes classifier (NB); (2)

the C4.5 decision tree (C4.5); (3) the Naïve Bayes decision tree (NBT); and (4) the Support Vector Machine (SVM) [38,39]. The classifiers are widely used because they are fast, easy to implement, and explain. The SVM generally performs the best, but it requires more complex processing and computing. The feature sets used to train the classifiers and the feature selection are personalized for the distinct features of negative emotions expressed by each participant.

Two types of 2-level *t* tests are applied for feature selection. The manner in which we grouped the sets for each level is illustrated in Figure 4. For the first 2-level *t* test selection, the features with *P* values less than .05 were chosen either in the first or second level. If less than five features were chosen, features with the smallest *P* values were selected. The *t* test was replaced by the homoscedastic *t* test for the other 2-level *t* test selection. This was different from the initial *t* test such that a smaller value represented greater similarity in the two testing sets. With the homoscedastic *t* test, all features were chosen in the beginning, and the features with *P* values less than .05 in the first or second levels of the test were deleted from the chosen set [40].

The best first feature selections used greedy algorithms to find the best feature set for classification instead of choosing each feature independently. These selection procedures were thus more likely to find multi-feature usage than the 2-level *t* test. We applied sequential forward selection, sequential backward selection, and bi-directional selection to do the best first selection. A detection classifier selection method was developed based on rank product scoring, which considered the rank order rather than the accuracy of the classification result, so that the influence of outliers was minimized. The process for detection classifier selection is depicted in Figure 5. After the combination for each feature selection method was determined, we selected the best classifier from the four classifiers based on the average predictive accuracy for the three VASs.

Figure 4. Two-level feature selection for scales of negative emotions.

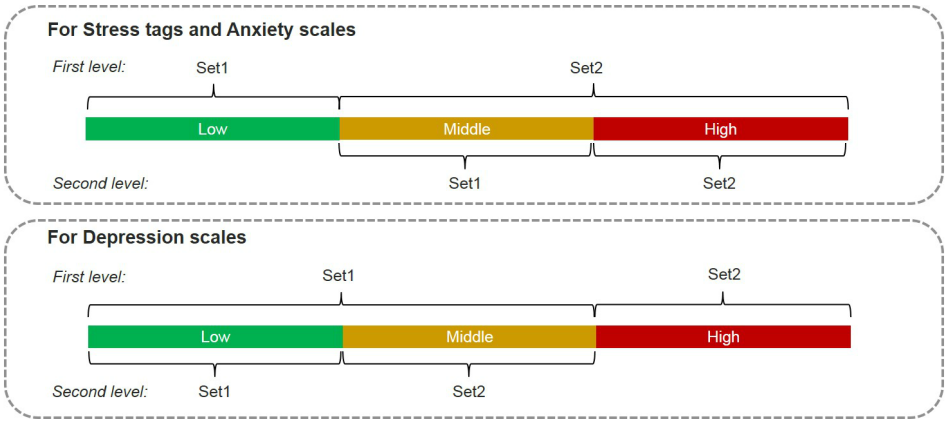
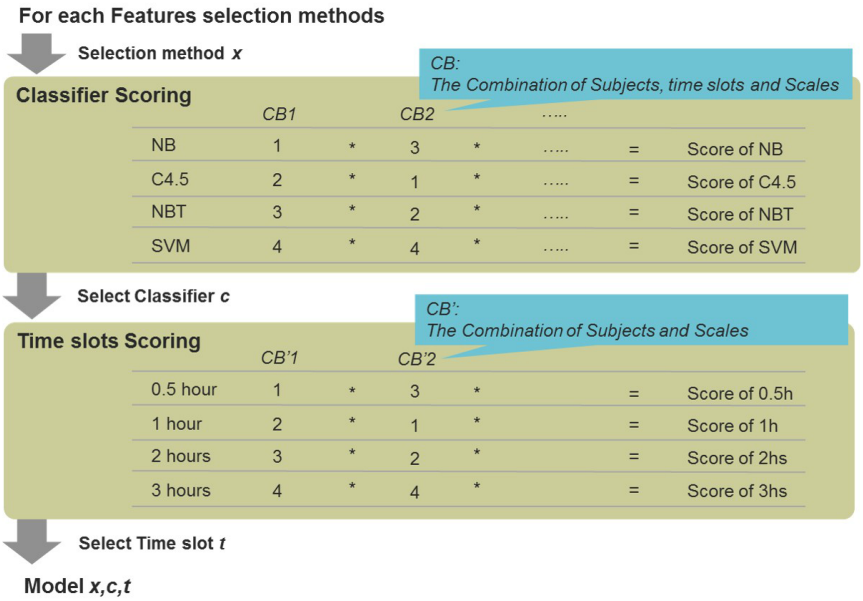


Figure 5. Detection classifier selection.



Evaluation

After the personalized classifiers were trained using data collected from the 2-week period, it was provided to the participants for an evaluation for at least 5 days. Using the identical VAS for reporting negative emotions, the classifier provided predictions for current state of depression, anxiety, and stress every 2 hours from 11:00 AM to 11:00 PM. A

notification was sent to the participants about the prediction, and they were allowed to correct it by dragging the slider to the exact level of current emotion. We divided the range of each negative emotion to three categories (low, medium, high). The prediction failed if any of the corrected ratings were not in the same category. We then compared the performance of our classifier with that of two benchmark models: multiple linear regression and general guess method.

Results

Study Sample

We recruited 40 healthy participants (30 graduate students and 10 medical professionals) who had contacted us to participate in the study. In the system-training phase, we used the data from 28 participants who had a minimum of 40 logs of negative emotions. Of them, 9 (32%, 9/28) were woman with a mean (SD) age of 29.2 (5.1) years. In the system-evaluation phase, we analyzed the data from 18 participants who had performed the evaluation for at least 5 days.

Machine-Learning Methods Selection

To select the appropriate classifier, we tested four classifiers. The combination of the NB classifier with 2-hour timeslots and greedy best forward feature selection had the highest accuracy for the depression and stress scales. Thus, this combination was chosen as the best classifier to detect negative emotion and was applied to evaluate the individual classifier (refer to Multimedia Appendix 1 for a complete list of the performance achieved by every combination).

Evaluation Outcomes

Among the 18 participants selected, they performed the evaluation for a mean (SD) of 10 (3) days. On average, an individual responded to 56 (20) predictions of their negative emotions. The results of the individual classifier evaluation are detailed in Table 1. In total, 1008 predictions were made and 995 of them (98.71 %, 995/1008) received feedback. Of those, 857 (86.1%, 857/995) indicated successful predictions, thus, the average rate of successful detections was 86.17%. Comparing with the predictive accuracy of multiple linear regressions (63%) and general guess method (77%), our classifier was substantially better in detecting negative emotions.

Table 1. Result of the personalized classifier evaluation.

User ID	Duration of system evaluation, days	Numbers of predictions responded[a]	Numbers of successful predictions	Predictive accuracy[b], %
Subject 1	13	75	69	92.00
Subject 2	10	56	47	83.93
Subject 3	13	77	68	88.31
Subject 4	9	51	38	74.51
Subject 5	10	58	55	94.83
Subject 6	5	30	28	93.33
Subject 7	5	30	28	93.33
Subject 8	5	30	23	76.67
Subject 9	8	48	41	85.42
Subject 10	8	48	45	93.75
Subject 11	8	48	41	85.42
Subject 12	8	48	42	87.50
Subject 13	8	48	41	85.42
Subject 14	8	48	40	83.33
Subject 15	8	48	39	81.25
Subject 16	10	60	50	83.33
Subject 17	16	96	79	82.29
Subject 18	16	96	83	86.46
Total	10 (mean)	995	857	86.17

[a]The personalized classifier routinely made 7 predictions daily, but participants may respond only to some but not all of them.

[b]Successful predictions/responded predictions.

Discussion

Principal Findings

We developed a mobile phone app capable of reporting negative emotions and collecting mobile phone usage patterns. The present study provides preliminary evidence that by adapting sophisticated machine-learning methods, it is possible to predict concurrent negative emotions via mobile phone usage patterns with substantial accuracy.

Limitations

The following limitations should be considered when interpreting the results of our pilot study. First, our participants were healthy professionals with moderate mobile phone usage and possibly better capability to define the degrees of negative emotions. A more extensive approach of validation would be recruiting a group of generally healthy controls, and another group with clinical depression. Second, mobile phone usage patterns is one but not the only indicator of underlying emotions. Other factors (eg, sleep, movement) are involved in manifesting the current emotional state and should be incorporated in future studies. Third, some participants either did not carry their mobile phones all the time or did not respond to emotion tags and predictions regularly, which interrupted data collection and prediction verification. Moreover, there were participants who used more than one mobile device. Therefore, data collected from a single mobile phone may not reflect the actual usage patterns. Lastly, users with higher suggestibility may be inclined to agree with the emotional state inferred. An alternative approach would be to ask users to report their momentary emotion before providing them with the prediction. Moreover, our system provided an individualized model for emotional prediction (ie, each participant had unique features of mobile phone usage patterns associated with her emotion). Due to the limited sample size, we were unable to identify any general patterns among the personalized features.

Comparison with Previous Studies

The predictive accuracy of our system (86.17%) is comparative to previous research using mobile phone usage patterns to infer human emotions, however, the training time required (2 weeks) is substantially shorter than other studies (3 weeks to 3 months) [11,20,37]. We have observed that participants' usage behaviors changed substantially over time. Data currently collected for emotion inference may be out of the range of data previously used to obtain the personalized classifier, leading to failed prediction. Consequently, the personal classifier may need to be retrained periodically to improve the predictive accuracy. Aimed at preventing clinical depression, our predictions involve three negative emotions (depression, anxiety, and stress), which frequently precede a full-blown depressive episode, while prior studies [35,37] often adapted the circumplex model of normal emotion (ie, pleasure and activeness) [41]. While many studies used simple regression to predict emotion, we applied a sophisticated machine-learning process in combination with timeslot and feature selections. Moreover, when performing system evaluations, instead of adapting the same dataset used to train the personalized classifier, we request the users to prospectively validate the predicted emotion.

Implications and Future Work

Though depressive disorders are becoming a global public health challenge, current treatment of depression has encountered considerable obstacles. A substantial portion of patients with depression either does not have access to standard treatments [1,42], primarily consisting of antidepressants and psychotherapy, or does not respond well to those treatments [43]. Outside of North America and Europe, there is a shortage of mental health professionals globally, and the stigma of mental disorders often prevents patients from actively seeking treatment [1]. Therefore, improving self-awareness and management of depression, or its antecedent negative emotion, can be a viable strategy for primary or secondary prevention. In addition, adopting the mobile phone interface can make it both accessible and scalable.

Analyzing mobile phone usage behavior to infer negative emotions is a pragmatic approach because it is possibly the single most prevalent, continuous, and traceable behavioral characteristic in the modern era. Future work should combine mobile phone usage patterns and other indices available for continuous monitoring via mobile phone(eg, location, weather) to collectively infer the underlying emotion. Moreover, emotion is a temporary state, which follows a dynamic pattern over time. A time-series analysis should be employed to account for the temporal alterations of negative emotions. With automatic detection of negative emotions, EMI becomes possible so that cognitive or behavioral suggestions may be provided seamlessly, and therefore bypassing the necessity of users having to acknowledge their negative emotions before receiving support. We are currently collaborating with the Taipei City Psychiatric Center, and are recruiting patients with depressive disorder to examine the feasibility and usefulness of this system in the clinical setting. The study protocol has been approved by the institutional review board (TCHIRB-1030206).

Conclusions

In the present study, we developed a system capable of predicting negative emotions based on mobile phone usage patterns. The performance of our system appears to be superior to that of predictive models used in prior studies. The combination of timeslot selection, machine-learning process, and multiple feature selections may have substantially improved predictability. This system has a potential for ecological momentary intervention for health individuals or patients with depressive disorders by promptly recognizing negative emotion and providing them with preventive treatments before it escalates to clinical depression.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Comparison of performance achieved by different combinations of machine-learning methods.

[PDF File (Adobe PDF File), 63KB - resprot_v5i3e160_app1.pdf]

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Abbreviations

EMI: ecological momentary intervention
GPS: Global Positioning System
NB: Naïve Bayes classifier
SMS: short message service
SVM: Support Vector Machine
VAS: visual analogue scale

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Original Paper

Application of a Web-Enabled Leg Training System for the Objective Monitoring and Quantitative Analysis of Exercise-Induced Fatigue

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Abstract

Background: Sustained cardiac rehabilitation is the key intervention in the prevention and treatment of many human diseases. However, implementation of exercise programs can be challenging because of early fatigability in patients with chronic diseases, overweight individuals, and aged people. Current methods of fatigability assessment are based on subjective self-reporting such as rating of perceived exertion or require specialized laboratory conditions and sophisticated equipment. A practical approach allowing objective measurement of exercise-induced fatigue would be useful for the optimization of sustained delivery of cardiac rehabilitation to improve patient outcomes.

Objectives: The objective of this study is to develop and validate an innovative approach, allowing for the objective assessment of exercise-induced fatigue using the Web-enabled leg rehabilitation system.

Methods: MedExercise training devices were equipped with wireless temperature sensors in order to monitor their usage by temperature rise in the resistance unit ($\Delta t°$). Since $\Delta t°$ correlated with the intensity and duration of exercise, this parameter was used to characterize participants' leg work output (LWO). Personal smart devices such as laptop computers with wireless gateways and relevant software were used for monitoring of self-control training. Connection of smart devices to the Internet and cloud-based software allowed remote monitoring of LWO in participants training at home. Heart rates (HRs) were measured by fingertip pulse oximeters simultaneously with $\Delta t°$ in 7 healthy volunteers.

Results: Exercise-induced fatigue manifested as the decline of LWO and/or rising HR, which could be observed in real-time. Conversely, training at the steady-state LWO and HR for the entire duration of exercise bout was considered as fatigue-free. The amounts of recommended daily physical activity were expressed as the individual $\Delta t°$ values reached during 30-minute fatigue-free exercise of moderate intensity resulting in a mean of 8.1°C (SD 1.5°C, N=7). These $\Delta t°$ values were applied as the thresholds for sending automatic notifications upon taking the personalized LWO doses by self-control training at home. While the mean time of taking LWO doses was 30.3 (SD 4.1) minutes (n=25), analysis of times required to reach the same $\Delta t°$ by the same participant revealed that longer durations were due to fatigability, manifesting as reduced LWO at the later stages of training bouts. Typically, exercising in the afternoons associated with no fatigue, although longer durations of evening sessions suggested a diurnal fatigability pattern.

Conclusions: This pilot study demonstrated the feasibility of objective monitoring of fatigue development in real-time and online as well as retrospective fatigability quantification by the duration of training bouts to reach the same exercise dose. This simple method of leg training at home accompanied by routine fatigue monitoring might be useful for the optimization of exercise interventions in primary care and special populations.

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KEYWORDS

exercise intervention; cardiac rehabilitation; training equipment; online monitoring; exercise dose; muscle fatigue; heart rate; leg work output; fatigability

Introduction

Regular cardiac (aerobic/endurance) training is essential in the maintenance of health and considered as a key intervention in prevention, treatment, and rehabilitation of many human diseases [1]. However, cardiac rehabilitation (CR) remains vastly underutilized due to significant barriers such as the high costs of services and low exercise capacity of patients [2]. The most popular CR regimen is moderate-intensity continuous training (MICT). The consensus among experts is that MICT bouts should be performed at least 5 days per week for 30 minutes per day or 150 minutes per week [3,4]. These guidelines are similar for the general, clinical, and special populations.

It has been proposed that sustainable CR should be personalized because of variability in the individual fitness levels and physiological responsiveness to physical activity [5]. A conventional approach to personalization of CR is expressing the exercise intensity as a percentage of the maximal oxygen uptake (VO_{2max}) or heart rate (HR_{max}) [6]. It is generally accepted that the intensity of MICT in clinical and general populations should be within 50% to 70% of the VO_{2max} or HR_{max}[7]. However, the typical duration of conventional exercise tests does not exceed 10 minutes so that they may not fully reflect the changes in physiological responses at the later stages of the recommended 30-minute or longer MICT sessions [8]. Development of exercise-induced fatigue is expected to manifest as the slowing down of exercise intensity at the later stage of training bouts, particularly in untrained people [9].

Fatigue is not only the normal physiological response to physical activity but also the most common symptom of human disease and sign of ageing [10,11]. Further, even a relatively short immobilization results in markedly decreased levels of fatigue resistance [9]. There is also chronic fatigue syndrome, which is characterized by persistent fatigue and treated by physical exercise [12]. Therefore, CR programs prescribed to patients with chronic disease, overweight individuals, and aged persons should consider their higher fatigability than the general population [13,14]. However, despite the potential diagnostic and predictive value of fatigue measurements [15], clinically valid methods suitable for the assessment of fatigability are still lacking [16].

The existing methods used in clinical practice include the subjective rating of perceived exertion (RPE) [17,18], which is based on self-reporting and hence might be biased, particularly in obese participants [19]. Objective measurements of muscle fatigue require laboratory conditions and sophisticated equipment [20]. For example, a typical laboratory protocol involves electromyographic recordings from the participant using incremental cycle ergometry or treadmill running [21]. Modern technology facilitated the development of wearable measuring systems such as a fatigue monitoring system and body sensor network [22,23], although they have yet to be implemented in practice.

Therefore, the current methods of fatigue assessment are either subjective or based on complex technologies. In this study we report research protocols allowing for the monitoring and quantification of fatigue during routine exercise training with an innovative leg rehabilitation system [24,25]. Remote fitness testing, personalization of MICT doses, and quantification of fatigability demonstrated in this study might be useful for the optimization of CR [26].

Methods

Equipment and Data Collection

The MedExercise ST01 leg training system (MDXD Pty Ltd, Sydney, NSW, Australia) was used in this study. This portable system was developed for exercise rehabilitation on site and consists of a variable resistance unit with two pedals, means for attachment to the furniture, and a measurement module [24,25]. The resistance unit of the system is equipped with wireless temperature sensors (Monnit, Midvale, UT) positioned in two different locations allowing for the measurement of temperature at high and low sensitivity modes. Temperature data was transmitted in 1 minute intervals to the user's electronic device such as personal computers via MonnitLink Universal Serial Bus (USB) gateways and processed with stand-alone or cloud-based iMonnit software.

Before each training session, the temperature values were set to zero. The exercise-induced rise of temperature in the resistance unit ($\Delta t°$) was used for the measurement of a total leg work output (LWO). Since $\Delta t°$ depends on the resistance to foot motion, cadence of leg movements, and training duration, LWO reflects the energy expenditure of the user, similar to the calorie counting in cycle ergometers [24,25]. The automatic notification feature of iMonnit software allowed for the setting of email alerts upon reaching specified $\Delta t°$, reflecting the total LWO of the participant during a training bout [26].

Heart rates (HRs), expressed as a number of beats per minute (BPM), were monitored using fingertip pulse oximeters CMS-50E and the software supplied with it (Contec, Shanghai, China). HR was graded as the percentage to HR_{max} using the following conventional formula:

HR_{max}=220-age

The RPE was assessed using the Borg's scale 6 to 20 [27] and ranked as light (<12), moderate (12-14) or strenuous to continue (>14). Data was processed and analyzed using Excel worksheets software (Microsoft, Redmond, WA).

Study Design

It was hypothesized that the simultaneous monitoring of exercise intensity and participant's performance by HR and LWO, respectively, might detect the development of fatigue during exercise training. In order to test this hypothesis, two experimental settings were used. First, supervised training bouts at different intensities and durations were performed at the high and low sensitivities of LWO measurement. Then, the system was used at low-sensitivity for self-controlled training at home with automated monitoring of compliance. The duration of training and number of participants corresponded to the aim of the study; protocol development for the quantitative measurement of exercise-induced fatigue and fatigability.

Participants

The inclusion criteria were (1) absence of known medical contraindications to regular exercise training; (2) capacity to install the training equipment and use it at home; and (3) connection to the Internet and ability to manage electronic data. The reasons for exclusion included (1) inability to provide informed consent; (2) not adhering to a prescribed training regimen; and (3) failure to use technology reliably. Overall, 7 eligible volunteers (25 to 52 years old) participated from 2013 to 2015.

Results

High-Sensitivity Recording

The monitoring of participant's performance during exercise bouts of various intensities using $\Delta t°$ to characterize LWO is exemplified in Figure 1. Vigorous training, as indicated by HRs over 130 BPM or greater than 70% HR_{max}[28], is illustrated in the top left panel of Figure 1. The RPE rating was considered more than 14 throughout the entire exercise bout. The $\Delta t°$ rose to approximately 57°C (interval 1), plateaued for a few minutes (interval 2), and then progressively declined (interval 3) despite a steady state HR. Upon cessation of training, both the participant's HR and $\Delta t°$ in the training device dropped (interval 4). This experiment demonstrates that reduction of LWO (interval 3) started after around 7 minutes of training despite the participant maintaining a high intensity level of exercise as indicated by a HR over 130 BPM.

The LWO kinetics at a HR of 120 (SD 10) BPM or around 70% HR_{max}, moderate to vigorous intensity levels of exercise for this participant, is shown in the top right panel of Figure 1. The corresponding RPE score was considered at first as 12 to 14 and then over 14. Compared to the vigorous intensity of training (Figure 1, top left), a lesser intensity of exercise caused a slower rise and lower maximum $\Delta t°$ of around 51°C. The plateau level of LWO lasted about 9 minutes before a gradual reduction so that the duration of steady-state performance was about 15 minutes, the sum of intervals 1 and 2.

The top panels in Figure 1 demonstrate an inverse correlation between training intensity and the participant's ability to maintain LWO at the steady-state level, for example for 7 and 15 minutes, respectively. An inverse correlation between these parameters suggests that participants' muscle fatigue manifest as a reduction of LWO despite the same intensity of training.

The bottom left panel of Figure 1 shows recordings from the experiment, which intended to reproduce the recommended amount of daily exercise achieved by 30-minute MICT [4]. The corresponding initial exercise intensity was 100 (SD 10) BPM or 55% to 70% HR_{max}, indicating a moderate intensity of exercise. The steady-state level of LWO with the RPE of 12 to 14 was maintained for the entire 30 minutes of the training bout. Nevertheless, the HR was moderate only for about 10 minutes and then gradually rose to the maximum of approximately 130 BPM or greater than 70% HR_{max}. This suggests that maintaining a steady-state LWO at this level requires progressive increasing of exercise intensity from the moderate to vigorous level as indicated by a rising HR from 100 to 130 BPM.

In contrast, the bottom right panel of Figure 1 exemplifies a 30-minute MICT session at a HR of 100 (SD 10) BPM, where neither muscle fatigue (reduction of LWO) nor the increase in exercise intensity (rising HR) was manifested. The RPE score was 12 to 14. Therefore, this training session might be considered as a fatigue-free MICT bout matching the recommended "dose" of daily exercise for this participant. It might be suggested that repeating this amount of training at least 5 days per week would match the recommended weekly volumes of exercise [4].

The variability of LWO patterns between the participants during 30-minute MICT at a HR of 100 (SD 10) BPM is demonstrated in Figure 2 (left panel). The corresponding RPE scores were 12 to 14. These recordings exemplify individual differences in the LWO profiles demonstrated by the variability of plateaus levels, where $\Delta t°$ varied from 24°C to 42°C, with a mean of 34.2°C (SD 5.7°C, N=7).

The LWO recordings of the participant, who performed MICT bouts of various durations on different days, are shown in Figure 2 (right panel). Since the $\Delta t°$ plateau levels were reproducible, the volumes of MICT were proportional to the duration of training. In this example, MICT for 15, 30, and 60 minutes could be considered as corresponding to 0.5, 1.0, and 2.0 daily exercise doses for this participant [4]. The MICT volume equal to or less than 1.0 indicates "taking" a recommended daily exercise dose, whereas a value 0.5 is a half of the dose, and a value 2.0 means that two daily MICT doses were "taken" during a single exercise bout.

Figure 1. High-sensitivity Δ*t*° measurements showing the simultaneous recording of participant LWO (left scale, blue curve) and HR (right scale, brown curve) during vigorous >130 (SD 10) BPM (top left), vigorous-moderate 120 (SD 10) BPM (top right), variable 100-130 (SD 10) BPM (bottom left), and moderate 100 (SD 10) BPM (bottom right) levels of exercise intensity. Intervals 1-4 on top of arrows indicate Δ*t*° phases during exercise bouts of various intensities.

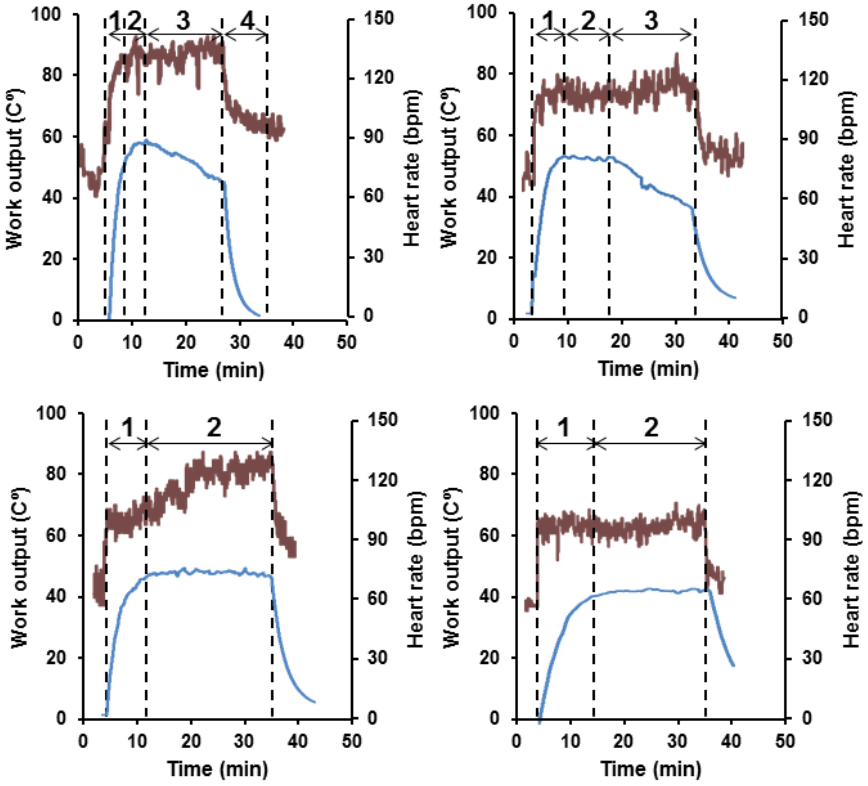
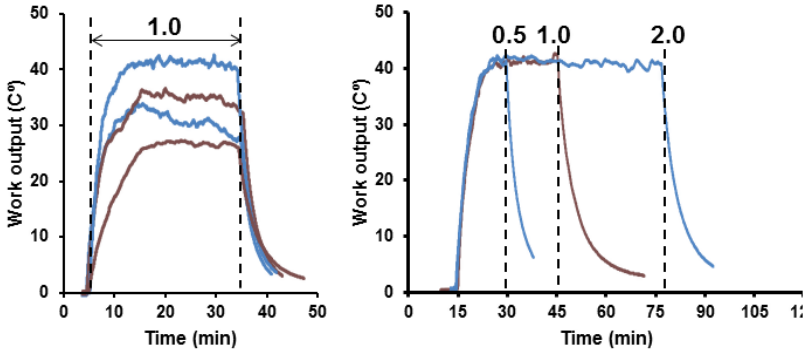


Figure 2. High-sensitivity Δ*t*° measurements showing variability of Δ*t*° at moderate exercise intensity of 100 (SD 10) BPM (left) and Δ*t*° recordings of the same participant training at the HR of 100 (SD 10) BPM for 15, 30, and 60 minutes on different days (right). Vertical dashed lines and numbers indicate amount of daily training as a proportion to the recommended 1.0 dose of MICT [4].



Low-Sensitivity Recording

While high-sensitivity measurements allow real-time visualization of fatigue development, quantification of MICT doses is complicated due to variability of LWO plateau levels, as exemplified in Figure 2 (left panel). It is also evident that the HR reflects the intensity of training, whereas the right panel in Figure 2 suggests that Δ*t*° could be used for selecting daily exercise doses. Conversely, we used a low-sensitivity mode to express the daily MICT doses in single-item numbers, as shown in Figures 3 and 4.

Low-sensitivity recordings of the participant, whose high-sensitivity recording were presented in Figure 1 (top right) is shown in Figure 3 (left panel, curve a). In both cases, the participant was training vigorously at a HR of 120 (SD 10) BPM, but low-sensitivity did not allow Δ*t*° to plateau within at least 30 minutes of training. This suggests that during less intensive exercise, (eg, MICT), rising Δ*t*° should be linear without reaching the saturation level within 30 minutes. Therefore, Δ*t*° achieved by MICT in 30 minutes would reflect the daily dose of exercise [4]. Curves b-d (Figure 3, left) exemplify low-sensitivity LWO recordings of participants training at HRs of 100 (SD 10) BPM for 30 minutes to reach the recommended amounts of daily MICT. The associated RPE scores were 12 to 14. This shows that Δ*t*° values varied from 7.1°C to 10.0°C and could be considered the personalized doses

of recommended daily MICT for these participants expressed as single numbers. The mean Δ*t*° is 8.1°C (SD 1.5°C, N=7).

Next, we tested the reproducibility of "taking" the personalized LWO doses expressed in Δ*t*°, and the recordings of 3 MICT sessions at a HR of 100 (SD 10) BPM performed by the same participant on different days to reach a personalized Δ*t*° dose of 10°C are shown in Figure 3 (middle). While the dose was reached on all occasions, their duration varied between 26 and 37 minutes (arrow 2). Providing that the time required to achieve a half of the dose was similar (arrow 1), wide variability of bout durations depended mostly on the time required to reach Δ*t*° from 5°C to 10°C. Conceivably, longer second halves of the bouts were likely due to fatigue, which typically manifests as slowing down of physical activities at the later stages of training sessions, which can result in reduction of walking speed and shorter distance of walking [29].

In order to test whether fatigue contributes to a longer duration of Δ*t*° rise from 5°C to 10°C, the participant "took" two 10°C doses consecutively using different devices to start each dose at "zero" temperature. The right panel in Figure 3 shows that the first 10°C dose was reached after 27 minutes of exercise, whereas it took about 40 minutes to take the second dose (interval 2). It also demonstrates that an extra 4 minutes (arrow 1) was required to reach 5°C at the second bout, which was likely due to fatigue accumulated during the first bout. In contrast, the durations to achieve 5°C were similar in exercise bouts taken by the recuperated participant on different days as shown (Figure 3, middle panel). Taking 2 daily MICT doses in one session also resulted in leg muscle strain reported by the participant on the next day. Therefore, this experiment corroborated that the duration required to take daily MICT dose may reflect the level of participant's fatigue.

We further hypothesized that fluctuations of durations to "take" the same dose of MICT might reflect the diurnal variations of participant fatigability [30]. In order to test this notion the device was installed at the participant's home to use every day in the afternoons or evenings, when it was feasible. The personalized MICT dose of 10°C was prescribed for overall 8 weeks with automatic email notifications.

Figure 4 exemplifies continuous Δ*t*° recordings from the device installed at the participant's home. An automatic notification was sent when Δ*t*° reached 10°C as marked by arrows, which also indicates the time of the day the MICT doses were taken. During these 15 days, notifications were received 11 times, suggesting that the dose should be taken on 11 out of 15 days. It was found that training in the morning/afternoon sessions took place on days 1, 2, 5, 7, 11, 12, and 15, and in the evening sessions (after 5 pm) on days 3, 6, 8, and 9. Crosses mark the days when the device was not used (days 4, 10, 13, and 14).

Over the 8 weeks of the experiment, 20 automatic notifications were received before 5 pm and 20 notifications after 5 pm. A representative bivariate plot of bout durations versus the time of day when training was performed is shown in Figure 5 (left). The plot demonstrates that Δ*t*° of 0°C to 5°C was achieved in similar periods of time regardless of the time of day, whereas the total durations of training bouts varied, particularly during the evening sessions.

The statistical analysis of training times grouped into the afternoon and evening sessions is shown in Figure 5 (right). The analysis demonstrates that in the afternoons there was no statistical difference between durations to reach Δ*t*° 0°C to 5°C and 5°C to 10°C, suggesting afternoon training as fatigue-free. In contrast, the second halves of evening training sessions, 13.5 (SD 0.5) minutes, lasted 50.9% longer than the first halves 20.3 (SD 3.5) minutes ($P<0.05$). The longer Δ*t*° 5°C to 10°C in the evenings, 14.3 (SD 2.1) minutes, compared to the afternoons, 20.3 (SD 3.5) minutes ($P<0.05$), resulted in significantly longer total durations of training of 27.4 (SD 2.4) minutes and 33.8 (SD 3.6) minutes before and after 5 pm, respectively ($P<0.05$). This data suggests the diurnal fatigability developed in the evenings results in longer durations of training required to take the same MICT dose as in the afternoons. Other participants of this study tested the system at home for 1 week. The individual Δ*t*° produced at the MICT bouts exemplified in Figure 3 (left) were set as the thresholds for automatic notifications, which were received on 4.2 (SD 1.2) days per week (N=6). Analysis of these recordings demonstrated that the mean duration of training (afternoons and evenings) was 30.3 (SD 4.1) minutes (N=25), as it was expected for these doses of training.

Figure 3. Low-sensitivity recordings of changes in Δ*t*° at a HR of 120 (SD 10) BPM (curve a) and 100 (SD 10) BPM (curves b-d) (left panel). Low-sensitivity recordings of different durations to reach Δ*t*° dose of 10°C on different days by the same participant (middle) and two consecutive bouts to reach a Δ*t*° dose of 10°C by the same participant consecutively using two training devices (right). Vertical dashed lines represent durations needed to reach a half (arrows 1) and the full LWO dose of 10°C (arrows 2) delineated by horizontal dashed lines.

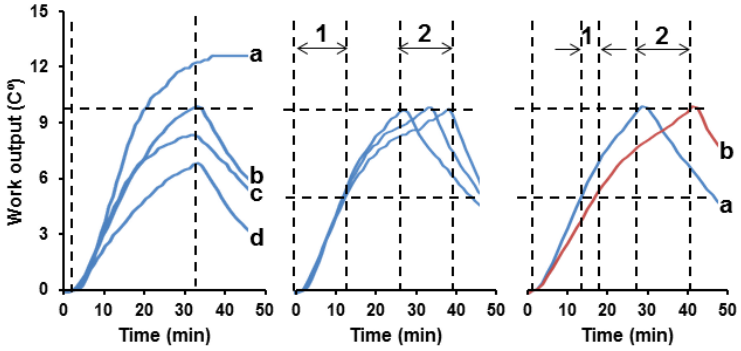


Figure 4. Low-sensitivity recordings of a continuous Δt° recording from the training device installed in a participant's home during 15 days. Horizontal dashed lines indicate the levels of "zero", half, and full LWO dose of 10°C. Arrows indicate days and times of the day when the automated notifications were sent. Crosses mark days without training with the device.

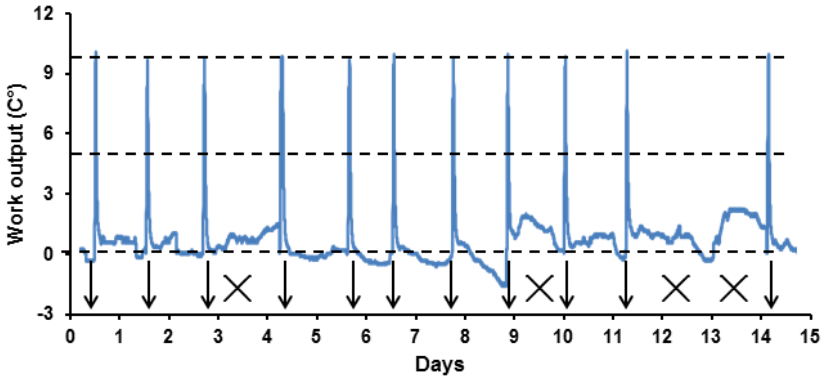
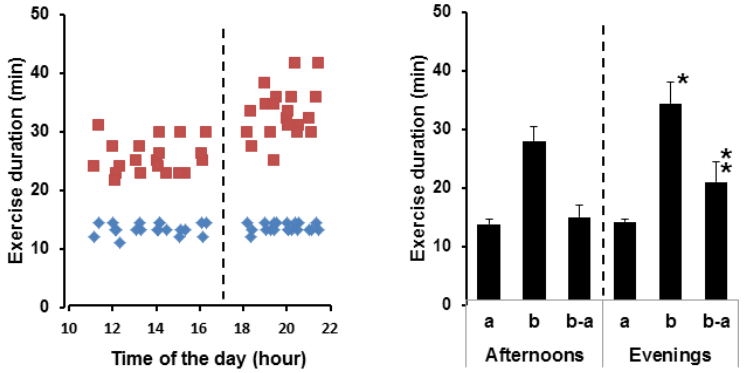


Figure 5. Bivariate plot of times required to achieve 5°C (diamonds) and 10°C (squares) against the times of the day, when training was performed (left). A bar chart of training times grouped into the afternoon and evening sessions (right). Bars indicate times to achieve 5°C (a) and 10°C (b), and duration of the interval between 5°C and 10°C (b-a). *P<0.05.



Discussion

Principal Findings

Here we demonstrated the feasibility of an objective assessment of exercise-induced fatigue and fatigability using innovative technology and protocols. Since the measurable parameters were digitalized, remote management was possible including the online monitoring of training in real-time and automated notifications by email. Together, these suggest a potential value of this approach for the remote management of CR over the Internet.

The method was based on the simultaneous monitoring of HR and LWO by Δ*t*°. While HR is a conventional physiological indicator of exercise intensity [31], it cannot be used on its own to measure the amount of training such as energy expenditure [32]. The Δ*t*° is a unique characteristic pertinent to MedExercise technology allowing for the quantification of exercise intensity and volumes [24,25]. Since a direct correlation between HR and LWO during short training bouts was shown previously [24], the parallel measurement of HR and LWO was used as a standard approach to measure the intensity and amount of exercise, respectively [26].

A main finding of this study is that fatigue can manifest as an inverse correlation between HR and LWO during a sufficiently long and intensive training and can serve as a marker of fatigue development. At steady-state HR, the reduction of Δ*t*° may indicate muscle fatigue, or inability to maintain a constant LWO level otherwise, whereas maintenance of the same LWO requires additional physical efforts from the user. The latter resulted in increasing exercise intensity, as seen by a rise in HR. Therefore, the point of time when either LWO began dropping and/or HR started increasing might be considered as an objective indicator of fatigue setting during continuous exercise training.

This study demonstrates that starting training at moderate HR may not warrant the same level of intensity and performance for the entire duration of a 30-minute bout. It suggests the need for full-duration testing at the intended intensity to ensure fatigue-free exercising and prevent negative effects of fatigue on performance, particularly in untrained participants [9]. For example, in order to ensure sustainability of MICT, the doses should be based on fatigue-free performances for the entire 30-minute duration of the exercise bout [3,4]. However, long durations might not be feasible with the current methods of fitness testing, because they are based on the measurement of HR and/or VO_2 upon incremental (graded) increases of exercise

intensity by adjusting cycle ergometer resistance, speed of treadmill belt, or pace of over ground walking [33].

In contrast to the conventional fitness testing approach where HR is a measurable variable, we measured LWO at the desirable HR, thereby removing the limitation of fitness test duration and allowing for the selection of personalized fatigue-free MICT regimens. Further, low-sensitivity recordings enabled expression of personalized daily MICT doses as single numbers. Duration of taking the same MICT dose on different days indicated relative levels of fatigability and hence could be used for the objective assessment of fatigability in health care settings. An advantage of digital dosage is the capacity for the automated notification of dose “taking” and monitoring of compliance in the network of participants remotely, which might be useful in reducing the costs of CR services [2].

Limitations

The limitations of this study include a small sample size, a relatively short duration of intervention, and participation of healthy volunteers. Such limitations might be expected for the study focused on the development of application protocols using new CR technology. Therefore, this study should be considered as a validation study for innovative methods of measuring exercise performance and associated fatigue. Further research is warranted to establish the feasibility of this approach in larger cohorts of participants, including patients with chronic diseases and other medical conditions preventable and treatable by regular exercise training.

Conclusion

This study showed a new approach of assessing exercise-induced fatigue by monitoring the user's work output. Since it is based on easy measurable parameters ($\Delta t°$ and HR), it can be applied as an additive or possibly alternative method to the subjective rating of perceived exertion and VO_2-based fitness testing. The demonstrated feasibility of personalized exercise dosage and monitoring of compliance at distance may facilitate the delivery of exercise interventions in general and special populations.

Acknowledgments

A part of this study was presented at the Be Active Conference, Sports Medicine Australia (15-18 October 2014), Canberra, Australia.

Conflicts of Interest

Dr Vadim Dedov has a stake in MDXD Pty Ltd, which designed and produced the training equipment used in this study.

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Abbreviations

BPM: beats per minute
CR: cardiac rehabilitation
HR: heart rate

HRmax: maximal heart rate
LWO: leg work output
MICT: moderate-intensity continuous training
RPE: perceived exertion
VO2: oxygen uptake
VO2max: maximal oxygen uptake

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Original Paper

Evaluation of the Digital Alzheimer Center: Testing Usability and Usefulness of an Online Portal for Patients with Dementia and Their Carers

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Abstract

Background: Dementia is a progressive and highly disabling neurodegenerative disease that will likely become highly prevalent in the future due to the globally aging population. To improve health care efficiency and quality for dementia care, eHealth could help with, for example, an online portal, such as the Digital Alzheimer Center (DAC) of the Vrije Universiteit Medical Center Amsterdam. It provides up-to-date disease information, peer-to-peer contact, and methods for contacting the hospital and health professionals.

Objective: We aimed to investigate the usability and usefulness of the DAC for patients with dementia and carers to get insight into the feasibility and value of this eHealth app in dementia care and to recommend potential improvements.

Methods: A descriptive study among patients, carers, and health care professionals was performed. Mixed methods were used, consisting of observations (n=10, 4 people with dementia, 6 carers), an online survey (n=287; 88 patients, 199 carers), and semistructured interviews (n=18; 6 patients, 6 carers, 6 health care professionals). During the observations, participants performed a set of five different prescribed tasks on the portal. Speed, number of errors, and navigation were noted. The online survey aimed to assess users' opinions on the portal's usability and usefulness. Semistructured interviews were conducted in a subsample of patients, carers, and health care professionals to gain more in-depth information.

Results: In the usability assessment, eight categories of errors were distinguished, of which three were of critical, two of medium, and three of low severity. In the survey, 45% (40/88) of the patients and 53% (105/199) of the carers indicated they used the portal. In all, 33% (12/36) of patients and 61% (62/102) of carers found it easy to learn to work with the portal. Most considered the DAC generally useful: 65% (17/26) of patients and 78% (67/86) of carers found the DAC useful, especially for understanding dementia (patients: 64%, 16/25; carers: 62%, 53/86). In the semistructured interviews, the site was generally rated positively on usability and usefulness and being well designed. People with dementia and carers indicated it helped them to understand and deal with dementia.

Conclusions: To our knowledge, this is the first study investigating the usability and usefulness of an Internet portal especially designed for people with dementia and their carers. An online patient portal could be a useful means to help to support patients and carers in dealing with dementia: the majority of users positively evaluated usability and usefulness of the portal, and appreciated the information on it. However, only a minority of patients found it easy to work with the portal. Good design and frequent usability testing is essential to offer a good online portal.

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KEYWORDS

dementia; Alzheimer disease; patient portal; electronic health record; eHealth

Introduction

Dementia

Neurodegenerative diseases leading to dementia are highly disabling; they are characterized by cognitive decline, gradual loss of daily functioning, and eventually lead to complete dependency on others. Because age is the major risk factor for dementia, the global aging of the population will increase the prevalence of dementia worldwide in the coming years. Additionally, this aging population will lead to a decrease in the available workforce, including professional dementia carers. This will pose a great burden on the care system and on carers. It will also have great economic consequences: in approximately 25 years, dementia is projected to become the disease with the largest economic burden. Worldwide, the economic cost of dementia is estimated to be more than US $600 billion and increasing every year [1]. Therefore, novel solutions to efficiently provide dementia care are urgently needed. In addition to reducing costs, these tools should also improve the quality of life of those with dementia and their carers. One promising tool to deliver efficient care in the future is eHealth: “health services and information delivered or enhanced through the Internet and related technologies” [2].

Limited research into eHealth solutions for people with dementia has been carried out, but initial findings suggest certain applications can help to reduce the limitations that are encountered in daily life [3,4]: it can deliver information and coaching [5,6], it can allow remote consultation [7-14], and its use increases work satisfaction of care staff and improves care relations [15,16]. Additionally, communication tools can promote social contact and GPS- or sensor-based tracking can help to enhance feelings of safety by means of tracking and tracing systems, for example, that can help people with dementia when lost outside of the home [3,17-20].

A promising and increasingly used eHealth solution [21] is an online patient portal: a secure website for patients that offers access to a variety of functions, including secure messaging and protected health information [22]. Portals can offer more personalized health information and social contact. In a 2014 review, Otte-Trojel et al [23] studied 32 papers evaluating patient portals and concluded that these portals can lead to improvements in clinical outcomes, patient behavior, and patient experiences.

Background

Patient portals are being used for several different (chronic) conditions to offer different services, usually as part of electronic health record (EHR) services. One example is the American MyHealth portal, which uses patient data to generate a personalized health record in which patients can view detailed information about their disease. However, these portals are usually limited in functionality (eg, only offering contact with physicians or only offering access to the health record) and are aimed at the general population of the hospital. They are not optimized for specific patient groups, who may have different needs and wishes. Other portals exist separately from patient records and are often managed by external nonprofit (eg, patient federations) or commercial companies. One example is the patient portal for Dutch cancer patients, kanker.nl, which has more than 15,000 monthly users and is offered by the Dutch Cancer Society. Additionally, there are portals that focus on one specific aspect of support, such as offering information or education (eg, the Skills Training & Re-skilling [STAR] portal for informal and professional carers of people with dementia [24], which offers online e-learning modules), or offer only communication tools, such as the online patient portal nextmd.com offered by Nextgen Healthcare, which only offers contact between patients and their physicians. These are generally offered at a cost, either paid for by health insurance or by the user.

A literature review identified 176 studies that mention portals for viewing EHR data remotely [25]. Although most of these studies were reported to be of low quality, the authors did conclude that users appreciate the added convenience (ie, easy access to information) a patient portal offers. Another review identified 120 articles on patient portals [26]. They found highly variable outcomes: some studies indicated that patients felt that their physicians responded more promptly to their questions than through other means, yet other studies found that users felt an increased workload because of the online portal. However, none of these portals are intended or designed for people with dementia and focus mostly on other chronic diseases, such as diabetes or cancer.

We recently developed an online patient portal, the Digital Alzheimer Center (DAC): the first patient portal on dementia care in the Netherlands. The aim of this portal is to offer comprehensive information on dementia, to enhance social activities, support peer-to-peer contact, and to provide easy access to communicate with health care professionals. A reference group of patients and carers was continuously involved by giving feedback on design and content during periodic focus meetings and usability testing. The DAC was launched in 2012 and has issued more than 1000 accounts since then.

In this study, we aimed to investigate how patients with dementia and their carers value the DAC. We studied this by evaluating two important properties of eHealth and other care innovations that are important for them to succeed: usability and usefulness. *Usability* is defined by the International Standards Organization as “the effectiveness, efficiency, and satisfaction with which specified users can achieve goals in particular environments.” *Usefulness* determines to what extent users judge a website or application to fulfill specific needs.

By evaluating the usability and usefulness this study aimed to provide data on the feasibility and added value of a patient portal in dementia care which can contribute to the existing knowledge on the feasibility and added value of patient portals in dementia care.

Methods

Design

To evaluate the usability and usefulness of the DAC, a descriptive, exploratory study was carried out among patients, carers, and health care professionals in which mixed methods were used: observations of patients and carers while they perform prescribed tasks on the DAC; an online survey among patients and carers; and semistructured interviews with patients, carers, and health care professionals.

Ethics and Informed Consent

This study was approved by the medical ethical committee of the Vrije Universiteit (VU) Medical Center in Amsterdam. For both the observations and interviews, participants received verbal information (by phone) as well as written information (an information letter), after which they were invited to sign a consent form if they were willing to take part in the research. Participants who opened the online survey first were presented with a screen with information about the research after which they could choose to stop or continue with the survey. They could quit the survey at any time without providing a reason.

Setting and Participant Selection

All participants in the study were clients (patients and carers) and health care professionals of the Alzheimer Center of the VU University Medical Center. The Alzheimer Center is a memory clinic in an academic hospital with a main focus on diagnosing early-onset dementia (dementia with an onset age earlier than 65 years).

Inclusion criteria varied per method. For observations, participants (patients or carers) needed to have participated in at least one DAC workshop (informal workshops organized in the Alzheimer Center, during which participants learn to use the DAC) to ensure that the observed participants had at least some degree of experience with the DAC. This was decided because, for a first exploratory research into the usability of the website, a fully blind "hallway testing" (in which users have never used the site at all) was not warranted yet. Additionally, they had to be physically able to use a computer. Participants were randomly selected from a list of workshop participants of the past four workshops. For the interviews, patients and carers were randomly selected from the list of workshop participants; all professionals that worked with the DAC were approached. An invitation to participate in the survey was sent out to all users registered with an account.

To recruit patients and carers for the observations during prescribed tasks, 10 persons were randomly selected and contacted by a researcher (BH) and asked if they wanted to take part in a usability study on the DAC. For the semistructured interviews, six patients with dementia, six carers, and six professionals participated. Of all 287 users (patients and carers) that started the survey, 40 patients and 105 carers indicated they used the DAC. Of these, 25 patients (63%) and 85 carers (81%) completed the entire survey. Incomplete surveys were also part of the analysis. For an overview of participant flow through the questionnaire, refer to the flowchart in Multimedia Appendix 1. In Table 1, the characteristics of the study participants in each part of the study are presented.

Overview of the Digital Alzheimer Center

The DAC offers a comprehensive menu containing information on diseases, an overview of appointments and dossiers, community sections, and information on upcoming events and news. The information is written in an accessible fashion and illustrated with animations to clarify pathological processes. Patients and carers can find practical tips on living with the changes that are caused by the disease, financial and legal matters, how to avoid carer stress, and much more. In a specially secured section, patients can email their health care professionals at the Alzheimer Center and view their appointments and medical correspondence. A community hosts a forum for questions and exchanging experiences (eg, a photo and video gallery) and information among patients, carers, and health care professionals. In this forum, users can submit messages on several different subjects (eg, "how to tell family and friends" or "practical tips") and they can reply to one another's messages. With the "friends" functionality, users can find others in their area with the same diagnosis and can communicate by a private messaging service. The community section also posts upcoming events and other news from the Alzheimer Center and the national and international Alzheimer community are shared.

Detailed in images subsequently is a walkthrough of the DAC in screenshots. The first page, which all users visit after logging in, is a welcome page (Figure 1) where users are presented with an overview of the main functionalities of the DAC. Clicking on one of the options leads further into the website. For example, if they choose "community," participants are presented with the different functionalities within this section (Figure 2). Within the community, participants can select "forum" (Figure 3) to display all content. Within the "forum" function, participants can select different themes to discuss with others (Figure 3). The DAC can be accessed from anywhere through its URL [27].

Table 1. Characteristics of study population.

Characteristic	Observations during prescribed tasks (n=10)	Online survey (n=287)	Semistructured interviews (n=18)
Age (years), median (range)			
Patient	66.5 (60-79) (n=4)	67 (44-82) (n=88)	71 (61-78) (n=6)
Carer	72 (58-78) (n=6)	63 (36-82) (n=199)	70 (59-79) (n=6)
Professional	—	—	44 (29-58) (n=6)
Patient gender, n (%)			
Male	3 (75)	44[a] (50.0)	5 (83)
Female	1 (25)	35[a](39.8)	1 (17)
Missing	—	9[a](10.2)	—
Carer gender, n (%)			
Male	3 (50)	41[a] (20.6)	0 (0)
Female	3 (50)	80[a](40.2)	6 (100)
Missing	—	78[a](39.2)	—
Diagnosis patients, [b] n (%)			
Alzheimer disease	2 (50)	109 (54.1)	3 (50)
FTD	1 (25)	18 (8.9)	
DLB		17 (8.5)	
MCI	1 (25)	5 (2.6)	1 (17)
Other		52 (25.9)	2 (33)
Patient experience with using computers, n (%)			
None	1 (25)	3 (3.4)	1 (17)
Little	2 (50)	11 (12.5)	3 (50)
Average	0	34 (38.6)	—
High	1 (25)	39 (44.4)	2 (33)
Very high	0	1 (1.1)	0
Carer experience with using computers, n (%)			
None	1 (17)	3 (1.5)	1 (17)
Little	3 (50)	15 (7.5)	3 (50)
Average	2 (33)	82 (41.2)	2 (33)
High	0	78 (39.2)	0
Very high	0	21 (10.6)	0

[a]Due to an error, gender was not inventoried in the first questionnaire; therefore, these data were collected with a short follow-up questionnaire. Unfortunately, not all participants replied to this questionnaire, which explains the high number of missing values.

[b]DLB: dementia with Lewy bodies; FTD: frontotemporal dementia; MCI: mild cognitive impairment.

Figure 1. Main (welcome) page of the DAC.

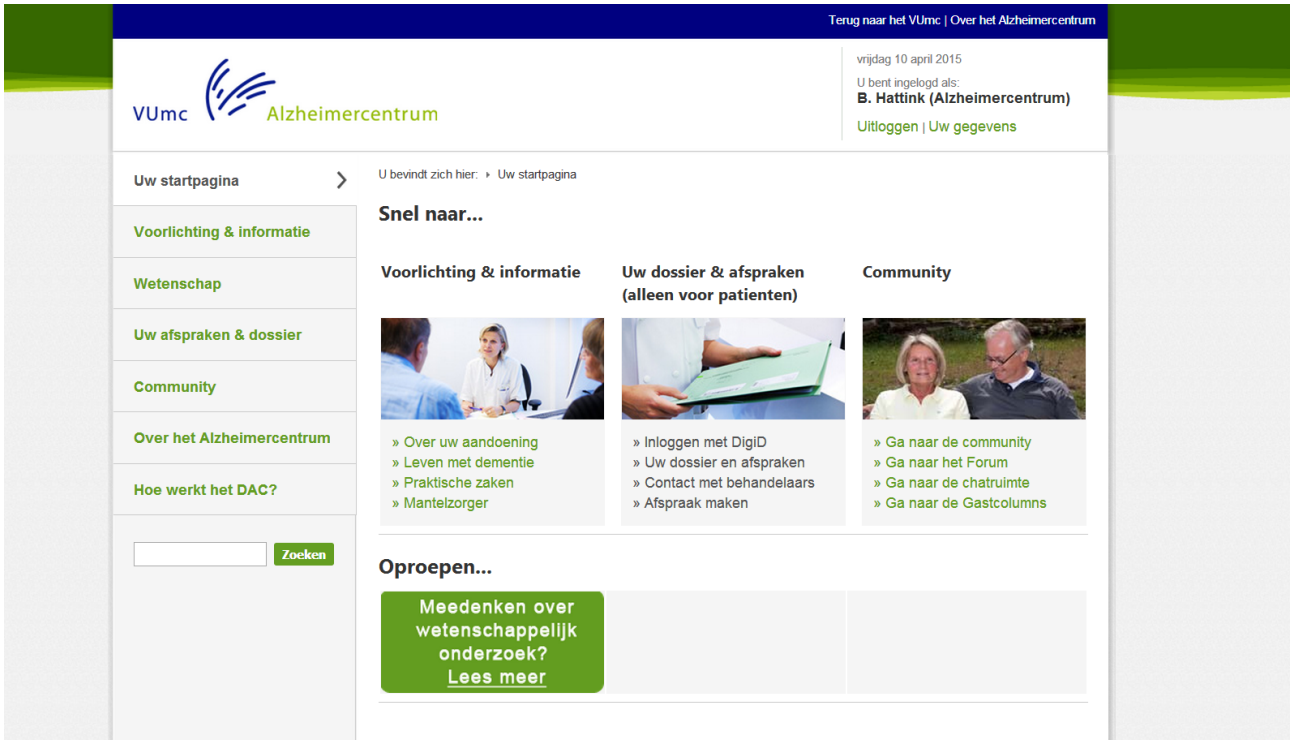


Figure 2. The "community" section.

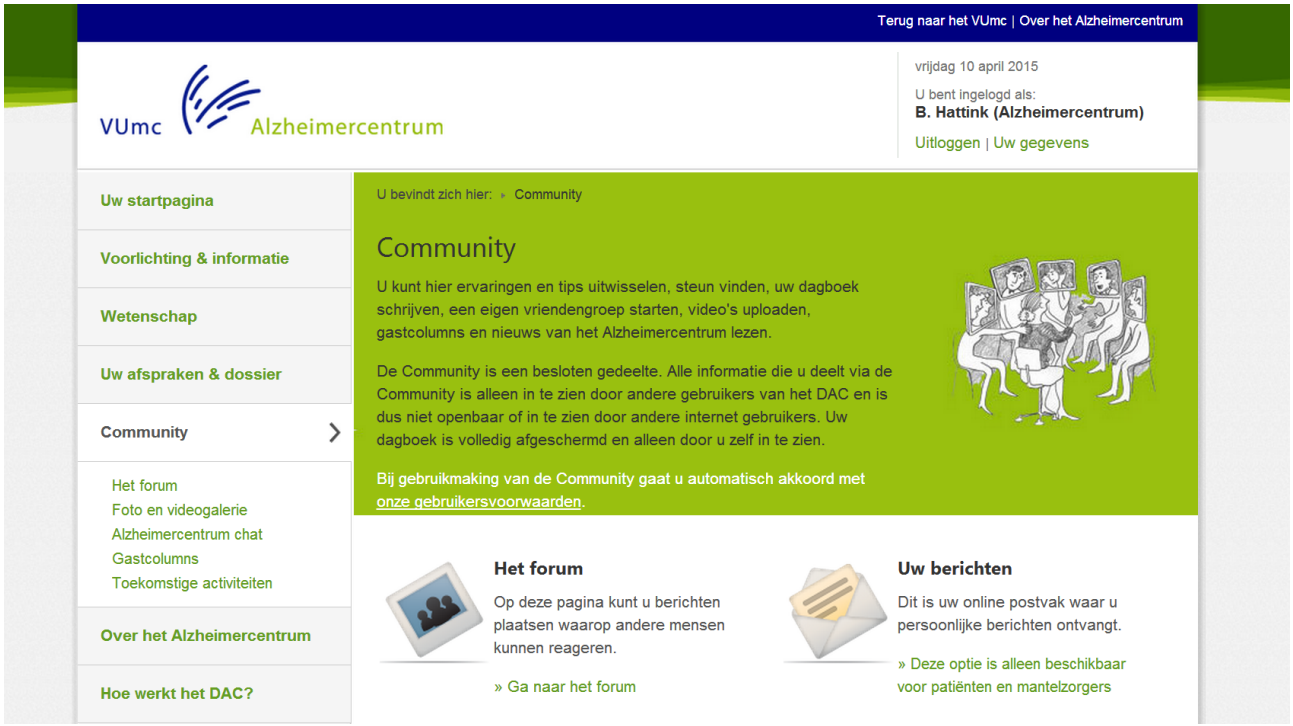
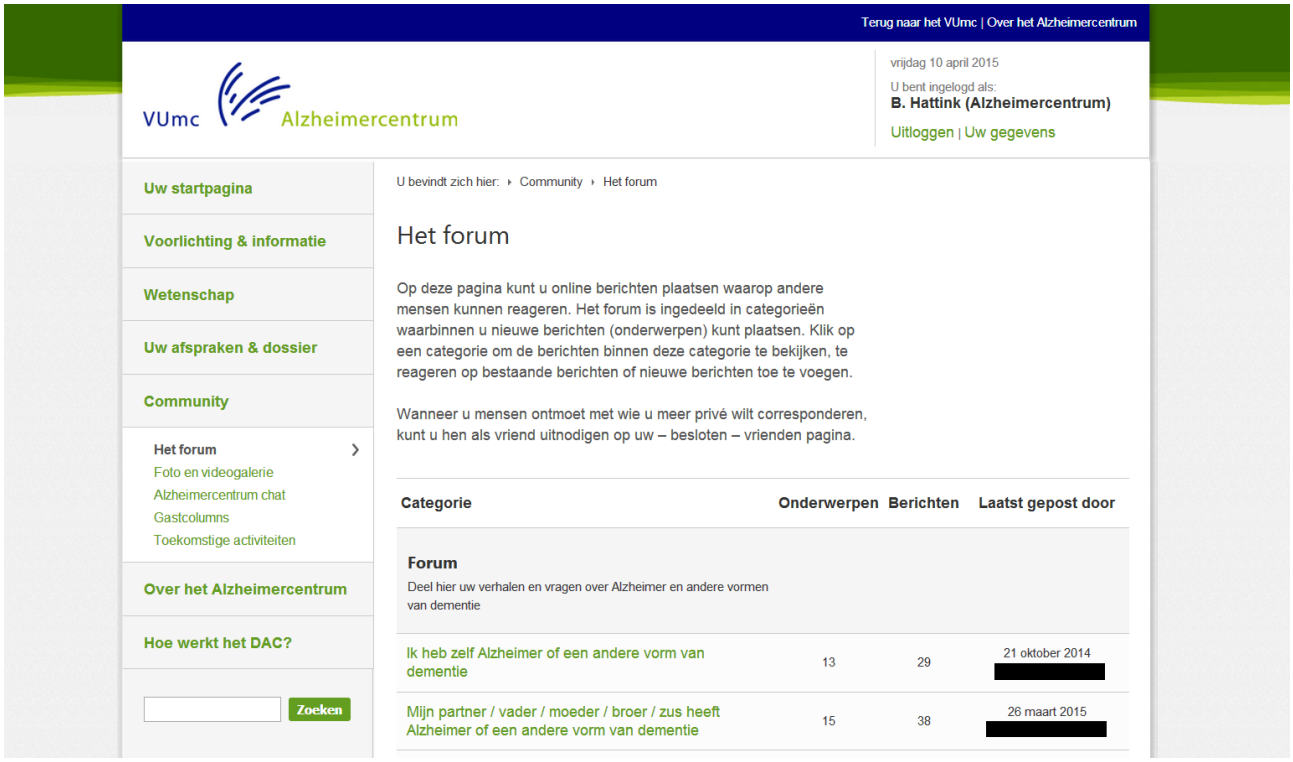


Figure 3. The "forum" functionality.



Evaluation Methods

The DAC was evaluated using mixed methods (ie, observations, an anonymous online survey, and semistructured interviews). This evaluation focused on two main outcomes: usability and usefulness.

Observations

To assess the usability of the DAC, participants (N=10) were observed while completing a number of predefined tasks on their own computers in their own homes. Several quantifiable measures were recorded during testing. These measures were derived from earlier reports on usability research [28-32]:

1. The type of errors participants made before reaching the end-goal, where “error” was defined by any interaction with the site that did not lead to reaching the goal;

2. The number of errors; and

3. Time on task, the time it took participants to accomplish each task.

The tasks participants were requested to complete involved tasks representative of all functionalities of the site: (1) log in to the DAC, (2) post a message on the forum, (3) find information on driving with dementia, (4) watch a video about Alzheimer disease, and (5) view correspondence with the hospital.

The types of errors noted were errors related to issues with operating hardware, such as the mouse; with operating software, such as the Internet browser; related to navigation of the website; to general understanding of the computer; or other issues that came up. Errors were categorized as low, medium, or critical in severity. For determining severity, the Severity Rating for Usability Problems by Nielsen was used [28]. To determine severity, the number of times “yes” was answered to the following questions was counted and one point was added, making a score of 1 to 4 possible:

1. Does the problem occur frequently or in a critical task?

2. Is the problem difficult to overcome?

3. Is the problem persistent?

Critical errors (score 4) are errors that disrupt website usage enough to prevent actual site usage. Serious errors (score 3) disrupt use and can be frustrating enough to stop users using the site or force them to find workarounds for problems. Medium (score 2) and low (score 1) errors can be bothersome to most users, yet are not likely to directly influence site usage.

Online Survey

The online survey contained multiple-choice questions with 4- or 5-point answer scales, regarding background characteristics, such as actual use (eg, “Does one use the DAC?”), and questions on usability and usefulness . Usability was divided into three sections: attractiveness (eg, “How do you appreciate the layout of the DAC?”), ease of use (eg, “How easy is it to find the information you need?”), and appreciation of the content (eg, “How understandable are the texts?”). Questions on usefulness concerned the experienced “value” (eg, “Does the DAC help in understanding dementia?”) and “added value” (eg, “Does the DAC offer added value over usual care?”). All questions on the survey are available in Multimedia Appendix 2. This online survey was created in Qualtrics (Qualtrics, Provo, UT, USA). The survey was accessible online for 1 month and contained 82 questions. Several questions were branched and were not shown to all participants (eg, only participants that indicated they did not like the font used on the site were shown the question “What do you dislike about the font?”).

Semistructured Interviews

The interviews contained both structured questions and open-ended questions on usability and usefulness of the DAC. The interviews were constructed specifically for this study, using a format of semistructured interviews based on standardized questionnaires, such as the System Usability Scale (SUS) and the User Satisfaction and Ease of use (USE) questionnaires previously developed for evaluation of other technical innovations [18,33] focusing on usability and usefulness. Usability was assessed on two domains: ease of using the site (eg, being able to use the site independently, finding it easy to find information) and attractiveness of the site (eg, appreciation of the layout, colors, font, and images). Two main questions were used to assess the usefulness: added value and areas in which people feel the DAC specifically helps. These questions were either structured with room for comments (eg, "Does the DAC save time?" with options "yes, it saves time; neutral; no, it costs more time") or open-ended (eg, "What could, in your opinion, be done to make the DAC look more attractive?"). On average, these interviews lasted 21 minutes.

Procedure

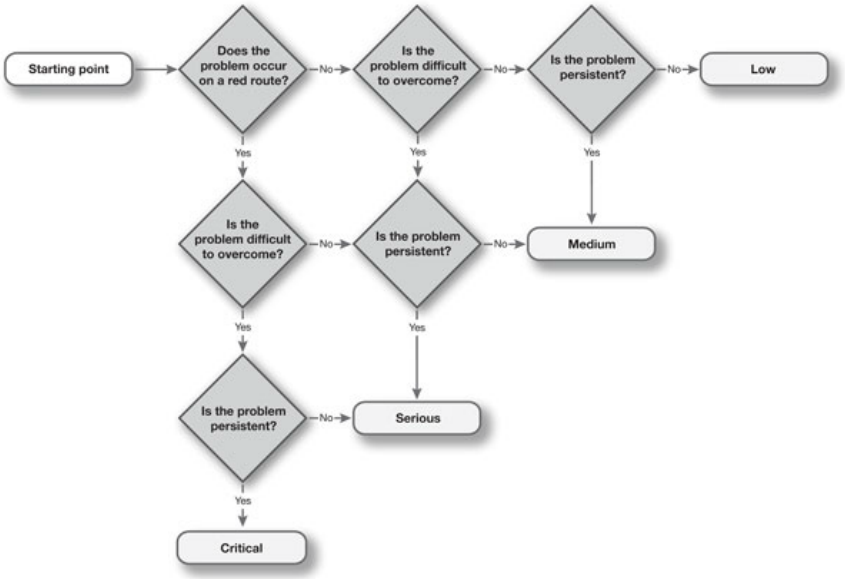
If potential participants consented after initial contact, a researcher (BH) visited them in their own homes, explained the research, and then invited the participants to conduct the prescribed tasks on their own computer, except for two patients who were approached during a workshop and participated directly on a university workstation. A link to the online survey, along with a short explanation of the survey, was included in the monthly DAC newsletter, inviting participants to participate. Patients and carers who participated in the semistructured interviews were recruited among visitors of DAC workshops; professionals were asked to participate via email. Patients and carers were visited in their own homes for the interview by the researcher (BH); professionals were interviewed at their workplace by the researcher (BH).

Analyses

The demographics of the participants in the different study parts and survey data were analyzed with descriptive statistics. Time on task and number of errors made during performing observation tasks were noted. The differences between groups (patients and carers) were analyzed using Mann-Whitney *U* tests ($P<.05$). Errors that occurred were first clustered in themes and subsequently analyzed by assessing the severity of the error. Every newly occurring error was categorized as a new error theme. We kept track of how many other participants made the same error. Subsequently, errors were categorized in the four possible levels of severity: critical, serious, medium, and low (see Figure 4). The online survey data were analyzed per group with descriptive statistics. Differences between the groups were analyzed using the Mann-Whitney *U* test for independent samples ($P<.05$).

Results from the semistructured interviews were analyzed with thematic analysis [19,34]. This was performed both quantitatively by noting the number and the percentage of participants who answered a certain response on structured questions and qualitatively by thematically analyzing answers to open questions or additional comments (eg, by looking for recurring themes in the answers). Some explanatory quotes from participants, representative of the themes we found, were selected to explain the results of the survey.

Figure 4. Nielsen's severity rating for errors.



Results

Usability: Prescribed Tasks (Observations)

Time on task of each prescribed task was measured from start to completion. In Table 2, the time on task and the number of errors are presented. A distinction was made between patients and carers. Table 3 shows the different themes of the errors that were made by patients and carers while performing the prescribed tasks and the results of the severity analysis.

Table 2. Time on task and number of errors for patients and carers and results of the Mann-Whitney *U* tests.

Task	Time on task (mins), median (range)				Number of errors, median (range)			
	Patients (n=4)	Carer (n=6)	*U*	*P*	Patients (n=4)	Carers (n=6)	*U*	*P*
1. Log in to the DAC	7.5 (0-11)	2.5 (3-10)	9.0	.61	1 (0-5)	2 (0-5)	9.0	.61
2. Post on the forum	10.5 (2-18)	5.5 (2-18)	12.0	>.99	0 (0-5)	0 (0-3)	7.0	.35
3. Find information on driving	8.5 (2-18)	3 (0-17)	11.5	.91	1 (0-7)	4 (0-2)	6.0	.26
4. Watch a video on Alzheimer disease	5 (1-10)	5.5 (1-9)	8.0	.48	0 (0-19)	12 (1-9)	6.0	.26
5. View correspondence	4 (3-10)	3 (3-4)	1.5	.57	0 (0-22)	0.5 (1-1)	5.5	.38

Table 3. Thematic overview and severity of errors made by patients with dementia (n=4) and carers (n=6), coded for severity.

Theme of error	Severity
Unable to log in to DAC	High
Entering wrong URL / not finding right page	High
Visiting sites external of DAC	High
Reading the sidebar as part of the other text	Medium
Following wrong links (that do not lead to required data)	Medium
Unnecessary clicking	Low
Unnecessary use of the “back” button	Low
Clicking nonlinks	Low

The biggest difference in time to completion was found, both for patients and carers, within task 2 (post a message to the forum), for which there was a 16-minute difference between the slowest and fastest performance. However, this task had a low variance in errors, with a minimum of zero and a maximum of five errors. The greatest variance in number of errors as well as the greatest difference in performance between patients and carers was found in task 5 (view correspondence with the Alzheimer Center), where the best performing participant did not make errors at all and the participant who had the most difficulty with the task (a person with dementia) made 22 errors before arriving at the right solution.

Patients and carers differed in the number of errors made in three of the five tasks: post a message on the forum, finding information on driving, and watching a video on Alzheimer disease. The tasks appeared more difficult for patients because they made more errors and took longer to complete the tasks. However, from the Mann-Whitney *U* tests, these differences between patients and carers did not appear to be statistically significant.

Both patients and carers made the same categories of errors (refer to Table 3), except for not understanding the sidebar, which only occurred in patients with dementia. All problem themes observed were analyzed by using the severity framework of Nielsen [28].

Usability: Survey and Semistructured Interviews

Layout

The results of the survey show that the design of the site was appreciated by a small majority: 19 of 36 (53%) patients and 60 of 98 (61%) carers indicated that the layout was clear. They appreciated that it “looks very calm, there’s no clutter [distracting elements] on the screen” (indicated by a carer). The font used in the design of the website was appreciated positively: only 2 of 98 (2%) carers did not like the font.

Content

The content of the DAC was rated understandable and clearly written by both carers (79/96, 82%) and patients (27/35, 77%) in the survey. The information was regarded “very well and comprehensively written” by all interviewed participants.

Ease of Use

Survey participants valued the site mostly positively with regard to ease of use (general use and navigation). In all, 50.0% of carers (52/104) found it easy to use, 36.5% (38/104) were neutral on this subject, and 13.4% (14/104) found the site difficult to use. For patients, 42% (15/36) rated the site as easy to use, 50% as neutral (18/36), and 8% (3/36) as hard to use. All but one patient of those interviewed thought that they would be able to learn to use the site.

Usefulness

Added Value

Overall, 17 of 26 (65%) patients and 67 of 86 (78%) carers indicated in the survey that the DAC was “very useful” or “useful” and both indicated it had an added value over the regular care offered by the center. Interviewed participants specified that it was “very helpful—it really helps me in staying at home by myself” and that it “should certainly be continued in the future.” One professional commented that it was “not yet useful enough,” although they later indicated that they expected

this would change by "adding more personalization [options]." A majority of users, 17 of 26 (65%) patients and 57 of 86 (66%) carers, would recommend the DAC to others: "It is certainly something you need in this day and age."

Understanding of and Dealing with Dementia

Participants indicated that the DAC was especially useful to them for understanding dementia and for dealing with dementia. In all, 53 of 86 (62%) carers and 16 of 25 (64%) patients who responded to this question indicated it was helpful for understanding dementia: "you can find all the information you might need" and "you can easily show this information to others."' In addition, 40 of 86 (47%) carers and 11 of 25 (44%) patients found the DAC useful for dealing with dementia. The availability of the information was appreciated: "you can check this information anytime, even in the middle of the night."

Usage

In the survey, 145 of the total 282 (51.4%) participants indicated that they had used the DAC at least twice. Of these 145 users, 40 (27.5%) were patients and 105 (72.4%) were carers. Participants in the semistructured interviews also indicated they regularly used the DAC; all but two indicated they did not use it. One interviewed patient specifically stated that he used the DAC "several times a week."

In Table 4, survey data are presented on the use of features of the DAC. It shows that both patients and carers make (more or less) use of all different parts of the site. Most used by patients are the information on the disease and the Alzheimer Center function. Most used by carers is information on the Alzheimer Center and information for carers.

Table 4. Use of functions: numbers (and percentages) of patients and carers that used a specific function.

Function	Patients, n (%) (n=25)	Carers, n (%) (n=85)
Information		
Disease	12 (48)	14 (16)
Informal carers	1 (4)	20 (24)
About center	10 (40)	44 (52)
Community		
Forum	7 (28)	13 (15)
Friends	4 (16)	3 (3)
Chat	3 (12)	2 (2)
Contact		
E-consult	6 (24)	17 (20)
Correspondence	2 (8)	9 (11)

Non-users

When participants indicated in the survey that they did not use the DAC, they were asked why they did not use it. Their answers were grouped into themes. The main reasons they indicated for not using the DAC are presented in Table 5.

Table 5. Reasons for not using the DAC.

Reason	Carer	Patients
1	No need (n=31)	Miscellaneous (eg, "I don't want anything to do with it") (n=12)
2	Technical or computer issues (n=23)	No need (n=9)
3	Miscellaneous (eg, "I don't like the Internet") (n=18)	Unfamiliar with DAC (n=8)
4	No time (n=13)	Too hard to use (n=7)
5	Unfamiliar with DAC (n=8)	No time (n=4)
6	—	Technical or computer issues (n=4)

Discussion

We found that, in general, patients with dementia, carers, and health care professionals who use the patient portal rate it positively with regard to usability, and consider it to be a useful addition to existing care that helps them to deal with dementia, among other things. Results for this study show that an Internet portal is a feasible means of offering support to people with dementia and carers. Both patients and carers indicate they appreciate such a portal positively. Although some had trouble in using the site or in learning to operate it, only a small percentage of users responded negatively to the patient portal as a means of offering support. The information sections especially appear to be well used and are indicated to be experienced as supportive.

Nonetheless, we did also find some usability issues. The most notable issues are those functionalities for which severe errors were found during usability testing: the log-in screen, the process of finding the right URL, and the confusion of leaving the DAC for a different linked site. A positive note is that these are all areas related to reaching and accessing the site, and have nothing to do with the actual (functioning of the) site itself. We did find that patients with dementia and carers largely make the same kinds of mistakes, which means this is likely to be related to familiarity with using computers and websites.

Findings from this study are in line with previous research in this area [4,17,35-41]. We found that older users and users with dementia are able and willing to utilize Internet-based resources and that at least some of them are capable of using the technology involved. Research by Ellis and Kurniawan [35] showed that older users consider the Internet a useful tool for finding information and that they were able to access websites on computers with relatively few problems. Research into website usability among people with dementia found that they prefer websites that have little cognitive load (ie, "the amount of mental processing power needed to use the site" [36]) and that minimize the amount of clutter [35] and other distractions on the screen, such as on-screen animations and advertisements [37]. Besides making sites harder to use, earlier research states that cognitive load and clutter may cause "knock-off effects," causing people to require so much cognitive effort for processing site usage that they cannot effectively process or engage with the material on the site [4,38]. The current research confirms these findings. In the observations, we found that users occasionally had trouble finding the correct links and, in the interviews, users mentioned that they appreciated how few distracting elements there were.

Additionally, decreased motor skills and slower movements that occur in older age could affect the use of scroll bars or links and buttons [38]. This was found in website use as well as in usability studies of other technology such as mobile phones [39]; when observing the difference in usability of mobile phones between older and younger users, it was found that older users could use mobile phones but had significantly more difficulty with more complex mobile phones [39].

Research by Chadwick-Dias et al [40] tested several enhancements to a website to make it more usable and found that clearer wording of links, more consistent visual identification of links, and the use of simpler terminology significantly improved performance on a website. These findings concur with the findings of our research: our users had some trouble identifying links. The simple and understandable language used on the DAC was appreciated by the participants. When research participants were offered two different versions of a website with the same information but with different layouts (one complex with lots of information on screen, one simple version with little information displayed at once), participants made fewer errors on the website with less complex screens [36,41]. Participants also rated the less complex site as more attractive and better to use [36].

This study highlights the importance of iterative development, in which user needs are assessed at the start, and the target audience participates throughout the process [19]. Design choices such as clear font, calm backgrounds, and contrasting colors are important to ensure optimal usability. These design considerations were all applied in development of the DAC and the majority of users evaluated these aspects positively or very positively. This is in line with earlier research into typography for websites [42,43]: when learning to work with computers, a 12- to 14 point sans serif typeface is best appreciated by older users and improves their reading performance on the screen. They also found that it is important to use contrasting colors (preferably black text on a white background) to ensure readability.

Based on findings from our study and on earlier research, we made several practical suggestions for good website design, which can be useful for others intending to design an online portal for people with dementia and their carers. It is recommended to resolve usability issues as soon as possible. For example, problems with finding the URL could be alleviated by adding redirects on more URLs (eg, variations and typos of the current URL www.digitaalalzheimercentrum.nl). Problems with leaving the site for another site could be solved, for example, by a warning page that lets users know they are about to leave the DAC and will be presented with another site with a different layout than the DAC. The different layouts of other sites, which are generally not specifically designed for older users or users with dementia, make them very confusing. Another critically severe error found during the observations was that participants had trouble logging in to the DAC. Because this is a very critical step—it being the first contact with the portal—it is highly relevant to find ways to fix this (eg, by allowing log-in information to be saved or by considering other means of logging in).

We did not find any indication of harmful effects of the website. Some participants indicated that they did not use the DAC because they did not want to be confronted with all the information about their prognosis (several of the nonusers presented in Table 5 mentioned this when they indicated "no need" as reason for nonuse). However, because use of the DAC is voluntary and not required for any services at the Alzheimer Center, there is no need for them to be confronted with this.

Limitations of the Study

The survey was sent out to all patients registered with an account for the DAC. Even though the response rate was relatively high for online surveys (39%; research generally reports rates from 5% to 40% for online surveys), there is no telling if the group that responded was representative of the population. It is possible that those positive toward the DAC were overrepresented in the group that responded.

To ensure that participants were familiar with the DAC, those taking part in the observations were selected from people who had participated in a workshop in which they learned to use the website. A group of participants that uses the site for the first time without any explanation may encounter different problems. It should be noted, however, that the latter group is not the target group of the current portal: it was specifically intended and designed for people with dementia who were patients of the

Alzheimer Center. They were all invited to join a workshop to learn to use the DAC.

To further elaborate on the outcomes of this study in the future, answers to both the survey and the interviews could be compared and verified using website statistics/flow tools. Because of software limitations in the current version of the DAC, it was not possible to install tools such as these for this study.

Conclusion

Overall, this study shows that usability and usefulness of the researched portal are well appreciated. The use of an online portal seems a feasible option for providing eHealth to patients with dementia and their carers. It shows that (beginning) dementia or older age do not have to be a hindrance to computer or Internet use, although cognitive abilities change with dementia and are likely to affect computer use (eg, working memory, perceptual speed). Good website design can help to deal with these dementia-related changes. Using the correct font, colors, writing style, and navigation layout can make websites easier for people with dementia and their (often-older) carers to access. Designing websites in close collaboration with the target group and usability and usefulness testing within this group warrants optimal design and use of patient portals. Based on findings from our study, and on earlier research, we made several practical suggestions for good website design, which can be useful for others intending to design an online portal for people with dementia and their carers. It is recommended to improve on usability issues as soon as possible. For example, problems with finding the URL could be alleviated by adding redirects on more URLs (eg, accessing websites easier for people with dementia and their [often-older] carers). Because this is a very critical step—it is the first contact with the portal—it is highly relevant to find ways to fix this, such as by allowing log-in information to be saved or by considering other means of logging in. For other practical tips on portal design, please refer to the Textbox 1.

Textbox 1. Practical tips for portal design.

Clearly identify clickable targets. Participants clicked even when not necessary, making it necessary to ensure that they do not click anything by accident to avoid confusion.

Break information into short sections. Long texts were found to be confusing to some participants; they found it hard to "follow the text."

Make use of the "recognize, rather than recall" principle. Users appreciated that they could quickly recognize that the site was part of the Alzheimer Center because it used the "theme" colors.

Minimize complex steps such as logging in. Both the main log-in and the log-in required for further personal file access were considered too complex for users.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Questions of the online survey.

[PDF File (Adobe PDF File), 1MB - resprot_v5i3e144_app1.pdf]

Multimedia Appendix 2

Survey participant flowchart.

[PDF File (Adobe PDF File), 20KB - resprot_v5i3e144_app2.pdf]

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Abbreviations

DAC: Digital Alzheimer Center
EHR: electronic health record
SUS: System Usability Scale
USE: User Satisfaction and Ease of use

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Original Paper

Patient Insights Into the Design of Technology to Support a Strengths-Based Approach to Health Care

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Abstract

Background: An increasing number of research studies in the psychological and biobehavioral sciences support incorporating patients' personal strengths into illness management as a way to empower and activate the patients, thus improving their health and well-being. However, lack of attention to patients' personal strengths is still reported in patient–provider communication. Information technology (IT) has great potential to support strengths-based patient–provider communication and collaboration, but knowledge about the users' requirements and preferences is inadequate.

Objective: This study explored the aspirations and requirements of patients with chronic conditions concerning IT tools that could help increase their awareness of their own personal strengths and resources, and support discussion of these assets in consultations with health care providers.

Methods: We included patients with different chronic conditions (chronic pain, morbid obesity, and chronic obstructive pulmonary disease) and used various participatory research methods to gain insight into the participants' needs, values, and opinions, and the contexts in which they felt strengths-based IT tools could be used.

Results: Participants were positive toward using technology to support them in identifying and discussing their personal strengths in clinical consultation, but also underlined the importance of fitting it to their specific requirements and the right contexts of use. Participants recommended that technology be designed for use in preconsultation settings (eg, at home) and felt that it should support them in both identifying strengths and in finding out new ways how strengths can be used to attain personal health-related goals. Participants advocated use of technology to support advance preparation for consultations and empower them to take a more active role. IT tools were suggested to be potentially useful in specific contexts, including individual or group consultations with health care providers (physician, nurse, specialist, care team) in clinical consultations but also outside health care settings (eg, as a part of a self-management program). Participants' requirements for functionality and design include, among others: providing examples of strengths reported by other patients with chronic conditions, along with an option to extend the list with personal examples; giving an option to briefly summarize health-related history; using intuitive, easy-to-use but also engaging user interface design. Additionally, the findings are exemplified with a description of a low-fidelity paper prototype of a strengths-based tool, developed with participants in this study.

Conclusions: Users requirements for IT support of a strengths-based approach to health care appear feasible. The presented findings reflect patients' values and lists potential contexts where they feel that technology could facilitate meaningful

patient–provider communication that focuses not just on symptoms and problems, but also takes into account patients' strengths and resources. The findings can be used to inform further development of IT tools for use in clinical consultations.

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KEYWORDS

patient strengths; resilience; patient participation; patient-centered care; patient–provider collaboration; user-computer interface; participatory design; chronic disease; patient requirement

Introduction

Life with chronic conditions is often very demanding, and requires patients not only to manage different symptoms, problems, and complex treatments (eg, taking medications, adhering to difficult life style adjustments, dealing with emotional consequences such as fear, frustration, and depression), but also to engage various resources (psychological, social, spiritual) [1]. Research shows that to successfully manage chronic illness, patients require support both to learn about and manage their symptoms and problems, and to activate their resources and find new ways to live the best possible life with a chronic illness [2-5]. However, in clinical consultations, health care providers tend to focus on patients' symptoms, disease diagnoses, and biomedical treatments, without bringing up the topic of patients' strengths and resources that are vital to making the lifestyle changes needed to manage ongoing chronic illness [6,7]. New ways are needed to support patients as active agents in patient–provider collaboration, to help them discuss both their symptoms and issues but also their resources and strengths, empowering them to develop and adopt new personalized and meaningful self-management plans and strategies.

The term "personal strengths" originates from the field of positive psychology, a discipline that emphasizes health and well-being more than dysfunction and problems [8]. Personal strengths have been defined as the characteristics people use to achieve well-being and to flourish, and include attributes such as hope, gratitude, love of learning, honesty, and humor [9]. Various Web-based strengths inventories can be found to help people identify their personal strengths in workplace and academic settings (eg , Values in Action Survey of Character Strengths [10], Strengths Finder 2.0 [11]). The mere act of filling out this type of survey and being aware of one's strengths can be a helpful intervention [12-14]. However, researchers have suggested that providing some type of support and guidance on how to better use one's personal strengths through coaching [15], development programs [11], or counseling [16], for example, is even more beneficial.

Although the concept originated in psychology, studies have also explored the use of personal strengths in chronic illness management. Rotegård and colleagues [7] identified a rich repertoire of internal and external strength qualities that cancer patients mobilized to meet their daily living challenges (eg, good mood, optimism, will power, and trust in health care provider). Similarly, Sturgeon and Zautra [17] show that people with chronic pain use various traits and mechanisms to maintain a good life despite their condition (eg, positive emotions, optimism, purpose in life, pain acceptance, active coping, and social engagement). Research suggests that the use of personal strengths attributes has positive effect on health behaviors and outcomes. For example, positive emotions are related to higher patient activation [18] and increased creativity, problem-solving ability, and openness to new experiences and information [19]; resilience is positively related to developing and implementing adaptive coping strategies among patients with chronic pain [17].

To enable easier identification and mobilization of personal strengths, various projects in the areas of psychology, social work, and mental health care have investigated how personal strengths can be identified and used to promote health and well-being. For example, standardized strengths-based assessment tools (both questionnaires and interview guides) have been developed for children and youth with mental health problems [20,21]. Monsen and colleagues [22] propose using a standardized terminology (Omaha System) to describe the strengths of older adults with chronic illnesses and aid development of a whole-person assessment tool. Additionally, various theoretical and practical instruments and guides have been developed for assessment, mobilization, and development of personal strengths in different patient groups (eg, frail elderly persons [23], psychiatric patients [24], and young adults with disabilities [25]).

Despite these guidelines and related work, patients' personal strengths and resources still often seem to be overlooked in clinical consultations. In a recent study of cancer care, patients reported that clinicians seemed unaware of, did not ask about, discuss, or build on their strengths, which the patients expressed might have helped them become more aware of and better use their potential to improve well-being [7]. A similar finding was outlined by McCammon [26], who concluded that even though strengths-based planning was presented as one of the guiding principles of the care system for children and youth with emotional challenges, and the care teams often require child and family to list their strengths, the care plans frequently neglect to incorporate these strengths into strategies and interventions. These obstacles may be partially related to the dominant paradigm of problem-focused care, as well as difficulty in verbalizing one's personal strengths [27]. Furthermore, strengths are highly context-specific [28,29], making standardized instruments less meaningful. Computer tailoring, allowing patients to branch into those areas of strengths that are personally relevant, might be a promising approach to support patients, and care providers in eliciting and using patients' strengths in consultations.

Therefore, in our study we employed participatory methods to explore the requirements and perspectives of patients living with chronic illness on how technology could facilitate bringing the topic of personal strengths and resources into clinical

consultations. This study is part of a larger research project called "Incorporating Patient-Identified Personal Strengths into Patient Care" that explores the use of patients' personal strengths in chronic illness management. The overall goals of the project are to explore how to support patients in identifying and leveraging their personal strengths in health management and how the use of strengths may affect patient activation, motivation for positive change, and patient-centered health care outcomes. The study is done in international collaboration between Case Western University, USA and Oslo University Hospital, Norway, with parallel studies on both sites. In this paper, we describe part of the Norwegian arm of the study, where our main objective was to identify patients' requirements for an information technology (IT) tool that facilitates awareness and communication of personal strengths in consultation settings, as a means to promote more constructive collaboration and development of strengths-based self-management plans and activities. Additionally, in collaboration with patients, we developed a low-fidelity paper prototype of an IT tool that meet their requirements and can fit into different potential contexts of use.

Methods

Study Design

This study uses a rigorous, iterative, qualitative participatory approach to garner the insights and requirements of key end-users of technology to bring patient strengths into health care. The study was conducted between January 2014 and August 2015, and had 3 main phases with the following overall goals:

1. Identify the strengths of people living with chronic illness;

2. Explore patients' requirements on how technology could be used to promote awareness and discussion of patients' strengths in consultation settings and grouping strengths into meaningful categories; and

3. Develop a low-fidelity paper prototype for a strengths-based IT-tool in close collaboration with patients, and verify strength category labels.

The goals and methods used in each phase are presented in Table 1.

Table 1. Overview of the design process, phases' aims and methods used.

	Phase aims	Methods
Phase 1 (N=39)	Identify the strengths of people living with chronic illness	Interviews Focus groups
Phase 2 (N=18)	Explore patients' requirements on how technology could be used to promote awareness and discussion of patients' strengths in consultation settings Explore patients' barriers to using technology Explore possible contexts of use Group strengths into categories that are meaningful to patients	Workshops Card sorting exercise
Phase 3 (N=8)	Develop low-fidelity paper prototypes for a strengths-based IT tool in close collaboration with patients Further explore design and functionality requirements and potential new contexts for use Verify strengths category labels	Low-level prototyping Design scenarios

Participants and Recruitment

Participants were people with chronic obstructive pulmonary disease, chronic pain, or morbid obesity who received care from primary and specialized health care. They were recruited from 4 outpatient rehabilitation or self-management programs in a specialized health care setting. A purposive sampling procedure was used to select information-rich participants of both genders who had lived with one or several chronic illnesses for an extended period of time.

Inclusion criteria were that the person was (1) diagnosed with one or multiple chronic illnesses, (2) more than 18-years old, (3) able to speak and understand Norwegian, and (4) willing to share his/her experiences of living with chronic health challenges. Clinicians from the 4 specialized departments identified potential participants. Those who met inclusion criteria received a letter with information about the study, and the clinicians collected contact information for those patients expressing interest. A researcher (US) then contacted the patient to schedule interviews, focus groups, and workshops. Additionally, a patient representative (TK) was included as a member of the research team with the aim that patients' voices were integrated into all discussions and final decisions.

This study was planned and performed in compliance with the principles outlined in the Declaration of Helsinki [30], and was approved by the Regional Committees for Medical and Health Research Ethics in Norway and by the Privacy Protection Committee at Oslo University Hospital.

Phase 1: Identifying Strengths of People Living With a Chronic Illness

In the first phase of this study, we explored how participants described their strengths on personal and interpersonal levels. We conducted 4 focus groups involving 18 patients, 3 paired interviews, and 15 individual interviews between January 2014 and June 2014. During the interviews and focus groups, participants described their strengths and how they used them in managing their everyday lives with chronic illness. Data were analyzed by 2 members of the research team (US, OBK) using qualitative content analysis [31]. Results from this phase,

including the detailed list of strengths shared by participants, are being published elsewhere.

Phase 2: Identifying Patients' Requirements and Grouping Personal Strengths in Meaningful Categories

This phase involved 5 workshops, with 18 of the same patients who participated in first phase. The workshops were conducted between October 2014 and March 2015.

The first aim was to explore participants' requirements and barriers for using technology to enhance their awareness of personal strengths and resources, and support discussion of these assets in clinical consultation. Workshops and focus groups are often used for generation of ideas and quickly flush out users' impressions about a topic or concept, including their opinions, attitudes, preferences, and initial reactions [32]. We created a set of semistructured questions that addressed the topics of possible contexts of use and facilitators and barriers that might potentially emerge. We used an open-ended question format that allowed participants to state their preferences and raise and discuss issues they regarded as important in the group. Because another prototype of the IT tool for patients with low socioeconomic status had been developed in the meantime as part of the other project arm at Case Western University, we showed it to the participants as part of the last 2 workshops to make discussion more concrete and promote generating more ideas. Participants were asked to share their thoughts about how such tools could be used in their care and consultations and to suggest improvements. Workshop sessions were audio-recorded and transcribed. Sessions were analyzed separately by 2 members of research team (JM, TK) using thematic analysis [33]. Coding discrepancies were discussed until consensus was reached.

The second aim of this phase was to explore how participants would expect the personal strengths to be grouped and labeled. We used a card-sorting exercise, asking participants to group strengths identified in Phase 1 into meaningful categories. Card-sorting is a method that reveals how users expect some content to be organized and provides insights into how they group, sort, and label content [34] . We started the exercise with an explanation of the method, after which participants were presented with a stack of 91 cards in random order, each labeled with one strength item. Participants were then asked to sort the cards into groups that they felt belonged together and afterward label each group. During the first 3 workshops, some of the participants noted that the large number of items made the card-sorting task very demanding. Therefore, for the next workshop we decided to group strength items that were very similar and present them as one card. To do this the research group together went through the list of strength items and decided in consensus which items were conceptually so similar that they could be grouped together. For example, the strength items "I always look at the things from different perspectives and choose the positive one" and "I am an optimist" were grouped and presented on 1 card. As a result, the number of cards was reduced from 91 to 70 (57 with 1 item, 10 with 2 similar items, and 2 with 4 similar items). The new card organization was used in the final 2 workshops.

At the end of the second phase, the research group analyzed the results of the card sorting exercise from all workshops by going through the list of all proposed categories and organizing and grouping them based on their name, meaning, and the strength items they contained. All decisions were discussed in the research group and made by all team members in consensus.

Phase 3: Development of a Low-Fidelity Paper Prototype and Verification of Strengths Category Labels

We used collaborative design workshops and iterative low-fidelity prototyping to identify users' needs regarding the tool's design and features. Low-fidelity prototyping is a technique often used to visualize possible tool interfaces that could serve as the common language to support discussion with participants about more concrete ideas and requirements [35]. The research team, together with programmers and designers at our research center developed the first version of the prototype based on participants' insight and feedback in previous study phases. In addition, a design scenario was created that described one hypothetical situation where the tool might be used. The combination of low-fidelity prototyping and design scenarios enabled us to explore functional and design specifications and further discuss potential contexts of use both in the research group and with participating patients [36].

We organized 5 iterative workshops with 6 participants from previous phases and 1 workshop with 2 new patient representatives. Workshops were conducted between May and August 2015. Participants were first given the printed version of the design scenarios that introduce the tool's context of use. Next, participants were asked to go through the screenshots of the paper prototype, offer feedback and propose changes for both the prototype and the scenario. Each session was audio recorded and participants' feedback was summarized separately by 2 members of the research team using thematic analysis (JM, TK) [33]. The results were then merged to achieve concordance. The proposed prototype design changes were then jointly discussed among all research team members until consensus was reached concerning which changes to keep, based on the frequency and fundamentality of the issues raised and their alignment to the purpose of the tool.

In this phase, we also performed a final verification of the strength category labels identified in the previous phase. Participants received the list of proposed names for the 6 strengths categories, and were then asked to select and prioritize 3 names for each category that they considered most appropriate and intuitive. All feedback was subsequently analyzed and final category names were selected based on the labels the participants had given highest priority.

Results

Participants

A total of 39 patients participated (28/39 women, 72%). The age ranged from 31 to 71 years (mean 50.3, median 49.0). Eighteen were recruited from treatment for a chronic pain condition, 14 for morbid obesity, and 7 for a chronic pulmonary disease.

Personal Strengths Patients Use in Self-Management and Their Categorization

Phase 1 of the study revealed that patients use a variety of personal strengths to manage their chronic conditions. The strengths descriptions ranged from personal to interpersonal and from specific to general, and included personal characteristics (eg, being optimistic), health-related behavior (eg, exercising, making time for hobbies), and interpersonal and environmental factors (eg, supportive families and work places).

In analyses of data from the card-sorting exercise, with participants, we identified 6 meaningful categories that articulate how participants perceive and categorize their strengths: (1) relations and support, (2) my sources of energy, (3) knowledge about my health, (4) activity and rest, (5) emotions and self-awareness, and (6) positive thoughts and dispositions (Textbox 1).

Textbox 1. Strengths categories elicited from card sorting exercise with examples.

Relations and support

- I can ask my family for help
- I receive help from competent health care providers
- I appreciate meeting others in a similar situation; then I do not feel so alone

My sources of energy

- I have a hobby I am passionate about
- I spend time on advancing my skills
- I enjoy the feeling of managing my challenges
- I find joy and motivation by spending time with my children and grandchildren

Knowledge about my health

- I have knowledge about and insight into my condition that make me feel more secure
- I have the resources and knowledge to manage my medications
- I follow the physician's advice regarding medication

Activity and rest

- I do relaxation exercises
- I have a routine for exercising
- I try to find alternative ways to manage things so I can take part in activities that give me joy

Emotions and self-awareness

- I allow myself to focus on myself (not always prioritizing others)
- I do not accept being judged or talked down to
- I have learned to differentiate between sensible thinking and feelings

Positive thoughts and disposition

- I am an optimist
- I try to look at things as challenges, not problems
- I do not perceive myself as sick even if I am in pain

Technology as a Facilitator for Integrating Strengths Into Patient–Provider Consultations

Analysis of participants' feedback in workshops and interviews identified 4 main themes: (1) potential benefits of a strengths-based approach in clinical consultation, (2) potential contexts for introducing new strengths-based IT tools, and recommendations when designing (3) functionality, and (4) user interface and interaction.

Potential Benefits of a Strengths-Based Approach in Clinical Consultation

Participants confirmed that the consultations they have today most commonly focus on reporting and addressing problems and symptoms. They noted that they often experience the consultation as demanding and stressful, because they usually feel under pressure to remember and report all relevant problems and difficulties and to ask for all the information they need. As a result, they reported lacking the energy or drive to raise and discuss personal strengths and/or health-promoting factors,

and/or constructively collaborate with the health care provider in setting goals and making realistic and personalized plans.

Participants said that widening the focus of the consultation to include patients' strengths and resources could help them look at their situation from another perspective, and instead of focusing on negative aspects–problems and symptoms–see the bigger picture and the positive things and resources they have in their life. Additionally, they noted that paying more attention to personal strengths and resources would help promote active participation from patients during consultations, support them in holding the focus in the consultation on the issues and topics they perceive as relevant, and on defining and discussing personal plans and goals.

Participants also said that addressing strengths and resources in the consultation could motivate them to be more active in performing self-management activities. Many stated that they would like to use the technology not just to help them to identify and discuss their strengths and resources before and during consultation, but also to support them in using the strengths in self-management activities as part of everyday life (eg, in the form of a strengths-based self-management mobile app).

Potential Contexts for Introducing New Strengths-Based IT Tools

How and Where

Participants stated that technology should be designed to help them identify and reflect on their strengths in more relaxed settings (eg, at home) where they might also get help and support from family members and/or friends, rather than use technology right before or during consultation. In this manner, technology could play a key role in raising the patients' awareness of their resources and activating them prior to the consultation, and enabling them to prepare for greater participation and more efficient use of the short consultation time with the health care provider.

To further support building the consultation on the patients' strengths, participants agreed that the health care provider(s) should also prepare for this conversation, (eg, by reading a summary of reported strengths). In this way, health care providers could obtain a more holistic view of the patient and his/her situation. Some of the participants also expressed that it would be useful to begin consultations with the health care provider briefly commenting and reflecting on their summary of strengths and resources. This would give both parties a common understanding and agreement regarding the patient's current situation.

With Whom

Participants identified different contexts in which using strengths-based IT tools could be useful. One example is in preparing for clinical consultations and regular check-ups with different health care providers (eg, medical specialists, physiotherapists, occupational therapists, dieticians, nurses, and social workers). Additionally, it was proposed that this type of IT tools could be useful in preparation for meetings with a multidisciplinary care team (eg, including a physiotherapist, physician, social worker, psychologist, and care coordinator). The tool might help the entire care team get a better overview of the patient's situation and personal strengths and resources, which could also facilitate the development of personalized care plans. In addition to the use in consultation with health care providers, the participants underlined that strengths-based IT tools could be integrated as part of self-management courses (organized by both health care provider institutions and municipalities). The technology could be used in individual consultations with a course coordinator (to support identifying and mobilizing patient strengths and resources) and in group settings (to increase reflection and group support).

When During the Treatment and Recovery

Participants proposed various time-points in time in the process of treatment and recovery when it would be most appropriate to introduce IT tools to raise patients' awareness of, and to mobilize their personal strengths both for planning and carrying out self-management activities. Some reported that they found the first period after receiving the diagnosis very demanding and stressful, because they needed to adjust and manage the new life situation and treatments. Discussing their strengths and resources with health care providers in these early phases could be perceived as an extra burden rather than as support. They reported that identifying and mobilizing their strengths and resources would be more appropriate later in the illness trajectory, when they start to have better control of their condition and feel ready to try out new things. Conversely, other participants noted that discussion on strengths and resources should be included from the beginning of the treatment to promote valuable help and support for managing new situations and finding useful activities. Additionally, early introduction of patient's strengths and resources could help health care providers get to know the new patient, and provide support and guidance that fit his/her specific needs. It was concluded that the appropriate timing for introducing a strengths-based tool and having a conversation focused on patients' strengths varies, depending on the patient's support needs and readiness to try new health management approaches.

How Often

Rather than having just one specific consultation dedicated to identifying and reflecting on their strengths, the majority of participants expressed the need to do this task multiple times. In this way IT tools can be potentially useful to provide them better insights both into their current strengths, but also how they change and adapt over time.

Functionality Requirements

All participants agreed that it would be very useful if the IT tool offered them a predefined list of strength items that they could choose from. They especially appreciated the list of strength items that contained examples from others patients living with chronic illness. However, it was agreed that creating an infinite list of strength items would not be feasible. Rather, the proposed best solution was a tool that outlined some relevant strength items and used them as examples and inspiration for identifying and adding one's own personal strength items in one's own words.

Participants agreed that they should be given the possibility of identifying and listing their strengths, but also selecting the ones they considered to be most useful and relevant for managing their health at that time. However, using formal scales and ratings to prioritize strength items was found inappropriate in this specific context. Rather, participants universally recommended "prioritizing" and reflecting on up to 5 strengths they found most helpful in achieving their personal goals. Defining goals (both for the specific consultation and for managing health in general) and linking these goals to the identified strengths and resources was suggested as very useful. In addition to defining health-related goals, the participants agreed that it would be useful if the tool also provided them an option to summarize their illness and health-related background and history, as this would help them to concisely outline the information they would like to communicate to the health care providers during the consultation.

Design Requirements

Due to their health conditions, participants reported often having problems concentrating. Also, mainly due to age and/or motor problems, they felt that it might be hard for some users to perform long tasks that require complicated interactions. Therefore, the most prioritized design feature for developing strengths-based IT tools was the intuitive user interface and easy interactions. For example, tapping and using check boxes to select items on the screen were reported to be much easier than using more demanding gestures (eg, drag-and-drop). Participants also reported that the use of vertical and horizontal menus could possibly be misunderstood as a requirement to prioritize some items over the others. Therefore, a better choice would be to use alternatives, such as a circular menu where each menu item is color-coded and presented as an equal part of the circle.

Participants said that the interface and design should be engaging and motivating. Some reported irritation when filling out questionnaires, which were often perceived as too long and boring. Thus, advanced design elements (eg, metaphors, multimedia) were proposed to make the tool more attractive and enjoyable.

Example: A Prototype of a Strengths-Based IT Tool Developed in This Study

A low-fidelity paper prototype of a strengths-based IT tool designed in cooperation with participants in the third phase of the study is depicted in screenshots in Figure 1, Figure 2, Figure 3, Figure 4, Figure 5 and Figure 6. The prototype was designed to be applicable to various types of consultation settings that were identified in the study. For illustrative purpose, in Multimedia Appendix 1 we additionally describe a scenario for one potential context of use–preparation for a consultation with a specialist.

Figure 1. Specifying goal for consultation.

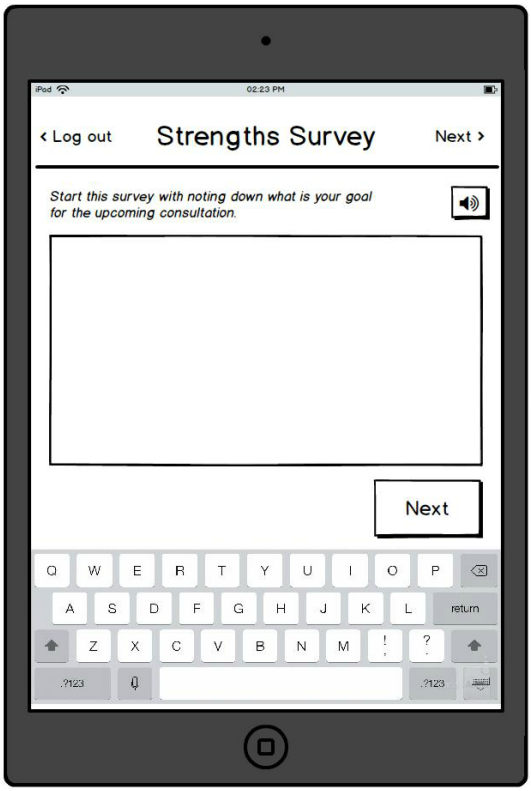


Figure 2. Menu with strength categories.

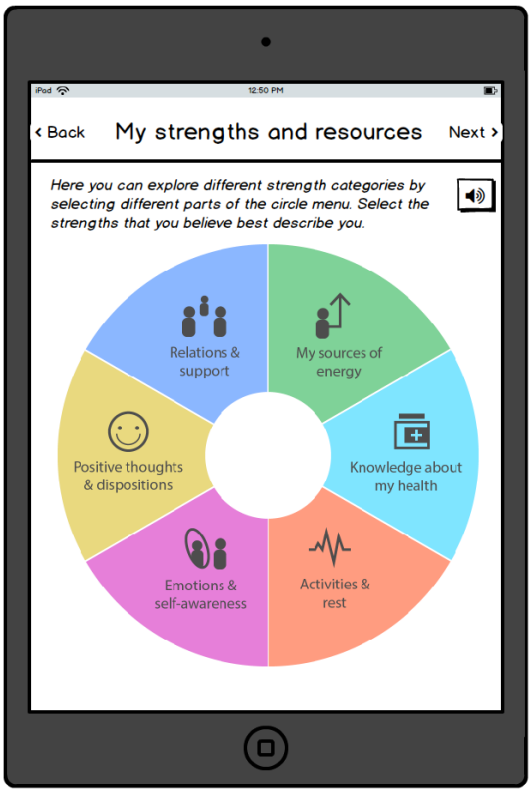


Figure 3. Examples of strengths within one category.

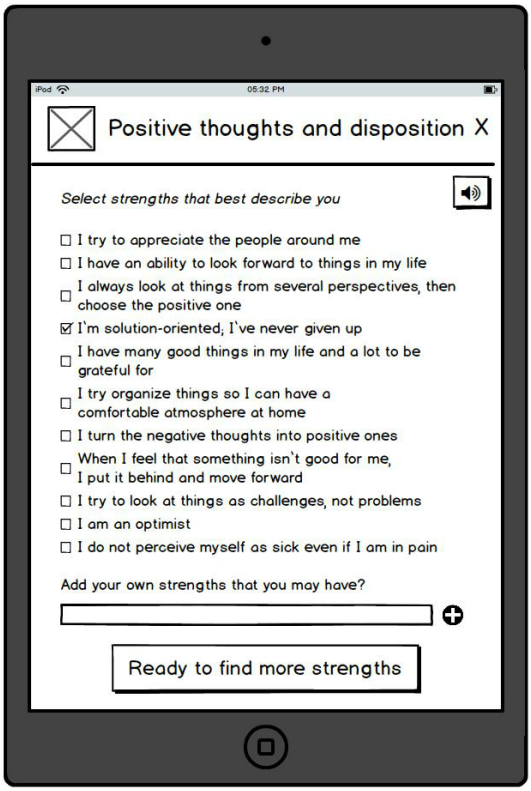


Figure 4. Selection of strengths in relation to a self-defined goal.

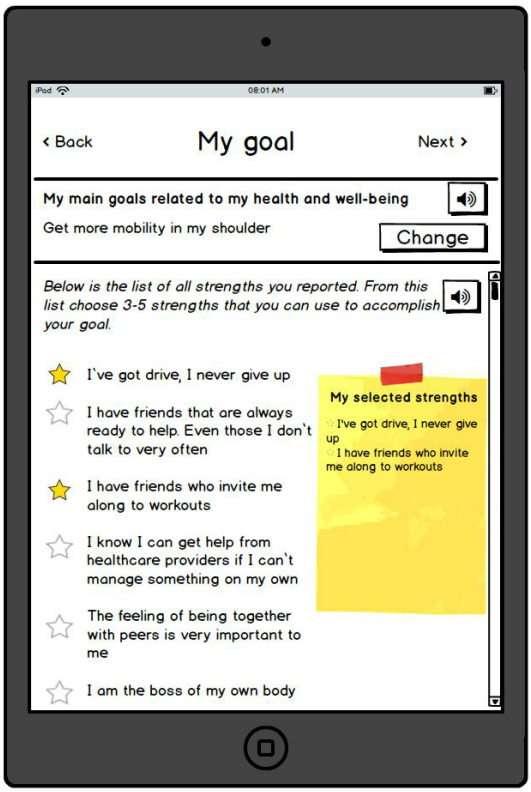


Figure 5. Linking strengths to the health-related goal.

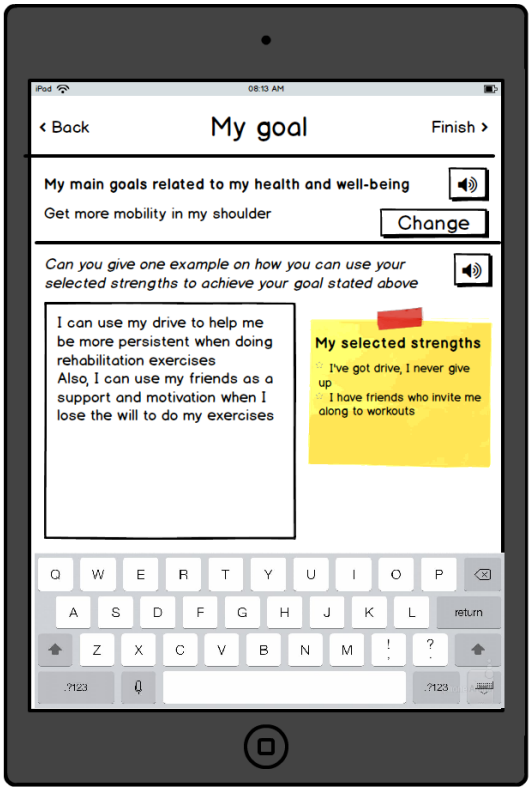
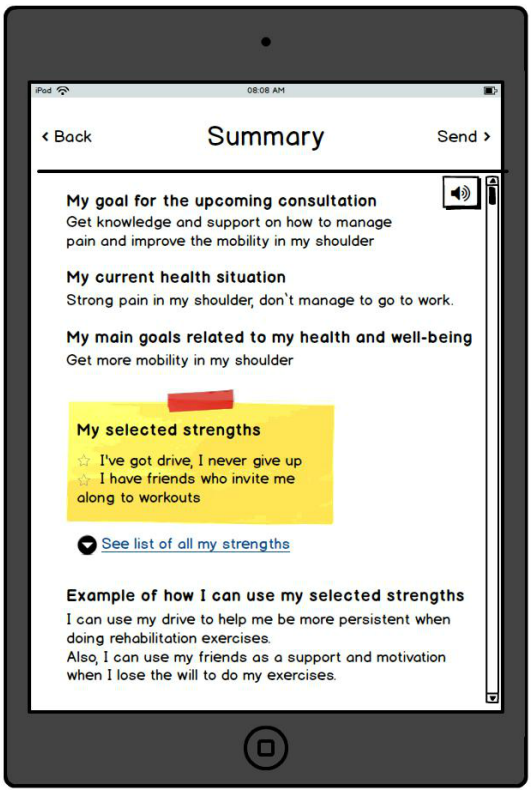


Figure 6. Summary of the strengths assessment.



Discussion

Summary of the Main Findings

Our findings show that patients desire a more holistic health care, and are willing to take a more active role in consultation with health care providers. They also show that patients believe that technology has potential to support them in taking that more active role, by helping them prepare in advance and think about new ways their personal strengths and resources could be used to support self-management activities. Having good, effective communication and collaboration with health care providers is one of the main requirements for successful care for the majority of patients with chronic conditions [1], and various research studies have explored and shown how technology can be used as a facilitator in this process [37,38]. However, most of these studies have mainly emphasized patients' symptoms and problems, rather than on ways of giving providers a better "whole person" view that integrates, besides symptoms, also patient's strengths and resources, and that could be used for establishing more personalized and attainable care plans [39,40]. The present study is, to our best knowledge, the first to explore what people with chronic illness consider important in the design of an IT tool to aid assessment of their personal strengths and support them in discussing these in a consultation with a health care provider.

Participants in our study outlined the requirements for a tool that would not just help them identify their personal strengths but also help them reflect and pinpoint the strengths they think could be useful for achieving their own personal health-related goal. This relation between personal strengths and goals has previously been addressed in related research. For example, coaching psychology shows that use of personal strengths to pursue meaningful, personally relevant goals is associated with better progress toward those goals, which is in turn associated with psychological need fulfillment and enhanced well-being [41]. Using technology to support people in linking their personal strengths and health-related goal(s), could therefore be an important first step for making more attainable and personalized self-management plans and choosing activities (on one's own or in collaboration with the health care provider).

Strengths and Limitations of the Study

Current trends in the development of health care interventions outline that they have to be designed not only to be useful, acceptable, and nonharmful, but also pleasant and engaging [42,43]. To accomplish this when creating an IT-based tool, it is important to elicit users' requirements regarding system functionality and usability, identify what creates positive value for individual persons in their own context, obtain meaningful user-experiences based on people's thoughts and beliefs, and map these to system design (value co-creation) [44]. In this study, we worked closely with patients to elicit their needs, opinions, values, and preferences, and on that basis jointly created the a prototype for a tool that would be both engaging (as it would help patients identify and use their own strengths and resources), and motivating (as it would inspire them to take a more active role in collaborating with health care providers and managing their health). We collected various feedback from users on how to make the tool more engaging, in terms of interface design (eg, use circular menus to make all strength categories look equally important, use of videos to help users understand concepts, and categories of strengths), and related to user experience (eg, giving examples of strengths reported by other patients with chronic conditions to help people relate and reflect on their own situation). Additionally, organizing the

strength items into categories that are logical and meaningful to users supports customizable design that enable users to select only categories that are relevant in their context. By inductively identifying the patient perspective, use of qualitative participatory approach and method supported us to set-up future work to design IT support that is relevant to the needs of chronic illness patients for a strengths-based approach to health care.

The main limitation of the work presented in this paper is that it includes the perspectives of just one group of stakeholders–patients. Therefore, subsequent phases of the project will involve a broader group of stakeholders–both the types of health care providers identified as potentially relevant in this study, and additional patients with the same and new diagnoses–to further explore feasibility and possibility for implementation of strengths-based IT tools.

Implications for Designing IT Support for a Novel Strengths-Based Approach to Health Care

All participants in our study agreed on the importance of a conversation about the patient's strengths and resources, and how to build on them in self-management of a chronic condition. Previous studies have suggested that although adding a discussion on personal strengths to the consultation may indeed require some extra time, this is assumed to result in better health care, user activation, and promotion of health [13,45]. However, the optimal time point for having this type of conversation remains unclear. Identifying consultation settings in which both the patient and the clinician agree that a new approach is needed, and then bringing patient strengths into these interactions is likely to maximize the receptivity to a new strengths-based approach. Such an approach can be used in both individual and group consultations, as well as outside health care settings (eg, self-management courses). Some previous research in related fields promotes paying attention to patients' strengths in a consultation setting by using informal qualitative methods, such as proposing an open question about personal strengths (eg, "We cannot only talk about problems. I also want to hear about your strong points. Which of these strong points do you normally use to stay (or become) well?" [46]). In this setting technology could have the great potential to help patients prepare for this conversation by supporting their efforts to select and specify their strengths in advance and potentially even come up with their own ideas about how would they like to use them to manage their health condition. The question of when this kind of dialogue should be initiated, by whom, and which is the best moment to introduce technology as a facilitator in this process remains open, and should be addressed in future research.

Conclusion

Our study provides initial insights into patients' requirements for developing new IT tools that help them in identifying and reflecting on their personal strengths and support discussion of these assets in consultations with health care providers. We conclude that technology has great potential to be used to create novel opportunities for activating and empowering patients. Developers and designers of strengths-based IT tools should be aware of these requirements and attempt to accommodate them during design and development of new technologies for use in clinical consultations.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Scenario illustrating potential use of the strengths-based IT tool and associated procedures.

[PDF File (Adobe PDF File), 20KB - resprot_v5i3e175_app1.pdf]

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Abbreviations

IT: information technology

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Original Paper

Get Checked… Where? The Development of a Comprehensive, Integrated Internet-Based Testing Program for Sexually Transmitted and Blood-Borne Infections in British Columbia, Canada

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Abstract

Background: Testing for sexually transmitted and blood-borne infections (STBBI) is an effective public health strategy that can promote personal control of one's health and prevent the spread of these infections. Multiple barriers deter access to testing including fear of stigmatization, inaccurate health care provider perceptions of risk, and reduced availability of clinic services and infrastructure. Concurrent increases in sexually transmitted infection (STI) rates and demands on existing clinical services make this an even more pressing concern. Web-based testing offers several advantages that may alleviate existing clinical pressures and facilitate appropriate testing access.

Objective: This paper describes the planning, development, and usability testing of a novel Web-based testing service, GetCheckedOnline (GCO), as a complementary testing option integrated within existing sexual health services within British Columbia (BC).

Methods: From 2009 to 2014, we engaged a multidisciplinary team in the design and development of GCO. We conducted 3 initial research studies to ascertain the opinions of youth, men who have sex with men (MSM), and STI clinic clients regarding Web-based testing and elicited perspectives of sexual health care providers through focus groups. We developed an informed consent process, risk assessment questions, and test recommendations based on provincial and national guidelines and evaluated these through consultations with clinical and community stakeholders. We also conducted a preliminary health equity impact assessment whose findings also informed the GCO program mode. Finally, from April 2011 to December 2012 we gathered qualitative data from 25 participants on the functionality and usability of a GCO prototype and incorporated their recommendations into a final model.

Results: GCO launched in the fall of 2014 across 6 pilot sites in Vancouver, BC. The service involves 3 main steps: (1) create an account, complete an assessment, and print a laboratory requisition, (2) provide blood and urine specimens at participating laboratory locations, and (3) receive test results on the Internet or by phone. During this pilot phase, we promoted GCO to existing STI clinic clients and MSM in the Greater Vancouver region. A rigorous mixed-method evaluation of GCO's uptake, acceptability, and health system impacts is currently underway.

Conclusions: GCO is the first comprehensive Web-based STBBI testing program in Canada that is integrated with existing sexual health services, with the potential to reduce pressures on existing clinical services and reach populations facing the greatest barriers to testing. Our experience highlights the facilitators and challenges of developing and implementing novel complex eHealth interventions within the health care system, and underscores the importance of considering broader implementation contexts.

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KEYWORDS

Internet; sexually transmitted diseases; testing; health care delivery; health services research; intervention studies

Introduction

In 1999, an outbreak of syphilis among gay, bisexual, and other men who have sex with men (MSM) in San Francisco who were users of online chat room heralded the beginning of a "new era" for prevention of sexually transmitted infections (STI) [1]. The recognition that the Internet posed both a new risk environment for STI and offered unique opportunities to reach populations affected by STI has since led to the development of a wide array of Web-based interventions, including partner notification programs, tailored educational interventions, and Web-based outreach [2,3]. Around the same time in British Columbia (BC) as elsewhere, community surveys and STI clinic records demonstrated increasing use of the Internet to find sex partners by MSM and other populations at higher risk of infection [4]. As a result of these behavioral and intervention paradigm shifts, the British Columbia Centre for Disease Control (BCCDC) prioritized the development of Web-based sexual health services, starting in 2004 with the first nursing-led cyber-outreach program in Canada [5]. Following further consultation with international experts in this nascent field and assessment of local service gaps, development of a Web-based testing program for sexually transmitted and blood-borne infections (STBBI) was prioritized in 2008.

While promoting testing is a longstanding cornerstone of public health strategies for control of STBBI, multilevel barriers to appropriate testing persist in BC as in most jurisdictions. These include individual (eg, risk perception, privacy concerns, fear of disclosing sexual behavior, knowledge of testing locations, discomfort with health care professionals), provider (eg, discomfort with questions about sexual orientation, inaccurate perceptions of risk), and clinic barriers (eg, travel requirements, limited clinic hours, wait times), and these can be particularly pronounced in rural areas [6-9]. BC is also similar to other jurisdictions by having increasing STI rates and demands on STI clinical services that coincide with overall reductions in clinical capacity and infrastructure [10,11]. Web-based testing services may overcome some of these barriers and demands, as these services promote a patient-centered approach and allow clients to access testing without presenting to a provider or clinic.

Typically, Web-based testing involves visiting a website to request a home self-collection kit or to print a laboratory form to take to a laboratory to provide specimens, with results being provided through a website, text messaging, or by phone. Web-based testing programs take a variety of forms, the most common being population-based screening for a single infection (usually chlamydia by self-sampling) [12,13]. Comprehensive models testing for multiple STBBI are less common [14,15]. Programs can be stand-alone programs or be fully integrated with clinical services [15-19]. Evidence of acceptability, reach, and satisfaction with these programs is robust, confirming that Web-based STBBI testing is in high demand, particularly among youth and MSM. Some programs have demonstrated uptake of Web-based testing in high-risk or target groups and found high positivity rates, including clients from diverse socioeconomic positions and races, clients with a history of STI diagnosis, and clients with behavioral markers of STI risk [20-27]. A small number of studies have suggested Web-based testing is cost effective [25,28-30].

Recognizing the potential of Web-based testing to reduce inequities in access to testing among populations with higher infection rates, in 2009 the Provincial Health Services Authority (PHSA) awarded the BCCDC (an agency within the PHSA) 5 years of funding to develop an Online Sexual Health Services Program. This included the development of an Internet-based testing program with 3 objectives: (1) to improve sexual health by increasing the uptake and frequency of STBBI testing and earlier diagnosis, (2) to reach populations with a greater prevalence of infection and barriers to access testing, and (3) to increase the capacity of STI clinic services and improve the use of clinician resources. MSM, youth younger than 25 years, and people living in rural areas were named as initial priority populations for this service, given high infection rates and Web-based sex-seeking behaviors [11,31], barriers to accessing confidential, culturally sensitive and appropriate care [6,8], and demonstrated acceptance of Web-based sexual health interventions [32-35]. In this article, we will describe the development of this Web-based testing service for STBBI – branded GetCheckedOnline (GCO) – and plans for its evaluation. In so doing, we hope that we will also provide helpful insights for other researchers and service providers interested in developing Web-based sexual health services within complex health care systems.

Methods

Theoretical Framework

Our approach to developing GCO involved the same steps and activities typically recommended for the development of eHealth interventions. These included: using a multidisciplinary approach (with involvement of different research and provider disciplines on the development team), involvement of stakeholders including potential users throughout the process, conducting continuous and systematic evaluation throughout

all phases of development, and use of robust, mixed-methods for formative and summative evaluation [36]. Our primary assumption and rationale was that GCO would reduce barriers to STBBI testing among individuals who are already motivated to test (and was not to change testing behavior among unmotivated individuals per se). As our focus was on adoption of GCO, we used elements of diffusion of innovation theory to inform the development and evaluation of GCO; for example, by considering the relative advantages and disadvantages of GCO from the perspective of potential users, identifying the characteristics of potential adopters, and considering the health system contexts in which GCO is implemented [37,38]. Finally, an important theoretical underpinning of GCO was our positioning of the intervention as being complementary to (not replacing), and fully integrated with, existing public health and clinic-based sexual health services in BC.

Planning Phase: 2009-2011

Establishing a Multidisciplinary Team

The development of GCO was led by the BCCDC Online Sexual Health Services (OSHS) program, which consisted of a medical lead, program manager, business analyst, and epidemiologist. At the outset, a program of research was established between the OSHS and the Youth Sexual Health Team, a research unit at the University of British Columbia, based on an integrated knowledge translation model (ie, where knowledge translation principles are applied to the entire research process, with involvement of knowledge users as equal partners) [39], and drawing on a range of qualitative and quantitative research disciplines including public health and clinical research, epidemiology, and social sciences.

Identifying, Engaging, and Consulting With Stakeholders

We identified 3 groups of stakeholders to engage in the development of GCO either on an ad hoc or continuous basis: internal stakeholders within the BCCDC; stakeholders within other PHSA agencies (eg, public health laboratory, privacy, information technology); and external stakeholders (Table 1).

We conducted a stakeholder analysis and developed a communication strategy for engaging stakeholders, including the development of fact sheets and standard presentations. Initially, we met with each stakeholder to provide an orientation to the concept of Web-based STBBI testing and GCO, and to discuss the nature of their involvement with GCO development. We provided ongoing updates about GCO development through a team blog and email bulletins, as well as seeking out opportunities to disseminate information about GCO through community agency networks, publications, and events [40-42]. We then established 3 stakeholder committees to guide the activities of, and provide updates about, GCO development:

1. Clinical Integration Committee (CIC): An internal decision-making group that met monthly to determine how GCO should be integrated with the provincial STI clinic at BCCDC, which would be responsible for clinical and public health follow-up of test results. The CIC was comprised of medical and nursing leads for the clinic, education and outreach programs at BCCDC.

2. Community Consultation Working Group (CCWG): An external advisory group that met biannually to ensure GCO would be a useful resource to community organizations and tailored to meet the needs of the populations they served. The CCWG was comprised of community organizations working in sexual health and STBBI prevention (including with youth and MSM).

3. Internet Services Committee (ISC): An advisory group that met monthly to receive updates about GCO and to guide its development, comprised of BCCDC, PHSA, and external stakeholders.

Reviewing the Literature and Expert Consultation

We reviewed published and gray literature to identify Web-based STBBI testing programs and evaluations of their impact, and to summarize barriers and facilitators of STBBI testing that are potentially mediated through Web-based testing. We then contacted program experts involved with comprehensive Web-based testing programs integrated with clinical services in San Francisco and Amsterdam, to learn about their experience with setting up these programs [14,15].

Based on this information and consultation, we developed a high level model for GCO to use in future consultations. This model described the program's 3 main steps: create an account, complete a risk assessment, and print a laboratory requisition; provide blood and urine specimens (only; no oral, vaginal, or rectal swabs); receive test results (with paths described if negative, positive, or if there is a problem with the result) (Figure 1). This model did not include mailing of home test kits for human immunodeficiency virus (HIV) as these are not yet licensed for use in Canada. We also did not propose including self-collection of specimens at home as sending collected specimens potentially containing infectious agents by general mail is not permitted in Canada. In this high level model, positive results are delivered by a health care provider by phone, which is consistent with current practice at the provincial STI clinic in order to provide appropriate posttest counseling and ensure treatment and appropriate follow-up. In contrast, all negative test results would be viewed on the Internet, as is the case for many Web-based testing programs in order to reduce barriers to accessing test results (ie, by eliminating requirements to contact the clinic).

Table 1. Key stakeholders involved in the development of GetCheckedOnline.

Stakeholder	Role in relation to GCO[a]	Involvement with GCO development
BCCDC[b]		
Provincial sexually transmitted infection clinic	Responsible for clinical aspects of GCO implementation (authority for ordering tests, review and management of results, entering results into app)	Continuous; part of ISC, CIC, GWG[c]; key knowledge user involved in research activities
Education and outreach programs	Provide support for or lead other Web-based/clinic-based sexual health services with which GCO is integrated	Continuous; part of ISC
Communications	Provide support for media and public communications	Continuous; part of ISC
Executive	Responsible for overall strategic direction and operations of BCCDC including the Division responsible for GCO	Ad hoc; key knowledge user involved in research activities
PHSA[d] (government agency within which BCCDC is located)		
BC Public Health Laboratory	Responsible for conducting all tests ordered through GCO	Continuous; part of ISC, GWG; key knowledge user involved in research activities
Privacy	Provides privacy-related advice on GCO	Continuous; part of ISC
Risk management and legal	Provides legal advice regarding risk management of GCO	Ad hoc
Information management/IMITS[e]	Responsible for approving the technical specifications and final application	Continuous; part of TWC[f]
Executive	Responsible for overall strategic direction and administration of PHSA (including BCCDC, BC Public Health Laboratory, privacy, risk management, and IMITS	Ad hoc; key knowledge user involved in research activities
External stakeholders		
Health care providers conducting STBBI[g]	Interact with users of GCO (eg, refer clients to GCO)	Consulted during planning phase
Community organizations working with youth or men who have sex with men, and/or in sexual health	Interact with users of GCO (eg, refer clients to GCO). Promotion of GCO as part of education or outreach programs to clients.	Continuous; part of ICS, CIC[c], CCWG[h]; key knowledge user involved in research activities
LifeLabs	Private laboratory company that operates the specimen collection sites for GCO	Consulted during development, testing, and implementation planning
Public Health programs in the other 6 regional or provincial health authorities in BC	Oversee regional public health testing initiatives with which GCO must be aligned	Ad hoc
Ministry of Health	Sets provincial strategies for STBBI testing and oversight for provincial testing initiatives with which GCO must be aligned	Continuous; part of ISC; key knowledge user involved in research activities
Professional practice regulatory bodies (College of Physicians and Surgeons of BC; College of Registered Nurses of BC)	Determines acceptable scope of practice for physicians and registered nurses involved with GCO	Ad hoc

[a]GetCheckedOnline.

[b]British Columbia Centre for Disease Control.

[c]Internet Services Committee (ISC); Clinical Integration Committee (CIC); GetCheckedOnline Working Group (GWG).

[d]Provincial Health Services Authority (PHSA).

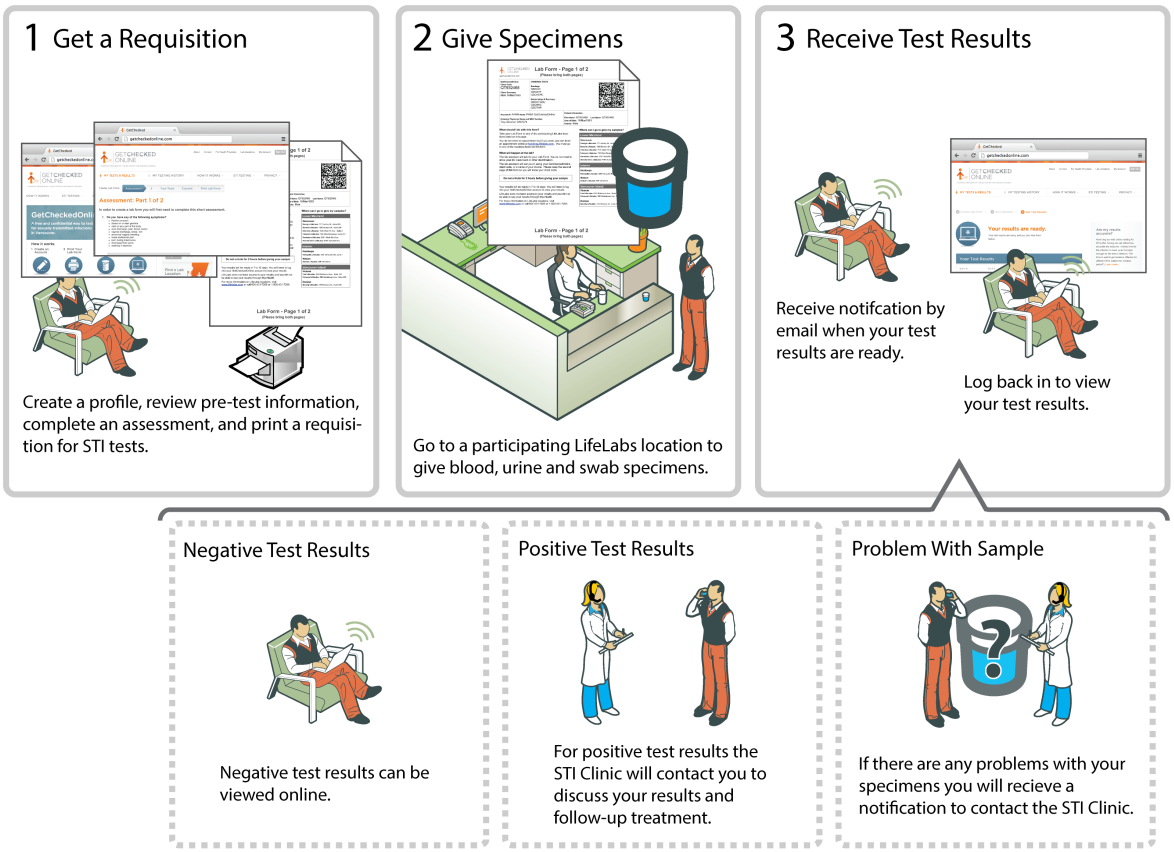
[e]Information technology services (IMTS).

[f]Technical working group (TWC).

[g]Sexually transmitted and blood-borne infections testing (STBBI).

[h]Community consultation working group (CCWG).

Figure 1. High level overview of GetCheckedOnline used during formative research.



Consulting With Potential Users

Given the importance of end-user input at early stages in the development of novel eHealth interventions, we conducted 3 research studies to ascertain the opinions of youth, MSM, and STI clinic clients about Web-based sexual health services and our Web-based testing model [32,34,43]. Overall, GCO was perceived as private, convenient, and providing greater control over testing. We elicited a number of concerns, including privacy of data and security of the app, reliance on outdated technologies (eg, printing), and anxiety at receiving a positive result on the Internet. In these studies, the participants proposed mitigation strategies for these concerns, many of which were incorporated into the GCO model (Table 2).

Determining Regulatory and Practice Requirements

As a new testing paradigm, Web-based testing raised a number of questions regarding its relation to existing regulatory and practice requirements for physicians and nurses in BC (eg, can a physician order tests recommended through a Web-based app, and if so how, and is any liability assumed?). To answer these questions, we consulted with provincial practice regulatory bodies for physicians and nurses, and the national medical protection insurance agency. We established that GCO's model, where a BCCDC STI specialist physician is the ordering physician with results reported to and followed up by provincial STI certified registered nurses and managed according to standard protocols, is an extension of acceptable clinical practice. We also developed policies to address identified clinical nursing practice gaps, including guidelines for providing nursing services on the Internet and for emailing clients.

Table 2. Key findings from potential users on the acceptability and perceptions of Web-based sexual health services/testing and how these influenced the design of GetCheckedOnline.

Activity	Key findings	Influence on GCO[a] design
Interviews and focus groups with youth to determine their perceptions of sexual health websites [32]	For sexual health–related websites youth preferred practical information, professional approaches to design and content (vs colloquial or explicit language or images)	Adopted professional tone using every day, noncolloquial language and select use of imagery
Interviews and focus groups with youth, MSM[b], and clinic clients to determine their perceptions of Web-based testing in general and GCO specifically [43]	Web-based testing perceived as convenient, offering immediate access to testing, greater privacy, reduced anxiety compared with face-to-face testing, and greater control over the testing process	Minimum data is collected with rationale for questions provided
		Account creation requires email validation
	Concerns about providing personal information via the Internet, potential for abuse (eg, if an account was created using email belong to someone else), distrust of security of data provided via the Internet, lack of comprehensive pretest information, lack of support for individuals receiving a positive result.	Explicit privacy policy and terms of use developed to explain how data is collected, stored, and used
		Advice provided for additional privacy measures (eg, clearing cache)
		Detailed pretest information provided
	Expectations that Web-based testing would be professional, adhere to standard guidelines (and advise when different, such as lack of swabs), be fully on the Internet (eg, from booking appointments for specimen collection, to electronic ordering of tests, to getting results and prescriptions), ability to control how and when they receive notifications	No positive results provided via the Internet, only by phone, with links to other services accessible throughout the website
		Testing reminders can be turned off
		Tailored educational information is provided for other sexually transmitted and blood-borne infections testing or prevention strategies not available through GCO (eg, emergency contraception, throat, and rectal swabs)
Web-based national survey of Canadian MSM to determine intention to use Web-based testing [34]	Overall intention to use Web-based testing was 72%, with little variation by participant characteristics.	
	Greatest perceived benefits were privacy, convenience, and testing any time.	GCO clearly identified as a program of the British Columbia Centre for Disease Control
	Greatest drawbacks were inability to see a doctor or nurse, wanting to talk to someone about results, not wanting Web-based results, and low trust in the service	Wording on the GCO website and promotions emphasize privacy and convenience of the service

[a]GCO: GetCheckedOnline.

[b]MSM: men who have sex with men.

Consulting With Sexual Health Care Providers

As GCO is implemented in an existing sexual health care system where Web-based testing clients may also be accessing sexual health services at other clinics not operated by BCCDC, we conducted focus groups with local sexual health care providers to understand their opinions of GCO [44]. Providers perceived GCO as an inevitable evolution within the current system of care, with perceived benefits including shifting the locus of control from providers to patients, addressing testing barriers (eg, privacy concerns, clinic hours of operation), facilitating increased engagement in sexual health care (eg, including reminders for pap testing), and freeing up provider time and ability to see more complex patients. Providers also considered that these benefits may be offset by perpetuating existing inequities in populations GCO is trying to reach (eg, youth who do not have access to a private printer, MSM requiring swabs for diagnosis of oral or rectal STI) or predominantly being used by individuals who already have the resources necessary to access testing (eg, tech "savvy," higher income). A number of potential personal or clinical harms were identified, such as anxiety at receipt of result notifications, repeated use by individuals at lower risk ("worried well"), misunderstanding test limitations, such as window periods, inadequate pre- and posttest counseling, and missed opportunities for education and prevention such as contraception. As with potential users, mitigation strategies for these harms were also proposed and incorporated into GCO (Table 3). At the same time, providers recognized that many of these harms could also occur within face-to-face clinical testing encounters.

Table 3. Potential harms and mitigation strategies recommended by sexual health care providers, and how these were addressed in the design of GetCheckedOnline.

Potential harm	Recommended mitigation strategy	How addressed
Anxiety related to viewing email notification or retrieving voicemail (if positive) outside of clinic hours	Provide after-hours support, send notifications early in the day	Links to BCCDC[a] sexual health website and provincial after-hours support services
	Notification emails should be generic and not include results	Generic wording used for notification emails
Not addressing underlying anxiety of repeat tests by the "worried well"	Ability to monitor and intervene if appropriate (eg, refer to clinic for care)	Monitored during the pilot evaluation
		Clinic protocol developed to handle this scenario
Misunderstanding information on the website, such as window periods, symptoms	Ensure appropriate educational content on website related to test limitations and symptoms	Information accessible throughout the site related to test limitations and window periods
		Links to British Columbia Centre for Disease Control sexual health website for more information about symptoms
Inadequate pre- and posttest counseling	Provide equivalent information on website, with some mandatory information	Content from provincial pre/posttest guidelines incorporated, with mandatory and optional content
	Include clear consent process and disclaimer regarding limitations of Web-based testing	Consent page including acknowledgement of limitations as final step before printing requisition
Missed opportunities for education and prevention that can be elicited during clinical testing encounters	Include information and referrals for pap testing, human papilloma virus vaccine	Tailored recommendations for sexually transmitted and blood-borne infections prevention provided based on assessment responses, including vaccines, oral and rectal swabs, emergency contraception, HIV postexposure prophylaxis
Does not include all potentially relevant tests (eg, Hepatitis C, swabs)	Include Hepatitis C testing	Hepatitis C testing included for men who have sex with men, or history of injection drug use
	Have clear referrals to clinics for other tests	
	On assessment include question about specific sexual acts (oral, vaginal, anal) and recommend swabs if appropriate	Swabs prioritized for inclusion after implementation
	Explain why certain tests are not offered	
Not answering assessment questions accurately and inappropriate tests recommended (or not)	Give option to skip assessment and recommend all tests	Importance of providing accurate information emphasized
		Clients have option of deselecting any recommended tests
	Encourage clients to provide accurate information (through disclaimer, encourage to select "prefer not to answer" option)	
Positive results not followed up because of client providing fake contact information	Encourage use of real name and phone number	Importance of using real name or consistent pseudonym, and providing telephone number emphasized

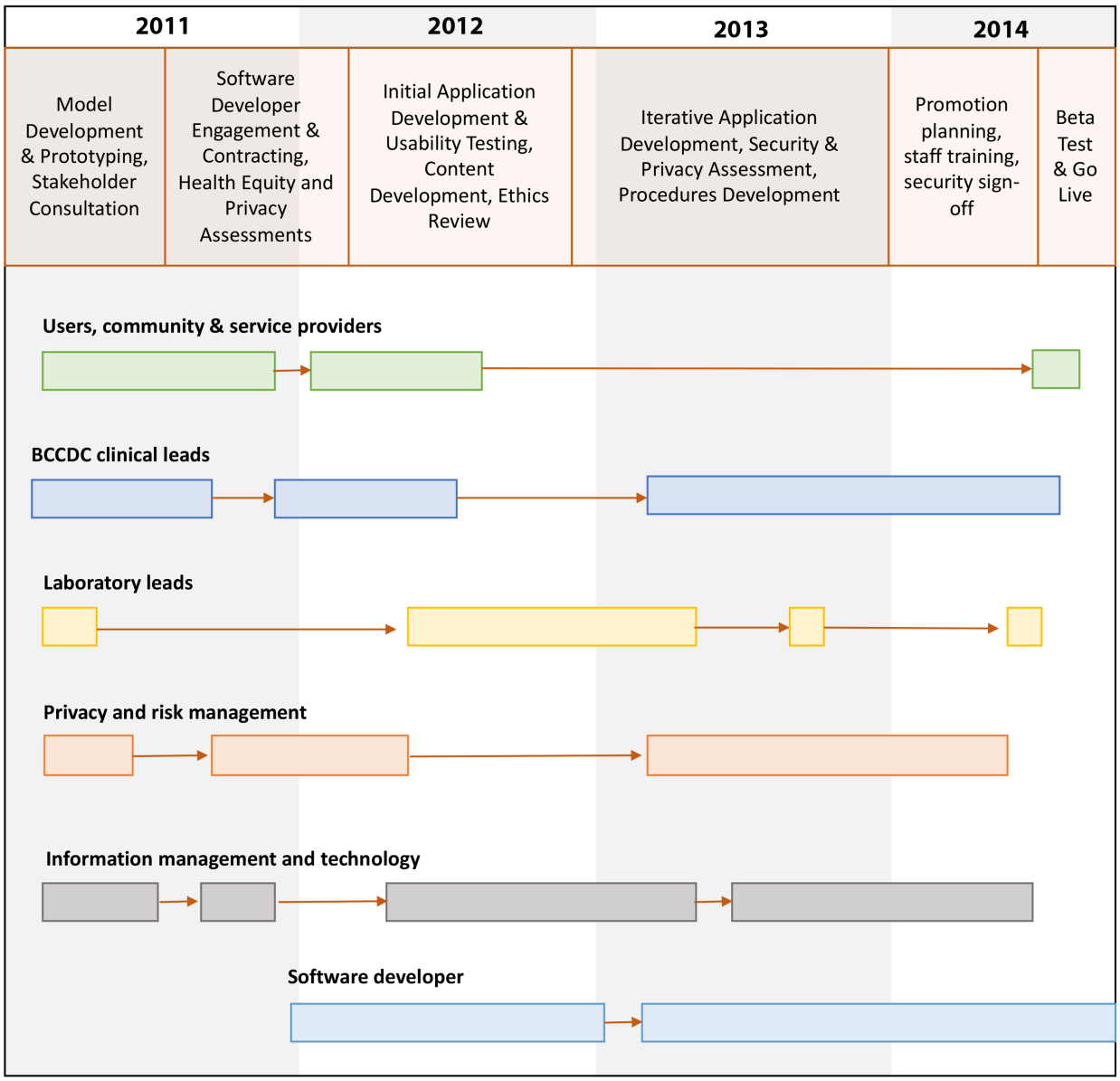
[a]BCCDC: British Columbia Centre for Disease Control.

Development, Usability Testing, and Revision: 2011-2014

Stakeholder and end user consultation continued throughout the development, usability testing, and revision stages (details shown in Figure 2).

We established a GCO Working Group including the core GCO development team and representatives from the BCCDC clinic (nursing and clerical) and the PHSA Public Health Laboratory (which conducts the testing for GCO specimens). The working group met approximately every 2 weeks to develop the detailed requirements (ie, blueprint) for the GCO app and the final GCO service. In addition, we established a GCO Technical Working Group, comprised of the GCO development team and representatives from different program areas in Information Technology (IT) (eg, databases, servers, network security). The group met every 2 weeks to develop the architecture, hosting, and other technical requirements for the app. The final model was informed by findings from the planning phase as well as the additional activities below.

Figure 2. Key players involved in the development, testing, and revision of the GetCheckedOnline app.



Assessing GetCheckedOnline's Impact on Health Equity

The "techno-optimism" with which Web-based health interventions are viewed is tempered by the reality that their adoption is patterned along social gradients (eg, digital divides) [45,46]. New testing technologies such as GCO may reinforce or reproduce the relationship between social position and health status if only taken up by individuals who already have the resources needed to access clinic-based STBBI testing (eg, social capital, education) [47]. We conducted a preliminary health equity impact assessment (HEIA; screening, scoping) consisting of a literature review and expert consultations. In so doing, we identified ways in which GCO was likely to reinforce or circumvent health inequities in sexual health for historically underserved and marginalized populations with a higher burden of STBBI (including: youth; MSM; people from ethnocultural minorities; intersex, transgender or gender variant populations; Indigenous people; residents of rural areas) [48]. HEIA recommendations that were incorporated into GCO design included: collecting information on ethnicity and gender identity; avoiding normative and stigmatizing language and images; expanding testing options to include hepatitis C.

Meeting Requirements for Pretest Counseling and Informed Consent

As flagged during consultations with end-users and sexual health care providers, we needed to determine how provider-delivered pretest counseling and the obtaining of informed consent could be translated to a Web-based app. We did so by: (1) reviewing the published literature to determine the effectiveness of alternate models of providing pretest counseling (eg, videos, written information), (2) reviewing national and provincial testing policies and procedures, and (3) consulting with a clinical ethicist, privacy advisor, legal counsel, and provincial nursing practice leads to determine the necessary app requirements in order to obtain informed consent on the Internet (eg, mandatory vs optional steps). We included a specific consent step on GCO that must be completed by users prior to printing a laboratory

test requisition, and conducted individual interviews with end-users following their participation in usability testing of the GCO app to probe specifically about their perceptions of the consent webpage (which overall were favorable) [49].

Determining Risk Assessment Questions and Test Recommendations

As GCO was conceptualized as an extension of clinical STBBI testing services offered by BCCDC, we intended the assessment step and testing recommendations to mirror routine clinical practice as much as possible. We reviewed national and provincial guidelines for STBBI testing, treatment and scope of practice, and the BC epidemiology of STBBI in our target populations. To identify assessment questions that could be used for recommending specific tests and tailored educational messages, we reviewed existing Web-based risk assessment tools and the published literature to identify models or variables that were predictive of STI infection [50,51].

Our final set of assessment questions, testing recommendations, and tailored messages were evaluated through usability testing and consultation with clinical and community stakeholders. These included routine recommendation for all clients of urine testing for chlamydia and gonorrhea, and serum testing for HIV and syphilis (as these are generally routinely recommended for BCCDC STI clinic clients and MSM); serum testing for hepatitis C was also recommended for MSM (optional) and individuals with a history of injection drug use. Clients can opt out (deselect) any of the recommended tests. Assessment questions were also designed to (1) provide tailored recommendations for additional testing or prevention interventions that may be indicated (including HIV postexposure prophylaxis, emergency contraception, and need for oral and/or rectal swabs for chlamydia and gonorrhea testing), and (2) to determine the recommended frequency of testing in order to set up testing reminders that are sent by email to GCO clients (ie, 3, 6, or 12 months).

Usability Testing and Revision

As the incorporation of user feedback is a key component of app development, we conducted testing of the website with potential end-users at 3 separate points during the development process. All usability testing was done in-person with participants recruited through Web-based advertising and from attendees of the Provincial STI Clinic at BCCDC. The first round of testing, performed on a prototype with 10 participants, was designed to observe how users interacted with the app and to validate the risk assessment; outcomes informed numerous changes to the app user interface. The second round of testing, with 8 participants, was performed on a functional but incomplete version of the website to test the overall functioning and content of the app; results led to a redesign of the homepage and changes to the website information architecture. The final round of usability testing, with 14 participants, was completed on a fully functional version of the website to test different options for presenting information via the homepage and the informed consent page; feedback informed the final homepage design and validated the informed consent process.

Final Model

The final model and flow diagram for GCO [52] is shown in Figure 3. The app screenshots and a video walk-through are included in Multimedia Appendices 1 and 2, respectively.

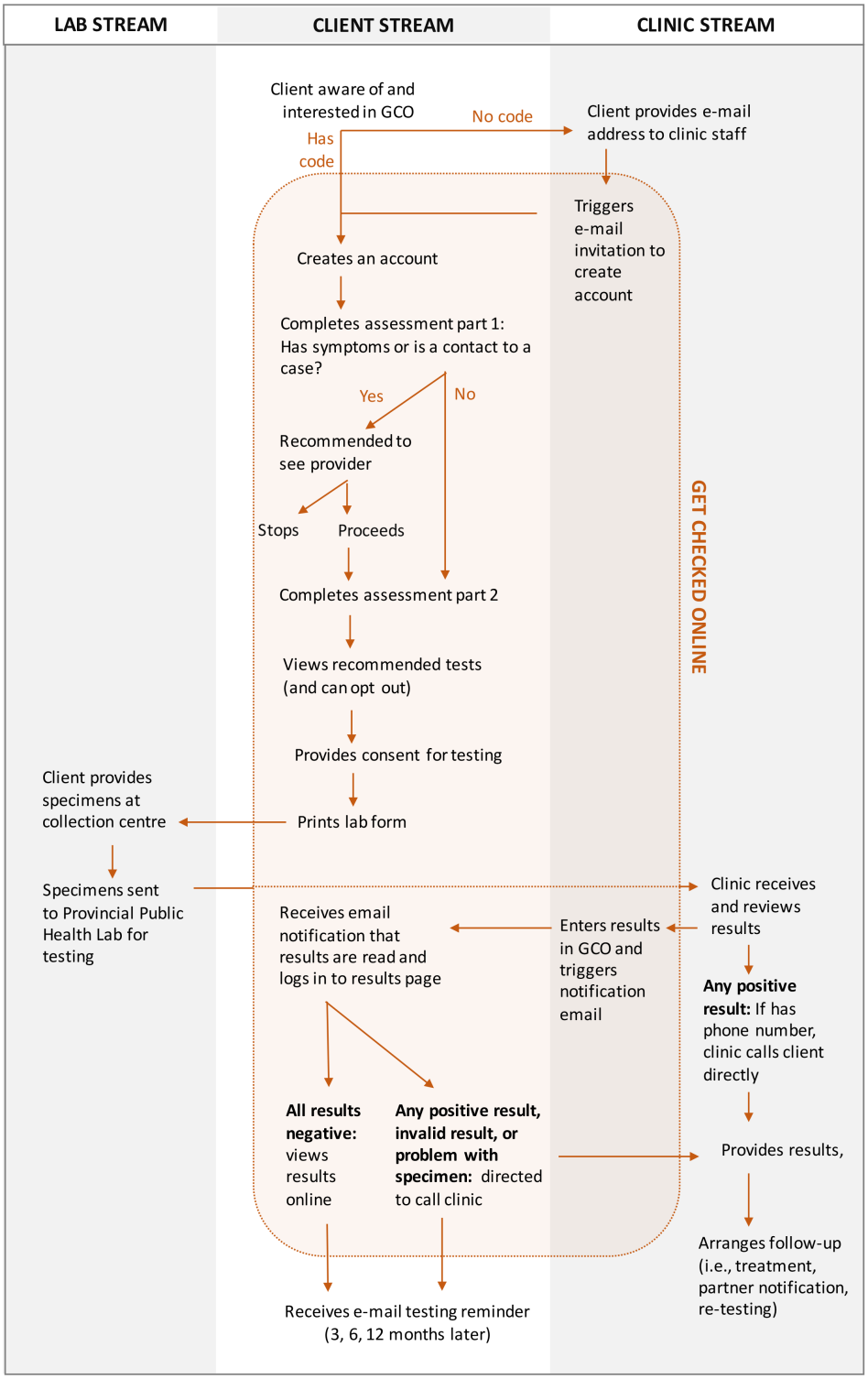
In brief, potential users (clients) of GCO can create an account if they have an access code (included with promotional materials, or provided by the BCCDC STI clinic or a local sexual health care provider) or have provided an email address, which is then used by BCCDC staff to send an invitation to create an account. During the account creation process, the client provides an email address to serve as their login (which is subsequently verified) and chooses a password. Both mandatory (name, date of birth, sex; not verified) and optional information (phone number, first 3 digits of postal code, ethnicity) are collected. Clients are advised to use their real name or initials although without verification pseudonyms are possible, a model consistent with low-threshold clinic-based testing services offered through BCCDC in order to reduce barriers for clients with privacy concerns. Clients are asked to provide consent to be contacted for research purposes, and must indicate their understanding of the terms of use and privacy policy. While there is no minimum age requirement for use of GCO, individuals less than 19 years are defined as children in BC legislation and can consent to their own medical care if capable. All clients indicating an age less than 19 years of age are recommended to seek testing at an STI clinic in order that capacity to provide consent can be assessed. However, as the majority of clients using GCO less than 19 years of age are expected to be capable of providing consent they are not barred from proceeding.

Clients then complete the first part of the assessment, where the questions are used to identify clients who have symptoms or are a contact to someone with an STBBI. These clients are subsequently recommended not to test through GCO but to seek standard clinical STBBI testing as other tests or immediate treatment may be indicated; clients do have the option to acknowledge the recommendation and continue with Web-based testing. The second part of the assessment includes questions used to recommend hepatitis C testing and provide tailored educational messages. Next, the GCO app provides test recommendations and educational messages as described above. Clients can deselect tests if desired, proceed to the consent page to indicate their understanding of key pretest counseling messages, and then print their laboratory test requisition (which is saved for later printing if needed).

Clients present their laboratory test requisitions, on which their name has been replaced with a unique GCO client code, at a private laboratory specimen collection site and provide urine and/or blood specimens. Specimens are shipped to the PHSA Public Health Laboratory for testing, with results reported to the BCCDC STI clinic for appropriate management. All results are entered into the GCO app by clerical staff who then trigger the app to send a notification email to the client that their results are ready to view. If all results are negative, the client can see their results in their GCO account and there is no interaction with clinic staff. If any of the results are invalid (for example, a problem occurred with the specimen), clients will view any

negative test results and see a notification to call the BCCDC clinic to arrange for retesting for the invalid result. If any of the results are positive, the client can see only a message directing them to call the BCCDC clinic for their results; at the same time, if the client has provided a phone number a BCCDC clinic nurse will attempt to contact the client directly. For each client, a testing history is maintained on the app with dates of testing and test types; test results are not retained within GCO after 1 month as a privacy and security precaution. Testing reminders are set for all clients at 3 or 12 months based on the degree of sexual risk reported on the assessment questions; clients can opt out or change these settings.

Figure 3. GetCheckedOnline program model demonstrating interactions between clients, clinicians, laboratories, and the GetCheckedOnline app.



Preparation for Implementation

Preparing for implementation of the GCO service involved numerous activities related to privacy and security, IT support, operational protocols, reporting, communications, and final validation. We collaborated closely with PHSA Privacy, Risk Management, and IT Security teams to conduct a thorough privacy impact assessment and security threat and risk assessment that included testing of the app's security model by an external vendor (penetration testing); recommendations from these assessments were incorporated into the final app. A privacy policy and terms of use specific to the program were developed, along with administrative policies around access control, auditing and data reporting, and all were vetted with PHSA Privacy and IT Security. A new software vendor was contracted to provide ongoing app support in partnership with PHSA IT, and extensive documentation was completed to establish internal IT support around client services, network, hardware, and software maintenance. Clinical procedures for the management of GCO clients were developed in consultation with clinical and clerical team leads, and multiple training sessions were conducted to familiarize staff with procedures and the app itself. A series of reports were developed to routinely monitor testing volumes, uptake of the service and drop-off of clients at different points in the testing process. Promotional materials (ie, sign-up sheets, posters, wallet cards, and brochures) were designed and a communications package was created, including email templates for the launch announcement, sample content for social media, a one-page overview of the program, and frequently asked questions. The last step prior to the official launch of the service was a comprehensive final validation (beta-testing) of the app, specimen collection and transport, specimen testing, and clinical procedures using actual clients; where possible, we used feedback from the testing to improve the overall user experience.

Funding Model

The pilot phase of GCO is fully funded by the PHSA, with costs shared between the BCCDC (costs of program operation, app revision, specimen collection) and the BC Public Health Laboratory (BCPHL) (costs of laboratory testing).

Results

GetCheckedOnline Pilot Phase

GCO [52] went live in September 2014, with 6 participating private laboratory specimen collection sites in Vancouver, BC and is now sustained through ongoing operational funding. During this pilot phase, we promoted GCO to existing BCCDC STI clinic clients and subsequently to MSM in the Vancouver region in April 2015. This pilot phase lasted until December 2015 and an evaluation of this pilot phase is underway (eg, number of accounts created, number of specimens submitted, positivity rates, and treatment outcomes).

How GetCheckedOnline Will be Evaluated

As recommended for the evaluation of eHealth interventions, we will use mixed-methods to evaluate the impact of GCO at individual, population, and health service delivery levels [53,54] (Table 4). Our objectives and outcomes of interest were identified from stakeholder consultations and by reviewing the eHealth implementation literature (eg, acceptability, mitigation of testing barriers, risk behavior, HIV knowledge, treatment and follow-up, uptake, reach). These will be evaluated using 5 methods (Textbox 1) funded through research grants obtained from the Canadian Institutes of Health Research [Gilbert et al, unpublished data 2011 and 2014].

Textbox 1. Five methods to evaluate objectives and outcomes.

Web-based survey of GetCheckedOnline (GCO) and British Columbia Centre for Disease Control (BCCDC) sexually transmitted infection (STI) clinic clients following a Web- or clinic-based testing encounter (baseline) and 3 months later

•To measure acceptability of GCO; identify characteristics of GCO compared with clinic clients; compare baseline and short-term HIV knowledge, and risk behavior.

Web-based surveys and community intercept surveys of men who have sex with men (MSM)

•To measure acceptability of GCO; measure awareness and diffusion of GCO among networks; identify characteristics associated with uptake; assess reach to MSM most at-risk of infection.

Interviews with individuals testing through GCO

•To measure acceptability of GCO; identify if and how GCO mitigates testing barriers.

An administrative data cohort using retrospective and prospective longitudinal testing data for GCO and BCCDC STI clinic clients

•To measure acceptability (repeated use) of GCO; identify differences in testing, treatment and partner notification, test frequency, and infection rates.

Analysis of GCO and BCCDC STI clinic health services data (eg, tests conducted, number of clinic and drop-in visits, estimates of physician and nursing time)

•To determine changes in STI clinic staff configuration, staff tasks, overall clinic capacity, and laboratory testing volumes following GCO implementation.

Table 4. Evaluation matrix showing level of potential impact, objectives, data collection methods, and metrics.

Level of impact	Objective to determine	Data collection method(s)	Outcome measures
Individual			
	The acceptability of GCO[a] (among both clients using the service and prospective clients)	Virtual cohort	Percentage and characteristics of clients who repeat-test
		Web-based client survey	Self-reported satisfaction and willingness to refer a friend
		Web-based community survey	Intention to use GCO (prospective clients)
		Client interviews	Qualitative analysis of comments on experience with GCO
	How GCO mitigates existing barriers to accessing STI[b]/HIV testing	Client interviews	Analysis of self-described factors which facilitate or limit clients' opportunities to access in-clinic or Web-based STI/HIV testing
	If GCO clients have any short-term differences in risk behavior and posttest HIV knowledge in comparison to clinic-based clients receiving traditional in-person pre/posttest counseling	Web-based client survey (0 vs 3 months)	Risk behavior measures; 5-point true/false scale including items related to HIV transmission, risk reduction, testing, and public health follow-up
	If outcomes differ for clients testing positive via GCO (ie, are less likely to access STI treatment, or to be reached by public health for follow-up including partner notification)	Virtual cohort	Percent of those who test positive who access treatment and public health follow-up
Population			
	The diffusion of GCO into priority populations (ie, men who have sex with men in Phase 1)	Web-based community survey	Percent of respondents who have heard of GCO, used GCO, and seen promotional materials
	The client characteristics associated with uptake and nonuptake of GCO	Web-based community survey	Ethnicity, education, income, STI/HIV testing history, sexual risk behaviors, perceptions of GCO, use of other health services and Web-based services
	Whether GCO reaches individuals who are most at-risk of infection	Web-based client survey	Measures of sexual risk behavior
		Web-based community survey	Measures of sexual risk behavior
	Whether GCO clients have higher rates of infection than those testing in-clinic	Virtual cohort	Incidence of infection (HIV, chlamydia, gonorrhea, syphilis)
		Web-based community survey	Percent reporting recent STI or HIV diagnosis
	If GCO results in increased test frequency and earlier diagnosis among individuals most at-risk of infection	Virtual cohort	Percent of clients who repeat-test and intertest intervals (including interval between positive test and last negative test)
Health services delivery			
	What changes in staff configuration and tasks will occur as GCO is integrated with existing clinic sexual health services	Sexual health systems data	Estimates of total/aggregate clerical and clinical staff time spent entering test results into system, seeing asymptomatic clients in-clinic, delivering test results, and following-up with positive cases; number of episodes and estimated clerical time spent on GCO user support
	If the introduction of GCO increases the capacity of existing clinic-based sexual health services		Number of drop-in appointments and turn-aways ; number and types of STI/HIV tests conducted
	The impact on laboratory testing volume as a result of introducing GCO		Number and types of STI/HIV tests conducted

[a]GCO: GetCheckedOnline.

[b]STI: sexually transmitted infection.

Model Changes Following Implementation

We made 2 major changes to the GCO model following implementation, reflecting further refinement based on the findings of the planning and development phases:

In the fall of 2015, we revised the risk assessment questions in tandem with an update of our preliminary HEIA in order to improve their appropriateness for clients of diverse gender identities. We also made revisions to prospectively collect the necessary variables to validate clinical prediction rules (CPR) developed by our team for urine testing for chlamydia and gonorrhea, and blood testing for HIV. These CPR were developed using test results from over 30,000 asymptomatic clients at STI clinics across BC [55,56]. Once these are further validated using prospective GCO data, we aim to include these CPRs prior to promoting GCO outside of our target populations, where our current model for recommending tests may not be appropriate.

In February 2016, we added self-collected rectal and throat swabs for chlamydia and gonorrhea testing. Swabs are recommended for MSM clients if reporting giving oral or receiving anal sex during the assessment step, women if reporting receptive anal sex (as per routine clinical practice). While always intended for future versions of GCO, we accelerated the inclusion of swabs as their absence was flagged as a clinical risk during provider consultations and a potential exacerbation of health inequities for MSM. Clients are given self-collection kits at the private laboratory collection sites when providing urine and/or blood samples, and clients can either self-swab on-site or take home for self-collection and return. Self-collection instruction guides (Multimedia Appendix 3) were developed through reviewing examples found on the Internet with 2 focus groups of potential users, and pilot tested with 12 users who found the guides easy to understand, sensitive to various genders and sexual identities, and conducive to successful self-collection [57].

Discussion

A Unique Opportunity

GCO is the first comprehensive Web-based STBBI testing program in Canada, with few global counterparts, and is integrated with existing sexual health services. It represents a new paradigm for offering testing services that we believe has great potential to reach populations in BC that have high rates of infection and face the greatest barriers to accessing testing. With other health authorities recognizing this potential, and GCO's alignment with recent provincial strategies and funding for expanding HIV testing services in BC [58], planning for scale-up to other regions began in early 2014, with the first specimen collection sites coming on board in March 2016. We have a unique opportunity to comprehensively study the implementation, impact, and transferability of a Web-based health service intervention within the Canadian health care system and across diverse populations and settings in BC. We will be conducting the research necessary to determine if we have successfully achieved our objectives both in Vancouver and in subsequent scale-up, paying particular attention to examining whether GCO improves or exacerbates existing health inequities (ie, whether the rhetoric of eHealth interventions matches the reality of their implementation) [45].

While we did not adopt a specific theoretical framework, our approach to the development of GCO was most consistent with van Gemert-Pijnen and colleagues' [36] principles for a holistic approach to developing eHealth technologies by: using a participatory process with involvement of stakeholders throughout, including potential users; applying continuous evaluation cycles that are iterative, flexible, and dynamic; considering conditions necessary for implementation from the outset; recognizing that GCO will change the organization of health care; use of persuasive design techniques; and use of advanced methods to assess impact. As others have recommended for successful development of eHealth apps, we also believe that a critical factor in the development of GCO was the skill set of our multidisciplinary team, including early establishing of research partnerships [59]. We would also particularly emphasize the iterative, flexible, and dynamic nature of the formative evaluation and work needed to develop GCO, which we have described as a sequential series of discrete steps out of necessity. In reality, these activities were overlapping, interconnected, and mutually reinforcing of our final program model.

Challenges With Developing GetCheckedOnline

An astute reader will have noted that while funded in 2009, GCO was not implemented until 2014, which was longer than we had anticipated. As a complex health system intervention involving multiple sectors, the development of GCO was dependent on the capacity and competing priorities of key stakeholders outside (and beyond the control of) the BCCDC. For example, the PHSA and other health authorities in the greater Vancouver region underwent a reorganization and consolidation of technical and support services during this time period, leading to substantial delays in engagement of stakeholders needed to provide the internal technical support essential to developing a Web-based intervention. Characteristics of GCO were also ground-breaking within PHSA, including automated use of email notifications and allowing patients direct Web-based access to their own personal health information. Developing the policy and technical infrastructure to support these novel aspects of GCO did take time to address, yet this has paved the way for the implementation of other eHealth apps within these agencies. However, institutional barriers remain that prevent the inclusion of features that our formative research indicates are desired by potential users of GCO. Most notably, our requirement for GCO clients to print a laboratory requisition was widely regarded as a barrier to using the service, yet receipt and storage of all laboratory requisitions is a laboratory accreditation requirement. Electronic ordering of laboratory tests is not yet widespread in Canada outside of specific electronic medical record systems such as in hospitals. Our private laboratory partner, which carries out the specimen collection is in the process of establishing electronic ordering of laboratory tests that we anticipate will be in place in the next year. This will permit barcode scanning from a client's smartphone, which we are planning to include in GCO once this is possible.

Implications for Development of eHealth Interventions

Our experience speaks to the challenges of developing and implementing novel, complex eHealth interventions, and adds weight to recommendations to expand technology adoption models to consider the role of broader implementation contexts that both facilitate and challenge the development and uptake of Web-based/digital health services [60,61]. The organizational context is particularly important; for example, in our experience, the commitment of ongoing operational funds, and a health agency environment that seeks to foster innovations in health care, have been critical to the successful implementation of GCO.

It is striking that while developing and advancing eHealth interventions is widely prioritized, there is relatively little practical guidance on their implementation. We hope that our detailed description of the steps taken to plan and develop GCO will be helpful not just to other jurisdictions developing similar Web-based testing programs, but more broadly to developers of similarly complex interventions that are integrated within health care systems.

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Authors' Contributions

All authors contributed to the development of the GetCheckedOnline app and writing of this manuscript. MG, DH and TH conducted the initial review of Web-based testing interventions; MG and TS led the Web-based survey analysis; JS, CC, TH, JF led the interviews and focus groups; AB led the informed consent evaluation; JF led the health equity impact evaluation. MG, DH, TH, and MB documented the development, implementation, and usability process and results. MG, GO, and JS lead the ongoing program evaluation.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Screenshots of the GCO application.

[PDF File (Adobe PDF File), 19MB - resprot_v5i3e186_app1.pdf]

Multimedia Appendix 2

Video walk-through of the GCO application.

[MP4 File (MP4 Video), 145MB - resprot_v5i3e186_app2.mp4]

Multimedia Appendix 3

Self-collection instruction guides for oral and rectal swabs.

[PDF File (Adobe PDF File), 2MB - resprot_v5i3e186_app3.pdf]

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Abbreviations

BC: British Columbia
BCCDC: British Columbia Centre for Disease Control
BCPHL: BC public health laboratory
CCWG: community consultation working group
CIC: clinical integration committee
CPR: clinical prediction rules
GCO: GetCheckedOnline
GWG: GetCheckedOnline Working Group
HEIA: health equity impact assessment
HIV: human immunodeficiency virus
ISC: Internet Services Committee
IT: information technology
MSM: men who have sex with men
PHSA: Provincial Health Services Authority
STBBI: sexually transmitted and blood-borne infections
STI: sexually transmitted infection
TWC: technical working group

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Original Paper

Design and Usability Evaluation of Social Mobile Diabetes Management System in the Gulf Region

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Abstract

Background: The prevalence of diabetes in the Gulf States is one of the highest globally. It is estimated that 20% of the population in the region has been diagnosed with diabetes and according to the International Diabetes Federation (IDF), five of the IDF's "top 10" countries for diabetes prevalence in 2011 and projected for 2030 are in this region. In recent years, there have been an increasing number of clinical studies advocating the use of mobile phone technology for diabetes self-management with improved clinical outcomes. However, there are few studies to date addressing the application of mobile diabetes management in the Gulf region, particularly in the Kingdom of Saudi Arabia (KSA), where there is exponential increase in mobile phone usage and access to social networking.

Objective: The objective of this paper is to present the design and development of a new mobile health system for social behavioral change and management tailored for Saudi patients with diabetes called Saudi Arabia Networking for Aiding Diabetes (SANAD). A usability study for the SANAD system is presented to validate the acceptability of using mobile technologies among patients with diabetes in the KSA and the Gulf region.

Methods: The SANAD system was developed using mobile phone technology with diabetes management and social networking modules. For the usability study the Questionnaire for User Interaction Satisfaction was used to evaluate the usability aspect of the SANAD system. A total of 33 users with type 2 diabetes participated in the study.

Results: The key modules of the SANAD system consist of (1) a mobile diabetes management module; (2) a social networking module; and (3) a cognitive behavioral therapy module for behavioral change issues. The preliminary results of the usability study indicated general acceptance of the patients in using the system with higher usability rating in patients with type 2 diabetes.

Conclusions: We found that the acceptability of the system was high among Saudi patients with diabetes, and ongoing work in this research area is underway to conduct a clinical pilot study in the KSA for patients with type 2 diabetes. The wide deployment of such a system is timely and required in the Gulf region due to the wide use of mobile phones and social networking mediums.

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KEYWORDS

mobile health; mobile diabetes management; social networking for health care; diabetes mellitus; telemedicine; electronic health; Kingdom of Saudi Arabia

Introduction

The global prevalence of diabetes is alarming, with approximately 366 million individuals living with this long-term condition. The prevalence of diabetes in the Gulf States is one of the highest globally; it is estimated that 20% of the population has been diagnosed with diabetes. According to the International Diabetes Federation (IDF), five of the IDF's "top 10" countries for diabetes prevalence in 2011 and of those projected for 2030 are in this region [1].There are different causes of such high prevalence, including social norms behavior, climate, diet, and lack of exercise [2].

The Kingdom of Saudi Arabia (KSA) has the seventh-highest prevalence of diabetes in the world; an estimated 20% of the population has been diagnosed with diabetes, most of the type 2 form [1]. However, the recent economic growth in KSA has significantly affected the living standards of the population, leading to adoption of unhealthy eating habits with limited physical activity [2]. Furthermore, type 2 diabetes mellitus prevalence has been increasing as a result of this lifestyle change among the Saudi population [3]. Managing diabetes in the KSA is a challenging task. Various factors contribute to this chronic disease's prevalence, such as family history, obesity, smoking habits, limited health awareness, social behavioral and culture norms, and health education. As a result, these factors along with coronary artery disease have become a major health burden in the Kingdom. According to the World Health Organization (WHO), it is estimated that noncommunicable diseases will be the principal cause of death in the Kingdom [4].

In recent years, there have been an increasing number of studies on the effectiveness of mobile diabetes management systems globally [5,6]. A recent meta-analysis study indicated the effectiveness of these technologies for both type 1 and type 2 diabetes management and improved glycated hemoglobin (Hb_{A1c}), especially for patients with type 2 diabetes [7].

Similarly, social networking has also become an important medium for exchanging health care information between users and patients in recent years [8]. For example, social sites like PatientsLikeMe aim to create a community Web environment for patients, nurses, and society to provide medical information and education, empower patients to share experiences, explore their medical conditions, symptoms, and routines, and support each other [9]. Other social networking health care sites including CureTogether, MedHelp, and mCare provide different health services supported by their delivery models [10-12].

A recent survey of existing social networks for health care illustrates the influence of social networking on health care outcome models [13]. It classified social network services into three categories: (1) health care social networking; (2) consumer personalized medicine; and (3) quantified self-tracking with four major health care interventions offered to the clients through the social networks including clinical trial access, emotional support and information sharing, quantified self-tacking, and questions and answers with a professional physician.

However, most of these studies are conducted for use in the United States, Europe, and developed countries. Although the Gulf region has one of the highest users globally of mobile phones and social networking sites such as Facebook and Twitter [14], to date there is no study on the use of social networking in the region. A recent review [15] by the authors on the use of mobile diabetes management systems and social networking in the Gulf countries found that only three studies have been published to date [16-18]. A study in Bahrain examined the use of mobile phones among a group of patients with diabetes with improved outcomes in Hb_{A1c} [16]. Another study in Iraq examined the feasibility and acceptability of text messages (short message service, SMS) with improved outcomes in diabetic patients' education [17]. The study in Qatar outlined a system for assisting people with diabetes and managing diabetes through glucose monitoring and diet management that indicated improved satisfaction of diabetic patient users [18]. These few pilot studies indicate that there is an urgent need for further work in the region considering the major challenges of the diabetes epidemic.

Furthermore, no study to date has examined the combination of using social networking and mobile diabetes management tailored specifically for Saudi patients. In this paper, we present the general structure of a mobile diabetes management system tailored for Saudi patients called Saudi Arabia Networking for Aiding Diabetes (SANAD). We also present a usability study of the acceptability of the SANAD system among Saudi patients with diabetes.

Methods

System Design

In order to design a mobile diabetes management system for Saudi patients, we conducted a preliminary study on the perception of managing diabetes mellitus through mobile technologies and social networking in the Kingdom [19]. In this study, a mixed-method design with interviews and a survey were used to gather data. Most of the participants were users aged between 10 and 30 years. The outcome of this preliminary study indicated that the acceptance of Saudi patients for using social networking as a tool for better management of their diabetes is relatively high. The acceptance is especially high in the younger population (10 to 30 years) who prefer to use Saudi social networking mediums for managing their condition. Another important finding was that the preferred social networking functionalities such as Ask a Doctor, messaging, blogs, and video tutorials had the highest percentages of suggested functionalities. Furthermore, we found that the proposed management system should include the following key functional components: (1) a mobile diabetes management component; (2) a social networking component; and (3) a behavioral change component.

The general architecture of the SANAD system is shown in Figure 1. The architecture consists of three functional components: the mobility module, the social networking module, and the behavioral change function based on cognitive behavioral therapy (CBT). The choice of a CBT module is based

on the effectiveness of this approach in diabetes management [20,21].

The building blocks of a general social networking system are shown in Figure 2. These building blocks are relationship control, social graph, actor profiles, social presence, a participation model, website contents and app, and an infrastructure services model. A detailed description of these blocks is given elsewhere [22]. Based on this architecture, we developed the building blocks of the SANAD system (Figure 3), which are described below.

Figure 1. General architecture of the Saudi Arabia Networking for Aiding Diabetes (SANAD) system. CBT: cognitive behavioural therapy; MDM: mobile diabetes management; SN: social networking.

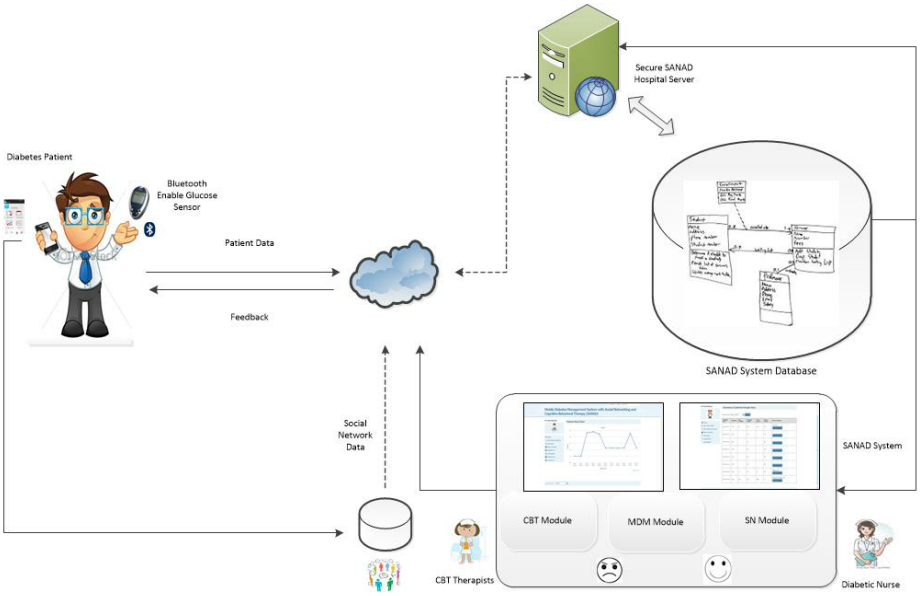


Figure 2. General building blocks of a social networking system.

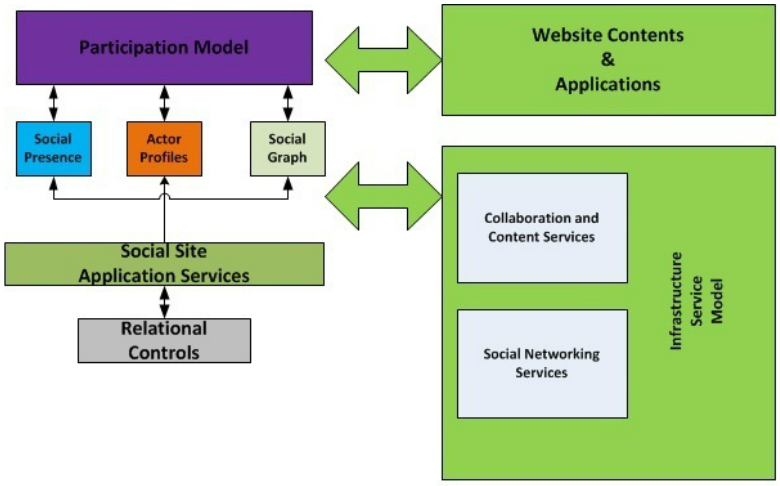
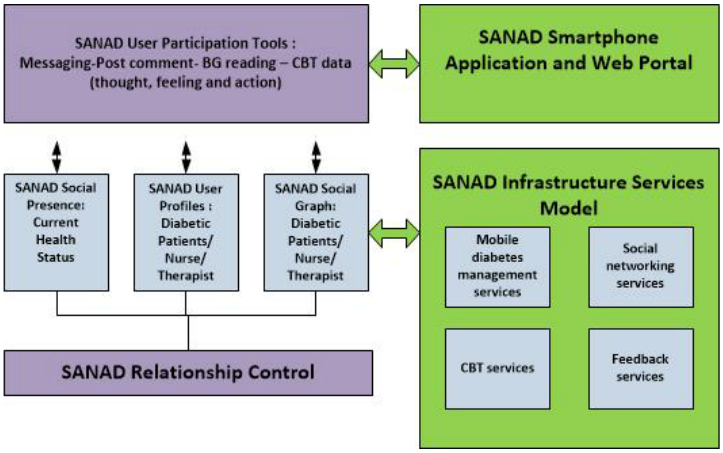


Figure 3. Building blocks of the Saudi Arabia Networking for Aiding Diabetes (SANAD) system. BG: blood glucose; CBT: cognitive behavioral therapy.



Relationship Control

Relationship controls define the relationship types users can create with each other [12,22]. The relationship control in SANAD is based on the friend relationship among patients with diabetes, nurses that treat patients with diabetes, and the CBT therapist.

Social Graph

The social graph theory used in the SANAD system signifies the following relationships: (1) patients with diabetes with patients with diabetes, (2) patients with diabetes with nurses that treat patients with diabetes, and (3) patients with diabetes with the CBT therapist.

User Profiles

User profiles are well known as actor profiles in the general social network. The actor profiles in SANAD are of three types: patients with diabetes, nurses that treat patients with diabetes, and the CBT therapist.

Social Presence

Social presence is a new model in social network frameworks. In earlier social networking, social presence was produced by being connected and available. However, nowadays it is well known as a user's current status, which is a description of a user's activity.

User Participation Tools

Participation tools provide techniques for users to communicate, interact, and participate with other users through instant messaging and message boards. The participation tools of SANAD are messaging between the users, the ability of users to post comments, the ability of patients to insert their reading information, and the ability of users to submit their therapeutic data.

Mobile App and Web Portal

A custom server hypertext preprocessor app is used to support remote log-in. It is also used to review patient data and user settings, and to provide such feedback by the medical staff. In addition to viewing patient data and assessment results, a key feature is allowing patients with diabetes access via the Web rather than mobile use. Patient data was stored on a remote Microsoft SQL secure database server portal. The mobile phone platform is implemented using Android operating system (Google, Mountain View, CA, USA) and the Java Software development kit (Oracle Corporation, USA). The blood glucose sensor (LifeScan, Inc ,OneTouch, USA) using Bluetooth (Polymap Wireless adaptor, Tucson, USA) is also used for transferring the data to the mobile app. GALAXY S III (Samsung, South Korea) is used as the mobile phone, running Android 4.0 to send the clinical data in a real-time to the server portal.

Infrastructure Services Model

In this model, the content and services of the SANAD system are presented as mobile diabetes management, social networking, CBT, and feedback services.

Usability Study

A preliminary evaluation study of the SANAD system was carried out in the Dammam region in the KSA in collaboration with the medical school in the region. The main objective of the study was to investigate the usability aspects of the SANAD system among the Saudi patients with diabetes. A total of 33 patients with type 2 diabetes (17 male, 16 female) participated in the study. Patients were recruited by clinical staff during an office visit or by sending a text message.

Three tasks were designed based on the functional components carried out by the SANAD system. Care was taken to ensure that the tasks were simple and met the purpose of the app. The tasks are described in Textbox 1.

Textbox 1. Tasks designed based on the functional components of the system.

Task
Perception toward the SANAD mobile diabetes management module
• measuring blood glucose level by using the module
• sending it to the the Saudi Arabia Networking for Aiding Diabetes (SANAD) mobile server
Perception toward the SANAD social networking module services
• sending a private message to the nurse or other friend
• watching videos
• searching
• finding a friend
Perception toward the SANAD cognitive behavioral therapy (CBT) module
• submitting their CBT data to the server
• the system displaying the data in chart and tables

The Questionnaire for User Interaction Satisfaction (QUIS) was used for designing the survey questionnaires. QUIS was developed by Shneiderman and is based on an Object-Action Interface (OAI) model [23]. The assessment of the satisfaction of the users is subjective and complex, so QUIS was used because it gauges the users' satisfaction with the software's usability in a standard, reliable, and valid way. QUIS was initially implemented using a 9-point Likert scale rating in a standard paper-and-pencil form. It focuses on the analysis of usability based on overall reaction to the system, screen factors, terminology, system feedback, learning factors, and system capabilities [24]. The QUIS version 7.0 was used and the questionnaire was arranged in a hierarchical format which included a demographic questionnaire and six scales for measuring overall reaction ratings of the system. Each item in the QUIS questionnaire was rated on a scale of 1 to 9, and an additional option of not applicable (N/A) was also provided [25]. The general characteristics of the participants are presented in Table 1.

Table 1. Patient demographics of the usability study (N=33).

General characteristics		Type 2 diabetes, n (%)
Gender		
	Male	17 (48)
	Female	16 (52)
Age group, years		
	18-40	14 (42)
	41-50	18 (45)
	51-65	1 (3)
Level of education		
	Secondary	16 (48)
	Diploma	7 (21)
	University or more	10 (30)
Marital status		
	Married	12 (36)
	Widowed/divorced	12 (36)
	Never married	9 (27)
Diagnosed with diabetes		
	≤5 years	13 (39)
	6-10 years	8 (24)
	11-15 years	5 (15)
	>15 years	7 (21)

Results

The SANAD system consists of two main components. First, the patient end is comprised of the SANAD mobile app. The second is a remote Web portal hosted in a hospital. The mobile app facilitates sending, receiving, and reviewing patient's diabetic data whereas the Web portal app provides framework to the diabetic and the CBT specialists to set the reading schedule, review the patient's statue performance and adherence, and provide a suitable feedback to the patient using text messages. Samples of the app's interfaces of the SANAD system are shown in Figure 4 and samples of the nurse and CBT therapist's portal interfaces are shown in Figure 5. The concept of the SANAD system is based on four modules: the mobile diabetes management module, the social networking module, the CBT module, and the feedback mechanism and messaging box module.

Figure 4. Snapshots of the diabetic patient mobile phone interfaces in the Saudi Arabia Networking for Aiding Diabetes (SANAD) system.

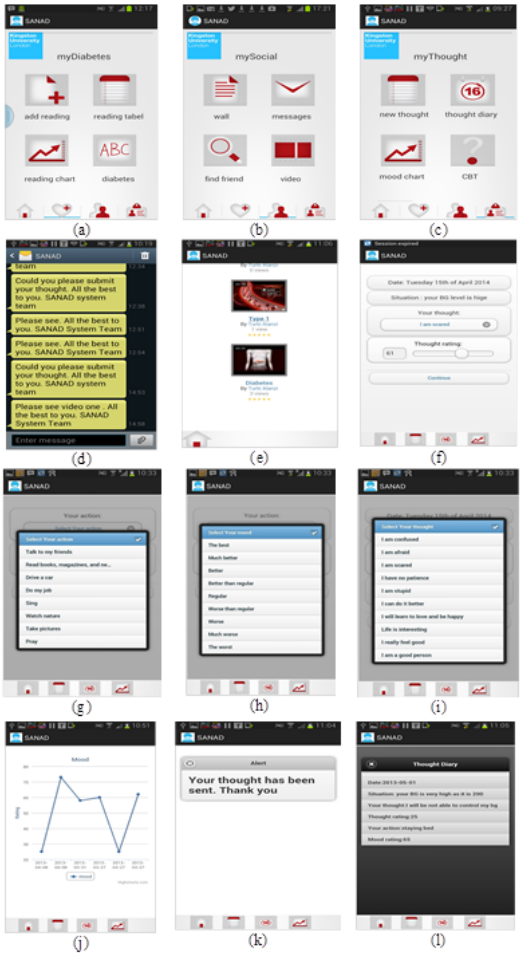
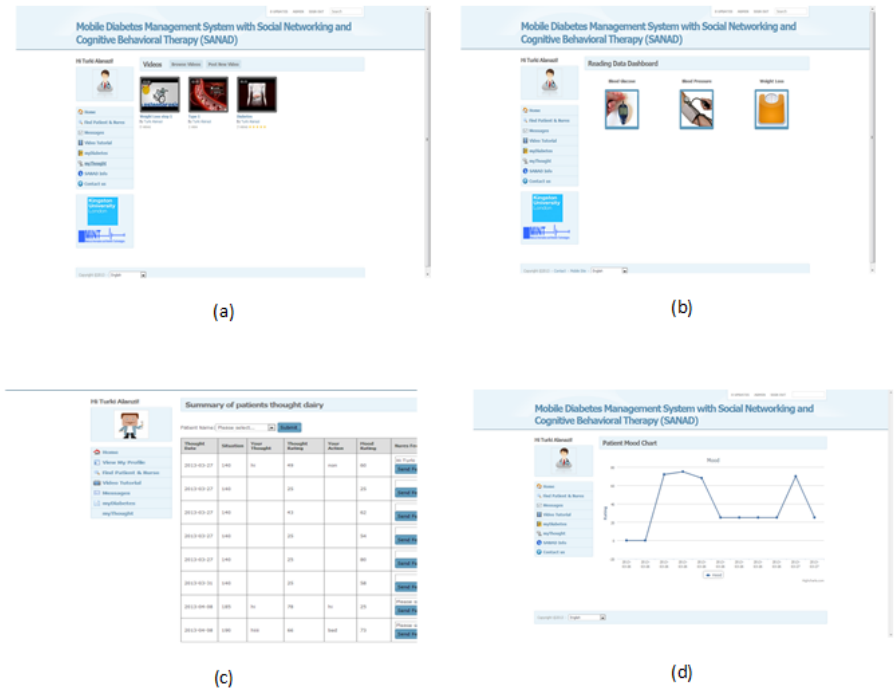


Figure 5. Snapshots of the diabetes nurse portal interface end (top panel) and snapshots of cognitive behavioral therapist's portal interface end (bottom panel) in the Saudi Arabia Networking for Aiding Diabetes (SANAD) system.



Mobile Diabetes Management Module

The key function of the mobile diabetes management module is to provide the mobility component of the SANAD building blocks. This module consists of patient's mobile diabetes component, which assists the patient to send their blood glucose data remotely via their mobile phone and display their blood glucose data graphically (eg, tables and charts). In addition, it consists of a Web portal medical staff end, which assists in scheduling the reading time and date, sending feedback, and observing patient status remotely.

Social Networking Module

The key function of the social networking module is to provide the necessary social information required for the SANAD system. This includes sharing information and providing emotional support among the users. This module consists of a patient's mobile social networking end, which provides a simple mechanism for interactivity between the patients and the clinicians, displays video education tutorials on diabetes, and contains a Web portal medical staff end, which assists them to interact with patients and post video education tutorials and useful information.

The CBT Module

The key function of this module is to provide the behavioral change component of the SANAD building blocks. This module consists of a patient's mobile CBT end, which assists the patient to send their CBT data remotely via the mobile phone and to display their CBT (thoughts, feelings, and actions) in graphic presentations (eg, tables and charts). In addition, it consists of a Web portal CBT therapist's end, which assists in sending feedback and observes the status of the patient's behavioral change remotely. This module aids in CBT intervention by applying a classification algorithm to decide whether to trigger an intervention text message telling the patient to submit CBT data.

Feedback Mechanism and Messaging Box Module

The key function of this module is to provide the necessary gate for the medical staff and the CBT therapist to set and send automated and manual feedback to the patients.

The statistical results of the patient's perceptions of the SANAD system are shown in Table 2. Preliminary results of this study indicate the general acceptance by patients with type 2 diabetes in using this system. Out of the six items, four were rated lower than the mean response (mean 6.40). These items were ease of use, perceived powerfulness, stimulating, and flexibility. The other two items were rated higher than the mean response. Depending on these results, it can be concluded that the system has a positive impact on patients with diabetes, but the overall impression and the satisfaction in using the system received a good response.

Table 2. Overall responses of patients with type 2 diabetes to the six items.

Overall reaction	Mean (SD)
Terrible/wonderful	6.79 (1.24)
Difficult/easy	6.33 (0.92)
Frustrating/satisfying	6.64 (1.32)
Inadequate power/adequate power	6.24 (1.30)
Dull/stimulating	6.39 (1.14)
Rigid/flexible	6.00 (0.97)
Mean	6.40 (N/A)[a]

[a]N/A: not applicable.

Discussion

Principal Findings

Results of this study, the first design and usability evaluation study of a social mobile type 2 diabetes management system in Saudi Arabia, provides evidence that SANAD has a potential positive impact to support the management of individuals living with type 2 diabetes.

We expect the addition of a CBT and social networking module within the diabetes management system will be effective in streamlining the lifestyles of the patients accordingly so that the chances or the risks of having diabetes-associated diseases, such as cardiovascular diseases, can be reduced with improved blood glucose monitoring and maintenance. The social networking module improves the user experience in using the mobile app and can be a source for knowledge sharing and query resolving. Integrating these two systems with the diabetes management module (DMS) results in a study with unique characteristics that could help find novel ways of diabetes management. Experienced medical staff including nurses that treat diabetes, a behavioral therapist, medical practitioners, and dietitians, along with high technology infrastructure that supports effective module integration, are used in the study. The overall reaction of the participants to using the system was good, supporting the use of behavioral therapy and social networking in diabetes management. There are studies that focus on using CBT as an intervention in managing diabetes and other diseases [26-28], but to the best of our knowledge, there is no study that integrates CBT and social networking for diabetes management in the region. As there are no prior studies in the region which used CBT and social networking modules for diabetes management, this study can be a major reference in analyzing the usability of the SANAD system. Though the setting is well-built, the results of the study cannot be generalized to all patients with diabetes.

Limitations

The study is designed and tailored according to the needs and expectations of Saudi patients with diabetes. Therefore the results of the study can be attributed in particular to KSA. As a result, the study may not be applicable in other regions internationally. However, the results can be a source to implement similar studies in the regions which are similar to the Kingdom and where the lifestyles, needs, and expectations of the patients match. Another limitation of the study is that only patients with type 2 diabetes were included. As a result, the study can only be streamlined to patients with type 2 diabetes from the Kingdom and cannot be generalized to all diabetes patients.

The impact of the system will be assessed in a follow-up study. If this study appears to have positive effects, the behavioral intervention along with social networking could be implemented in other care settings in similar regions, for effective mobile diabetes management.

Conclusion and Future Work

Here, we present a new architecture of CBT for a social mobile diabetes management system (SANAD) tailored for the Gulf region and the KSA. This system consists of three modules: (1) a mobile diabetes management module, (2) a social networking module, and (3) a CBT module. In addition, the method used in the usability evaluation of the study of a mobile app was discussed. The outcome of the usability study indicated that the acceptability of the system was high among Saudi patients with diabetes. In particular, patients with type 2 diabetes reported higher satisfaction with the overall impression, satisfaction, being stimulated, ease of use, perceived powerfulness, and flexibility. Ongoing work in this research area is underway to conduct a clinical pilot study in the Kingdom for patients with type 2 diabetes. The wide deployment of such a system is timely and required in the Gulf region due to the wide use of mobile phones and social networking mediums.

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Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavior therapy
Hb $_{A1c}$: glycated hemoglobin
IDF: International Diabetes Federation
KSA: Kingdom of Saudi Arabia
QUIS: Questionnaire for User Interaction Satisfaction
SANAD: Saudi Arabia Networking for Aiding Diabetes
SMS: short message service

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Original Paper

Evaluation of the Swedish Web-Version of Quality of Recovery (SwQoR): Secondary Step in the Development of a Mobile Phone App to Measure Postoperative Recovery

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Abstract

Background: The majority of all surgeries are performed on an outpatient basis (day surgery). The Recovery Assessment by Phone Points (RAPP) app is an app for the Swedish Web-version of Quality of Recovery (SwQoR), developed to assess and follow-up on postoperative recovery after day surgery.

Objectives: The objectives of this study are (1) to estimate the extent to which the paper and app versions of the SwQoR provide equivalent values; (2) to contribute evidence as to the feasibility and acceptability of a mobile phone Web-based app for measuring postoperative recovery after day surgery and enabling contact with a nurse; and (3) to contribute evidence as to the content validity of the SwQoR.

Methods: Equivalence between the paper and app versions of the SwQoR was measured using a randomized crossover design, in which participants used both the paper and app version. Feasibility and acceptability was evaluated by a questionnaire containing 16 questions regarding the value of the app for follow-up care after day surgery. Content validity evaluation was based on responses by day surgery patients and the staff of the day surgery department.

Results: A total of 69 participants completed the evaluation of equivalence between the paper and app versions of the SwQoR. The intraclass correlation coefficient (ICC) for the SwQoR was .89 (95% CI 0.83-0.93) and .13 to .90 for the items. Of the participants, 63 continued testing the app after discharge and completed the follow-up questionnaire. The median score was 69 (inter-quartile range, IQR 66-73), indicating a positive attitude toward using an app for follow-up after day surgery. A total of 18 patients and 12 staff members participated in the content validity evaluation. The item-level content validity index (I-CVI) for the staff group was in the 0.64 to 1.0 range, with a scale-level content validity index (S-CVI) of 0.88. For the patient group, I-CVI was in the range 0.30 to 0.92 and S-CVI was 0.67. The content validity evaluation of the SwQoR, together with three new items, led to a reduction from 34 to 24 items.

Conclusions: Day surgery patients had positive attitudes toward using the app for follow-up after surgery, and stated a preference for using the app again if they were admitted for a future day surgery procedure. Equivalence between the app and paper version of the SwQoR was found, but at the item level, the ICC was less than .7 for 9 items. In the content validity evaluation of the SwQoR, staff found more items relevant than the patients, and no items found relevant by either staff or patients were excluded when revising the SwQoR.

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KEYWORDS

mHealth; ambulatory surgical procedures; postoperative period; mobile phones

Introduction

Day surgery (outpatient surgery) is an expanding and well-established practice in the United States and in many European countries [1-3]. In the United States and United Kingdom, day surgery accounts for 70% to 75% of all elective surgical procedures [2,3]. Similar trends are seen in Sweden where National statistics show that the majority of surgical procedures are performed in day surgery settings (approximately two million per year), with no age restrictions for day surgery treatments [1]. Day surgery is usually defined as surgery performed on a patient who is admitted and discharged from the hospital on the same day, but can also include surgical procedures where the patient is discharged within 24 hours of the surgery [3]. Patients may experience several symptoms after surgery, such as pain, nausea, vomiting, dizziness, fatigue [4], sore throat, back pain, headache, urinary retention, coldness/shivering [5], and postoperative cognitive dysfunction [6]. After discharge from day surgery, patients are expected to take care of their own recovery by themselves or with relatives [7,8]. Many patients feel that the care given while in the hospital is very good, but feel a lack of professional support after discharge. This includes not knowing how to access help and support, and not getting the help that is needed and expected. Since the majority of day-surgical patients are sent home within the same day, it is important to empower them and their relatives to manage the postoperative recovery [8].

The access to reliable and validated instruments to measure and evaluate the quality of postoperative recovery is important in both research and clinical practice. Furthermore, an assessment of recovery can lead to reduced readmissions to the hospital after day surgery [9]. The Swedish version of Quality of Recovery has recently been developed as a Web-based version; the Swedish Web-version of Quality of Recovery (SwQoR), and it has been used to create a Web-based mobile phone app called Recovery Assessment by Phone Points (RAPP) [10]. RAPP assesses postoperative recovery and is used for follow-up after day surgery; however, there have been no studies examining the content validity of the items in the SwQoR or the feasibility of an app in this context. The objectives of this study are (1) to estimate the extent to which the paper and app versions of the SwQoR provide equivalent values; (2) to contribute evidence as to the feasibility and acceptability of a mobile phone Web-based app for measuring postoperative recovery after day surgery and enabling contact with a nurse; and (3) to contribute evidence as to the content validity of the SwQoR.

Methods

The first phase of this study was cross-sectional to estimate equivalency of the two versions of the SwQoR; for this estimate the order of the versions were randomized. The second phase used a prospective design. The study was approved by the regional ethical review board in Uppsala, Sweden (2014/456).

Recruitment

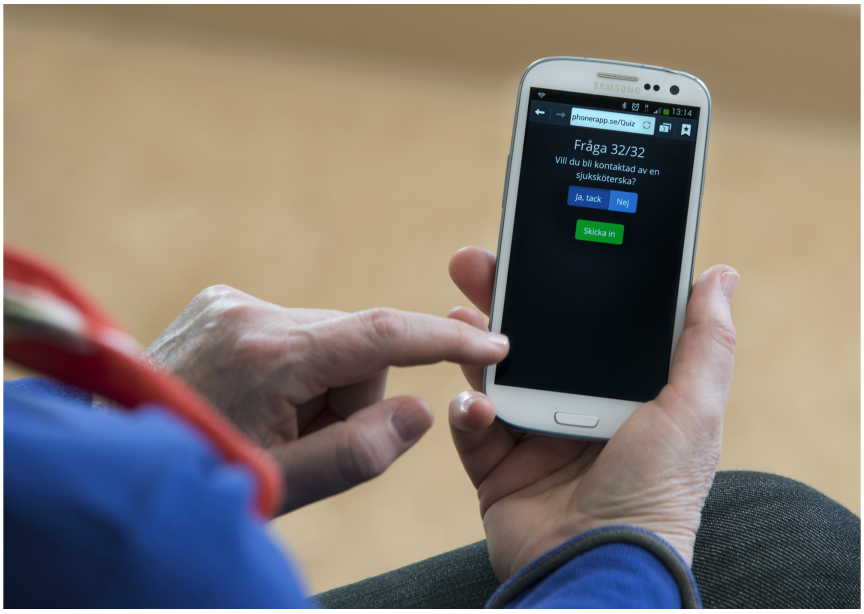
The study was carried out from January to May, 2015. A total of 70 participants were recruited consecutively in two day surgery settings in Sweden. The inclusion criteria were that patients must be adults over 17 years of age, be admitted for day surgery, be able to understand the Swedish language both in speech and in writing, and undergo general anesthesia. The exclusion criterion was that the patient does not having access to a mobile phone with Internet access and a Web browser (smartphone).

For evaluating the content validity of the SwQoR, 18 patients participating in the study and 12 staff members were recruited. The staff group worked in the day surgery departments participating in this study and included 4 anesthesiologists, 4 surgeons, and 4 nurses.

Mobile Phone App

RAPP is a Web-based app that is suitable for all mobile phone models. The participants' own mobile phones were used for this study, following the principle of bring your own device (BYOD) [11]. The mobile phone app contained the 31 items in SwQoR, which are answered using an 11-point numeric visual analog scale (VAS). On this scale, 0 represents "none of the time" and 10 "all of the time". In the app, only one item at a time is visible on the screen, and after the item is answered, the next item automatically appears. After an item is answered, it is not possible to go back to the previous item to review or change the answer. Every day that the patient answered the SwQoR items in the app, the final question was always, "Do you want to be contacted by a nurse?" The patient has to answer "Yes" or "No" to this question [10] (Figure 1).

Figure 1. The final question in the app ”Do you want to be contacted by a nurse?”. To be answered with ”Yes” or ”No”.



Procedure

When making the appointment for their operation, preoperative patients were provided with written information about the study and were requested to bring their mobile phone to the day surgery department on the day of surgery. At admission, the participants were verbally informed about the aim of the study, and those who agreed to participate provided informed consent. Both preoperatively and prior to discharge from the hospital, the participants were thoroughly trained and informed about the app's functionalities and navigation, and they learned how to document their postoperative recovery. Inclusion, information, and follow-up were conducted by one member of the research team (KD). If the question “Do you want to be contacted by a nurse?” was ever answered with “Yes” by a patient, an immediate email was sent with the participant's study code to one member of the research group who had access to the code set. This research team member then contacted a nurse at the day surgery department where the surgery was performed, and the nurse contacted the participant. In one of the day surgery settings, all the requested contact calls were conducted by one specific nurse, and in the other setting, the nurse in charge of all incoming phone calls that day made contact with the patient.

Equivalence Between the App and Paper Version of the SwQoR

To measure the equivalence between the app and paper versions of the SwQoR, participants were randomized into one of the following two conditions for answering its 31 items: (1) a paper questionnaire followed by the app questionnaire, or (2) the app questionnaire followed by the paper questionnaire. In both cases, 30 minutes elapsed between the app and paper measurements for both groups. This interval was guided by an earlier study conducted by Gower et al [12], which compared answers from the Quality of Recovery (QoR) questionnaire between a self-administered and a staff-administered survey. Here, the randomization was accomplished using sealed envelopes in a random order. The randomization was not blinded; both the participants and the researcher had knowledge of the condition assignment for each participant. From 2 to 5 hours after surgery, when the patient was ready for discharge, the app was installed on the participants' own mobile phone. Then the participants responded to the SwQoR questionnaire in the order according to the randomization.

After completing the first version of SwQoR, the participants were not able to see their previous answers when they responded in the second round.

Evaluating Feasibility and Acceptability

All included participants were asked to use the RAPP (answer the 31 items in the SwQoR, as well as the final question “Do you want to be contacted by a nurse?”) each day for 7 days after discharge. One member of the research team (KD) was always available during the study period (both by phone and by email) if the participants had any problems using the app. On the 7th day, a follow-up phone call was made by a member of the research team (KD), who used a questionnaire to ask the participants for feedback on using a mobile phone app to assess their postoperative recovery. The follow-up questionnaire was designed for this study and guided by a similar questionnaire used by Ainsworth et al [13] to compare a mobile phone app with text messaging to assess mental illness. The follow-up questionnaire included 16 questions, of which 11 statements were rated from 1 (“Strongly agree”) to 7 (“Strongly disagree”). Examples of the statements were: “Answering the questions took a lot of time”, “I would like to avoid answering the questions”, and “This type of systematic follow-up helped me and would help other patients in the same situation” . If the participants requested contact by a nurse via the app, the interviewer asked about the reason for the contact. All participants were also asked about how they experienced the opportunity to get in contact with a nurse via the app. Overall comments regarding the app were obtained, as well as the participants' opinions about how many days it would be useful to answer the questions in the app during the postoperative period. Finally, the participants were asked if there were any

questions that were not asked in the SwQoR that they thought should be included.

Questions that were suggested as missing yet relevant for postoperative recovery were included in the content validity review described below.

Content Validity of the SwQoR

To assess the content validity of the SwQoR used after a day surgery, staff and patients evaluated the SwQoR together with the items suggested by the participants as missing in the follow-up. The staff members and patients rated the items regarding intelligibility and relevance on a 4-point scale with 1 representing *not relevant*, 2 *somewhat relevant*, 3 *quite relevant*, and 4 *highly relevant*. The content validity assessment was conducted with pen and paper. The patients performed the content validity assessment 1 to 2 weeks postoperatively (ie, after the testing of the app was completed).

Confidentiality and Security

Each participant was assigned a study code and no personal data, such as social security number, name, age, gender or telephone number were stored in the app. Only one member of the research team had access to the code set and could identify who was answering the app. The paper questionnaires were also coded. The codes were stored separately from the questionnaires. Data transmission between the mobile phone and the server used for the test occurred via the mobile network General Packet Radio Service (GPRS), and the data were stored in a secure server that required a login and password to access the answers from the app.

Statistical Analysis

The equivalence testing between the paper and app versions was analyzed using the intraclass correlation coefficient (ICC) (one-way, single measures). An ICC value of .7 or above was considered acceptable [14]. Item-by-item differences between the paper and app versions were compared using Wilcoxon´s signed rank test, and the null hypothesis was rejected if the two-tailed *P* value was less than .01. Internal consistency was estimated by Cronbach's alpha, where .90 was considered a minimum value for clinical applications [15]. Results from the follow-up questionnaire were presented as descriptive statistics and were expressed as median, inter-quartile range (IQR), and min-max. The content validity of the SwQoR was presented as frequencies and the content validity index. The item-level content validity index (I-CVI) (ie, the number of participants who rated the item either 3 or 4), was calculated. It has been suggested that I-CVI should be at least 0.78 (with more than 6 participants) to indicate good content validity, and the scale-level content validity index (S-CVI) (average of all I-CVI) should be 0.9 or higher [16]. SPSS statistics version 22 (SPSS Inc., Chicago, IL, USA) for Windows was used for the statistical analyses.

Power

To our knowledge, no previous studies have compared paper and digital/electronic postoperative questionnaires. Thus, the number of participants for this study was guided by two earlier studies in other contexts that compared paper and electronic questionnaires. Salaffi et al [17] included 55 adult participants with axial spondyloarthritis and compared their answers on a paper-based patient reported outcome (PRO) questionnaire to answers using a touch screen tablet. Furthermore, Bushnell and colleagues [18] performed a similar comparison with 72 adult participants suffering from irritable bowel syndrome. In both studies, equivalence was shown between the two measurement formats; based on these results, the present study included 70 participants.

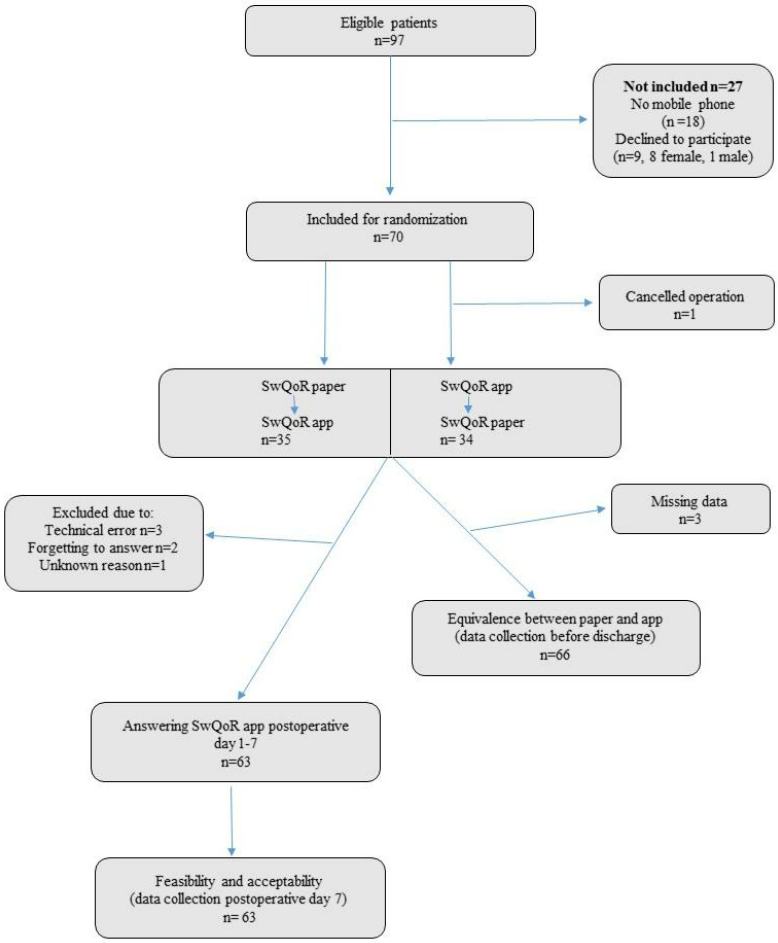
Results

Surgery was canceled for one of the 70 included participants. The characteristics of the remaining 69 patients are presented in Table 1. All participants started to answer the SwQoR according to the order determined by the randomization (ie, app or paper version first). Two participants could not submit the app answers due to technical problems (inability to connect to the network or log in). One participant misunderstood how to fill in the app version of the SwQoR (reporting opposite answers than in the paper version, not understanding that the scale was intact when items shifted from positive to negative) and was excluded from the equivalence testing between the app and paper version of the SwQoR. The technical issues and misunderstanding were solved and all three participants were then able to use the app from postoperative day one and thus contribute to the feasibility and acceptability testing of the app. In addition, 6 participants did not complete the feasibility and acceptability evaluation; 3 due to technical error, 2 for forgetting to answer, and 1 for an unknown reason, giving a total of 63 participants (Figure 2).

Table 1. Patient characteristics (N=69).

Characteristics	n (%)
Sex	
Men	41 (59)
Women	28 (41)
Age, mean (SD)	50 (15)
Surgery type	
General	33 (48)
Orthopedic	26 (38)
Gynecology	4 (6)
Hand	3 (4)
Ear, nose, throat	3 (4)

Figure 2. Flowchart describing the recruitment of participants and data collection.



Equivalence Between the App and Paper Versions of SwQoR

The agreement between the app and paper versions is presented in Table 2. The ICC for the total scale was .89 (95% CI 0.83-0.93) and it was in the range .13 to .90 for the items. The differences between the app and paper versions of the items in the SwQoR were not statistically significant except for three items (Table 2). Cronbach´s alpha was .91 for the app version and .91 for the paper version.

Table 2. Agreement between the app and paper versions of the SwQoR (N=66).

Category	Paper median[a] (IQR)	App median (IQR)	*P* value[b]	ICC (95% CI)
Able to breathe easy	10 (9.75-10)	10 (9.75-10)	.25	.81 (0.71-0.88)
Sleeping well	10 (8-10)	10 (8-10)	.28	.89 (0.82-0.93)
Being able to enjoy food	10 (8-10)	10 (8-10)	.12	.80 (0.69-0.87)
Feeling rested	9 (7-10)	8 (5-10)	.008	.80 (0.67-0.87)
Having a general feeling of well-being	9 (8-10)	9 (6-10)	.03	.73 (0.59-0.83)
Feeling in control	9 (8-10)	9 (7-10)	.75	.82 (0.72-0.88)
Feeling relaxed	9 (8-10)	9 (7-10)	.14	.77 (0.65-0.85)
Speaking normally	10 (9-10)	10 (8-10)	.013	.71 (0.57-0.81)
Able to look after personal hygiene	10 (9-10)	10 (8-10)	.63	.68 (0.53-0.80)
Able to write as usual	10 (10-10)	10 (9-10)	.04	.86 (0.78-0.91)
Able to return to work or usual duties about the home	5 (1-10)	5 (2-9)	.82	.90 (0.84-0.94)
Nausea and/or vomiting	0 (0-3)	0 (0-2.75)	.06	.89 (0.82-0.93)
Feeling restless	0 (0-1)	0.5 (0-4)	.001	.49 (0.28-0.66)
Shivering or twitching	0 (0-0)	0 (0-1)	.003	.36 (0.12-0.55)
Feeling too cold	0 (0-3)	1 (0-3)	.20	.76 (0.64-0.85)
Dizziness	1 (0-4.75)	1.5 (0-5)	.23	.61 (0.43-0.75)
Pain in the surgical wound	2.5 (0.25-6.75)	3 (0-7)	.27	.72 (0.57-0.82)
Anxiety	0 (0-2)	0 (0-2)	.87	.66 (0.50-0.78)
Depressed	0 (0-1)	0 (0-1)	.16	.80 (0.69-0.87)
Feeling lonely	0 (0-0)	0 (0-1)	.03	.68 (0.53-0.79)
Difficulties getting to sleep	0 (0-1)	0 (0-1.25)	.82	.64 (0.48-0.77)
Nightmares	0 (0-0)	0 (0-0)	.02	.87 (0.80-0.92)
Headache	0 (0-2)	0 (0-2)	.39	.81 (0.71-0.88)
Muscle pain	0 (0-2)	0 (0-2)	.67	.74 (0.61-0.83)
Back pain	0 (0-0)	0 (0-1)	.07	.83 (0.74-0.89)
Sore throat	0 (0-1)	0 (0-2)	.02	.79 (0.68-0.87)
Sore mouth	0 (0-0)	0 (0-0.25)	.05	.78 (0.66-0.86)
Difficulties concentrating	0 (0-2)	0 (0-2)	.22	.78 (0.66-0.86)
Trouble urinating	0 (0-0)	0 (0-0)	.37	.73 (0.59-0.83)
Diarrhea	0 (0-0)	0 (0-0)	.07	.30 (0.06-0.51)
Feeling constipated	0 (0-0)	0 (0-0)	.03	0.13 (-0.12-0.36)

[a]0= none of the time, 10=all of the time.

[b]Wilcoxon signed ranks test.

Feasibility and Acceptability

The RAPP was answered over a mean of 5 days (min 1, max 7). When asked about reasons for not answering the RAPP all 7 days, 8 participants reported not remembering to answer, 5 reported technical issues such as the app logging out or problems with the network, and 2 were re-admitted to the hospital. Those participants who forgot to answer declared that they wanted a daily reminder.

Results from the follow-up questionnaire showed that the participants had a positive attitude toward using the app, felt comfortable using the technology, and took a reasonable amount of time to answer the items in the app (Table 3). On average, the participants considered that 9 days (min 3, max 60) would be acceptable for measuring postoperative recovery after day surgery via an app. They also expressed that the items should be either all positive or all negative to make it easier to answer on the numeric VAS. This would allow the good/bad rating to be on the same side of the scale for all items, thus decreasing the risk of answering falsely.

Table 3. Results from the follow-up questionnaire, questions 1 to 11 (N=63).

Question	Median[a]	IQR	Min, max
I felt familiar with using this type of technology	1	1-1	1, 3
I would like to use this type of postoperative follow-up again if undergoing surgery	1	1-1	1, 4
I think other people would find the software tool easy to use	2	1-3	1, 5
This type of systematic follow-up helped me and would help other patients in the same situation	1	1-2	1, 4
Answering the questions made me feel better	5	3-7	1, 7
It was difficult to answer the questions	7	7-7	2, 7
I would like to avoid answering the questions	7	7-7	2, 7
Answering the questions took a lot of time	7	7-7	4, 7
It was difficult to keep track of what the questions were asking	7	6-7	4, 7
It was inconvenient to answer the questions using my smartphone	7	7-7	2, 7
Answering the questions made me feel worse	7	7-7	1, 7
Total score[b] (positive items reversed)	69	66-73	45, 77

[a]1= strongly agree, 7=strongly disagree.

[b]Minimum possible score 11, maximum possible score 77.

The request to be contacted by a nurse via the app was used 15 times (3.4%, 15/441) in relation to the total number of chances to request contact (441 instances with 63 participants using the app for 7 days each). The reasons for the contact were the following: (1) questions concerning the surgical wound regarding the dressing, stitches, swelling, etc (44%, 7/16), (2) pain and/or pain management (19%, 3/16), (3) general information (13%, 2/16), (4) constipation (13%, 2/16), (5) request for a medical certificate (6%, 1/16), and (6) nausea (6%, 1/16). The opportunity to get in contact with a nurse via the app provided a sense of security and was appreciated by all except one of the participants, who wanted to use the telephone for initiating contact instead of the app. Participants (25%, 16/63) also expressed that it is typically difficult to contact a caregiver and that this opportunity provided a simple solution for that problem. Three additional items were suggested by the participants: fever, reddened surgical wound, and swollen surgical wound.

Content Validity of the SwQoR

In total, 34 items were included when evaluating content validity (ie, the original 31 items and 3 additional items). Five surveys from the patients were incomplete, 13 (72%, 13/18) were included in this analysis. Results of the content validity are presented in Multimedia Appendix 1 with I-CVI and S-CVI. The I-CVI values for the staff group were in the range 0.64 to 1.0 (S-CVI 0.88), and the I-CVI values for the patient group were in the range 0.30 to 0.92 (S-CVI 0.67). The staff group rated all items higher than the patient group ratings.

Revising Items in the SwQoR

An I-CVI rating less than 0.78 by both patient and staff led to the removal of the following 7 items in the SwQoR: (1) able to enjoy food, (2) able to write, (3) feeling restless, (4) shaking or twitching, (5) feeling too cold, (6) feeling alone, and (7) backache. When calculating the S-CVI after removing these 7 items, the S-CVI was 0.94 for staff and 0.72 for patients. Four related items that were considered by patients to be very similar (had a good sleep, feel rested, had difficulty falling asleep, had bad dreams) were merged into one item: sleeping difficulties. Thus, guided by the results of the CVI and the feedback from the patients, the 34 items were reduced to 24 (Table 4).

Table 4. Revision of items in SwQoR.

Revision	SwQoR 31	SwQoR 24
Merged into one item	Sleeping well	Had sleeping difficulties
	Nightmares	
	Difficulties getting to sleep	
	Feeling rested	
Not changed	Able to breathe easy	Able to breathe easy
	Having a general feeling of well-being	Having a general feeling of well-being
	Feeling in control	Feeling in control
	Feeling relaxed	Feeling relaxed
	Speaking normally	Speaking normally
	Able to look after personal hygiene	Able to look after personal hygiene
	Able to return to work or usual duties about the home	Able to return to work or usual duties about the home
	Nausea and/or vomiting	Nausea and/or vomiting
	Dizziness	Dizziness
	Pain in the surgical wound	Pain in the surgical wound
	Anxiety	Anxiety
	Depressed	Depressed
	Headache	Headache
	Muscle pain	Muscle pain
	Sore throat	Sore throat
	Sore mouth	Sore mouth
	Difficulties concentrating	Difficulties concentrating
	Trouble urinating	Trouble urinating
	Feeling constipated	Feeling constipated
	Diarrhea	Diarrhea
Included after content validity assessment	N/A	Reddened surgical wound
		Fever
		Swollen surgical wound
Excluded after content validity assessment	Feeling restless	N/A
	Shivering or twitching	
	Feeling too cold	
	Being able to enjoy food	
	Able to write as usual	
	Back pain	
	Feeling lonely	

Discussion

Principal Findings

The present study shows agreement between the paper and app versions of the SwQoR, but on an item level in the SwQoR, the ICC was less than 0.7 for 9 items. The participants were very positive toward using the app for a follow-up survey after undergoing day surgery, did not find it to take too long to fill in, and were willing to use this follow-up method if admitted for a future day surgery. The content validity showed that more items were found to be relevant by the staff group compared to the patient group.

When measuring equivalence between the paper and app version of the SwQoR, we used parametric statistics even though the SwQoR collects ordinal level data. This allows results from the study to be compared with results from previous studies on the

QoR instrument [12,19-21]. Electronically assessed PROs have been shown to be at least equivalent to those from a paper assessment, but it was suggested that for every PRO converted from paper to digital format, the equivalence should be measured [22]. In this study, the ICC between the paper and app version of the SwQoR scale was excellent (ICC .89). This is similar to earlier results that reported test-retest values for QoR with ICC values of .92 [21] and .99 [20], a Spearman's correlation coefficient of .89 [23], and ICC .86 when measuring equivalence in patient- versus investigator-administered QoR 40 [12]. At the item level, however, the ICC was less than .7 for 9 items, and the difference was significant for 3 items. This is the first time that the ICC for each item is being presented regarding the QoR instrument, so there is no guidance from previous studies. One reason for the low ICC for some items could be that the app permits someone to accidentally answer with the default value before getting the chance to select a different value. Selecting a value is accomplished by moving a dot on the numeric VAS, and the dot is stationed in the center (at a value of 5) for every new item. However, the app allows a user to push the answer button without moving the dot, and this could have led to falsely reported values. Further, a low ICC was also noted in the items following after the items shifted from positive to negative (ie, a positive item being "Able to look after personal hygiene", and negative item being "Feeling restless"). This change was visually clearer in the paper version of SwQoR, since in the app only one question at a time is visible on the screen. The participants also expressed that it was hard to follow when the direction of the question shifted from positive to negative (ie, a positive answer is sometimes indicated on the right side of the scale and sometimes on the left side). Furthermore, it was not possible to go back and change prior answers without starting from the beginning. Some patients, after answering wrongly, would start again from the beginning to report their answers, but it was expressed that this was cumbersome and time-consuming. Three of the items with ICC less than .7 were excluded after the content validity evaluation. This indicates that changes in the layout of the items in the app may result in greater agreement on the item level than that achieved in this study.

In our study, both the app and paper version of the SwQoR showed excellent internal consistency (Cronbach's alpha .91 and .91, respectively), which is a similar result to previous studies regarding the QoR with Cronbach's alpha values of .93 [21], .95 [24], .93 [25], and .85 [20].

To our knowledge, there has been only one previous study that tested an app for follow-up after day surgery. Semple at al [26] followed orthopedic and breast reconstruction patients admitted for day surgery who participated in postoperative follow-up via an app. Of the participants, 87% reported that the overall experience using the app was excellent and they were willing to use the same technology if undergoing surgery again [26]. This is similar to the results in our study, where the participants found the app easy to use, thought that the systematic follow-up was helpful in the postoperative period, and wanted to use the app for follow-up after future day surgeries.

Similar results were also reported in a study by Stomberg et al [27] assessing pain for one week postoperatively via a paper-based questionnaire or a mobile phone app. Overall, the participants were willing to use the mobile phone assessment again. Further, the participants in our study wanted to use the app on average 9 days postoperatively (ie, longer than the duration requested in the study). Electronic questionnaires are described to be a user-friendly method [28] and preferred by many patients. They also result in less missing data compared to data collected by conventional pen-and-paper questionnaires [27]. In our study, the participants expressed that the ability to get in contact with a nurse via the app was one of its most valuable features. Participants expressed that, otherwise, it was difficult to get in contact with a caregiver due to not knowing who to call, what number to use, or what time to call. The contact function in the app was considered an easy solution to this problem. Further, participants expressed that the opportunity to get in contact with a nurse made them feel secure. This was also described in a study by Berg et al [29], in which patients felt more secure when there was an easy way of getting in contact with the caregiver by telephone. The results in the present study support the hypothesis and aim that the RAPP would contribute to both "a feeling of being cared for" and "being easy to understand for patients in the health care system", which are described by Jaensson et al [10].

The principle of BYOD was used in this study, which resulted in excluding 18 otherwise eligible patients. This could of course have affected the results regarding feasibility and acceptability, since it would be natural that a person with access to a mobile phone would have a more positive attitude toward using mobile apps. However, the number of mobile phone users is increasing and will most likely continue to increase in coming years. Further, a BYOD-approach eliminates the cost of providing tablets or mobile phones (smartphones) in the health care system and in the study [11]. Other advantages are that patients are most familiar with their own mobile phones and will be more likely to have their own devices available most of the time [30].

In the content validity evaluation in this study, the analyses for staff and patients were conducted separately as these two groups utilize the SwQoR assessment from different points of view. Staff members in the day surgery department assess postoperative recovery to follow-up on, evaluate, and improve anesthetic and postoperative care. Patients personally experience the postoperative recovery and thus use the SwQoR to report on that recovery. In the evaluation of content validity, staff rated the items higher than the patients. Only for 9 items was I-CVI greater than 0.78 in the patient group, whereas I-CVI was greater than 0.78 for 27 items in the staff group. The rank order of the items was similar in both the patient and staff groups, as the patients just tended to consider items to be less relevant than the staff in this study. In contrast to our results, Myles at al [31] found that the staff tended to rate the relevance of the items lower than the patients and their relatives. However, in the Myles study, the items were rated by inpatients and their relatives. In 50% of the cases, the ratings were made preoperatively [31]. In our study, patients performed the content validity assessment postoperatively and after testing the app for 7 days. This would probably lead to items not being considered relevant in the content validity testing if patients did not experience the symptoms as burdensome in their postoperative

period. Macario et al [32,33] described both differences and similarities between patients and anesthesiologists when rating most undesirable anesthesia outcomes (from the patient's point of view). The results also showed that anesthesiologists considered most of the complications due to anesthesia important to avoid [33], which is similar to the findings from our study, as the staff considered most conditions important enough for a follow-up.

When revising the SwQoR, the decision was made to retain any item with I-CVI greater than 0.78 in either the patient or the staff group, since that item was considered relevant for the perspectives and contexts of each group. Revision of the QoR was previously described by Stark et al [20] in order to improve its clinical acceptability and feasibility and to make it more useful in clinical practice and research. No content validity assessment was reported by Stark et al [20]; their revision was guided by literature studies and consultation with experienced staff, resulting in the 15 item QoR15.

The items in the QoR have been previously summarized and reported across the five dimensions *emotional state*, *physical comfort*, *psychological support*, *physical independence*, and *pain*; these reports indicated the quality of recovery in each dimension [12,19-21,24,25]. However, in this study and its context, the focus was on items, not dimensions. We believe that, when day surgery departments follow-up with their patients, the interest is in each specific item when evaluating and improving anesthetic and postoperative care. For example, when evaluating intravenous versus inhalation anesthesia and the postoperative differences in nausea and vomiting, the follow-up and evaluation would examine the values reported in the item "Nausea and/or vomiting", not the quality of recovery in the dimension *physical comfort*.

Limitations

This study was conducted in two day surgery departments in Sweden including participants familiar with using mobile phones and participants who spoke and could read the Swedish language. Only day surgery patients who underwent general anesthesia were included. Further studies including all types of anesthesia and surgeries should be conducted, as well as studies including non-Swedish speaking participants answering in their own language. There was also a technical limitation including no opportunity for the participants to change their prior answers in the app and this might have affected the reported answers.

Suggestion for Further Development

On the basis of our results, we recommend some changes to be implemented in the next version and further development of the RAPP app (Textbox 1).

Textbox 1. Recommended changes in the next version of the RAPP app

A value on the numeric VAS should be chosen before the respondent can continue to the next question.
Incorporate the ability to go back and check or change prior answers.
Reformulate all positive (n=8) items into negative items.
Include a daily reminder to fill in the app, which is only possible in a native app.
Develop the web-based app as a native app.
Testing of the new items that was included after the content validity.

Conclusions

Day surgery patients had positive attitudes toward using this app for follow-up after surgery and wanted to use the app again if admitted for future day surgeries. The ability to get in contact with a nurse via the app was very much appreciated and made the participants feel secure. Equivalence between the app and paper versions of the SwQoR showed agreement (ICC .89), but at the item level, the ICC was less than .7 for 9 items. This study shows the importance of evaluating an instrument converted from paper to electronic assessment formats and the need to evaluate the specific app for this assessment. In the content validity evaluation of the SwQoR, staff found more items relevant than the patients. The content validity evaluation of the SwQoR together with 3 new items led to a reduction from 34 to 24 items in the SwQoR.

Acknowledgments

KD, ME, MJ, and UN made substantial contributions to the conception and design. KD, ME, MJ, and UN drafted the article or revised it critically for important intellectual content. Final approval of the version to be published was made by KD, ME, MJ, and UN.

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Conflicts of Interest

Author Ulrica Nilsson and Örebro University Enterprise AB hold shares in RAPP-AB.

Multimedia Appendix 1

Content validity SwQoR.

[PDF File (Adobe PDF File), 204KB - resprot_v5i3e192_app1.pdf]

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Abbreviations

BYOD: bring your own device
ICC: intraclass correlation coefficient
I-CVI: item-level content validity index
PRO: patient reported outcome
QoR: Quality of Recovery instrument
RAPP: Recovery Assessment by Phone Points
S-CVI: scale-level content validity index
SwQoR: Swedish Web-version of Quality of Recovery
VAS: visual analogue scale

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Protocol

The Karlsruhe Metabolomics and Nutrition (KarMeN) Study: Protocol and Methods of a Cross-Sectional Study to Characterize the Metabolome of Healthy Men and Women

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Abstract

Background: The human metabolome is influenced by various intrinsic and extrinsic factors. A precondition to identify such biomarkers is the comprehensive understanding of the composition and variability of the metabolome of healthy humans. Sample handling aspects have an important impact on the composition of the metabolome; therefore, it is crucial for any metabolomics study to standardize protocols on sample collection, preanalytical sample handling, storage, and analytics to keep the nonbiological variability as low as possible.

Objective: The main objective of the KarMeN study is to analyze the human metabolome in blood and urine by targeted and untargeted metabolite profiling (gas chromatography-mass spectrometry [GC-MS], GC×GC-MS, liquid chromatography-mass spectrometry [LC-MS/MS], and ^{1}H nuclear magnetic resonance [NMR] spectroscopy) and to determine the impact of sex, age, body composition, diet, and physical activity on metabolite profiles of healthy women and men. Here, we report the outline of the study protocol with special regard to all aspects that should be considered in studies applying metabolomics.

Methods: Healthy men and women, aged 18 years or older, were recruited. In addition to a number of anthropometric (height, weight, body mass index, waist circumference, body composition), clinical (blood pressure, electrocardiogram, blood and urine clinical chemistry) and functional parameters (lung function, arterial stiffness), resting metabolic rate, physical activity, fitness, and dietary intake were assessed, and 24-hour urine, fasting spot urine, and plasma samples were collected. Standard operating procedures were established for all steps of the study design. Using different analytical techniques (LC-MS, GC×GC-MS, ^{1}H NMR spectroscopy), metabolite profiles of urine and plasma were determined. Data will be analyzed using univariate and multivariate as well as predictive modeling methods.

Results: The project was funded in 2011 and enrollment was carried out between March 2012 and July 2013. A total of 301 volunteers were eligible to participate in the study. Metabolite profiling of plasma and urine samples has been completed and data analysis is currently underway.

Conclusions: We established the KarMeN study applying a broad set of clinical and physiological examinations with a high degree of standardization. Our experimental approach of combining scheduled timing of examinations and sampling with the multiplatform approach (GC×GC-MS, GC-MS, LC-MS/MS, and ^{1}H NMR spectroscopy) will enable us to differentiate between current and long-term effects of diet and physical activity on metabolite profiles, while enabling us at the same time to consider confounders such as age and sex in the KarMeN study.

Trial Registration: German Clinical Trials Register DRKS00004890; https://drks-neu.uniklinik-freiburg.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00004890 (Archived by WebCite at http://www.webcitation.org/6iyM8dMtx)

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KEYWORDS

metabolomics; metabolome; humans; healthy subjects; cross-sectional studies

Introduction

The metabolome represents the complete set of small molecules or metabolites in a biological system, which in the case of blood and urine provides valuable information on human metabolism. The most frequently used analytical techniques for the identification and quantification of metabolites are nuclear magnetic resonance (NMR) spectroscopy, liquid chromatography-mass spectrometry (LC-MS), and gas chromatography-mass spectrometry (GC-MS). During the last decades, analytical techniques have significantly progressed allowing the measurement of hundreds of metabolites in a single sample. Today, the metabolomics approach is an important tool in biomedical research, which contributes to the identification of new potential biomarkers of diseases. Specific metabolites and metabolite patterns have been linked to various diseases, such as cardiovascular disease [1-3], cancer [4-7], and many others [8,9]. Further, metabolomics is also a promising approach in nutrition research [10-12]. It allows studying the association between human metabolism and diet more comprehensively compared to classical analytical methods. In addition, it may complement current methods of assessing dietary intake.

The human metabolome is characterized by a large variability. Endogenous and exogenous factors have been described to influence metabolic profiles. Examples of endogenous or subject-related factors are age [13-16], sex [17-20], body composition [21-23], hormone status (eg, menstrual cycle, menopause) [16,24,25], circadian rhythm [26-29], and physical fitness [30,31]. Among exogenous and lifestyle factors, smoking [32], alcohol intake [33,34], diet [35-37], and physical activity and exercise [38-40] have been addressed so far. In addition to these subject-related analytical issues, preanalytical aspects have also been identified to contribute to metabolome variability. These include sample and data collection, sample preparation, and storage issues [41-46].

Recently, the composition of the human metabolome has been reported for plasma [47], serum [48,49], and urine [50,51]. However, these studies primarily focused on expanding the knowledge of the entire human metabolome and thus did not consider age, sex, and other factors as contributors to the variability of the human metabolome [48,49,51].

Combining targeted and nontargeted NMR spectroscopy, GC-MS, and LC-MS methods may be favorable in identifying a broad spectrum of metabolites from a single sample compared to the application of only one metabolomics platform. Unfortunately, these procedures have not been applied in a single, but in different, sample sets [48], or have been applied in a small group of volunteers only [51]. Additionally, samples for metabolite profiling may be purchased from companies [49] with volunteer information totally missing.

Most studies assessing the composition of the human metabolome did not consider the preceding given factors, such as age, sex, body composition, diet, physical activity, and fitness, which may impact the human metabolome. Although some studies investigated the influence of factors such as age [13-16] on metabolite profiles, they did not report information on diet or physical activity. Similarly, studies investigating the impact of physical activity did not consider the role of sex [38,39].

Overall, there is currently no comprehensive consideration and understanding of the major endogenous and exogenous determinants of the human metabolome, such as age, sex, body composition, diet, physical activity, and fitness. A combined targeted and untargeted metabolite profiling (GC×GC-MS, GC-MS, LC-MS/MS, and ^{1}H NMR spectroscopy) of plasma and urine in a well-characterized population is missing. Therefore, we performed the Karlsruhe Metabolomics and Nutrition (KarMeN) study, in which we established a strictly scheduled experimental setting with a high degree of experimental standardization in order to minimize variations regarding examination, sample handling, and analysis. Based on standard operating procedures (SOPs), that were applied on recruitment, examinations, and on the preanalytical handling, all participants underwent the same procedures according to a specified timeline and all samples were treated identically.

The main objective of the KarMeN study is to analyze the human metabolome in blood and urine by targeted and untargeted metabolite profiling (GC×GC-MS, GC-MS, LC-MS/MS, and ^{1}H NMR spectroscopy) and to determine the impact of sex, age, body composition, diet, and physical activity on metabolite profiles of healthy women and men. Here, we report the outline of the study protocol. Details on clinical measurements will be published elsewhere, whereas the description of analytical procedures has already been published [52,53].

Methods

Study Design and Setting

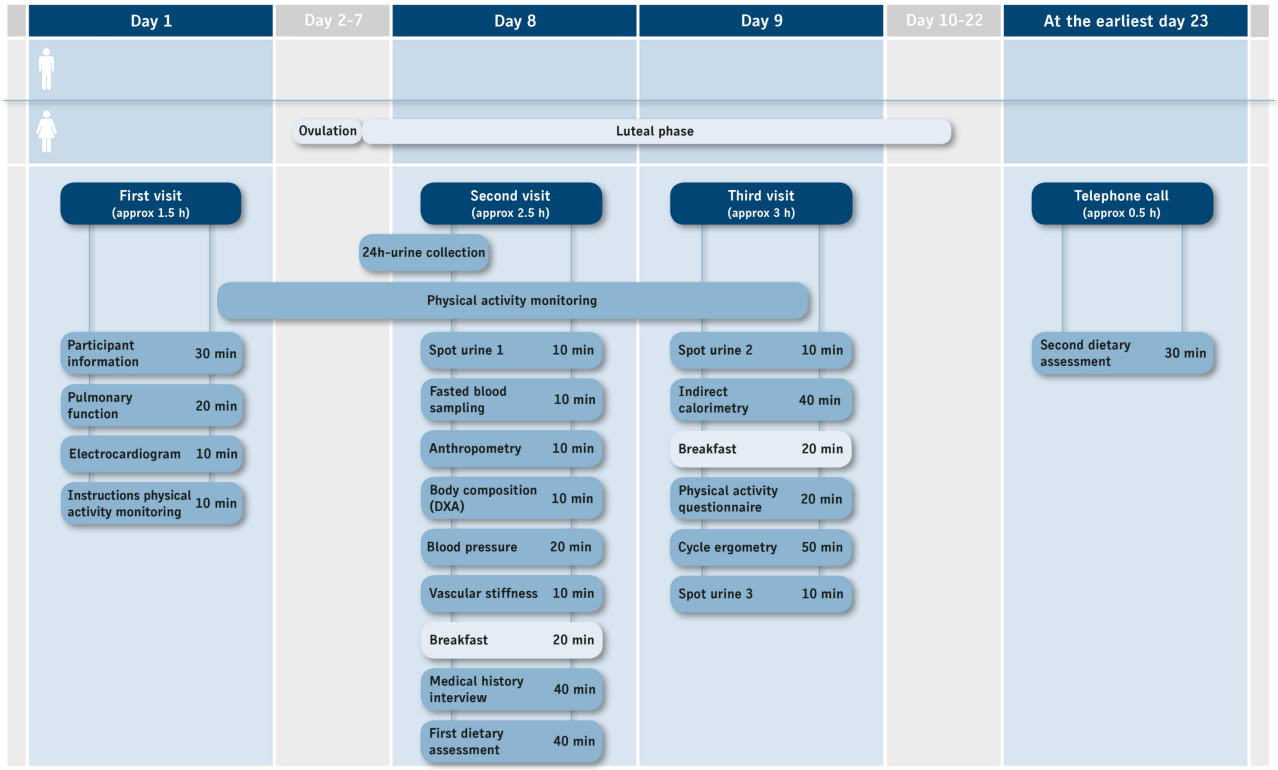
The KarMeN study was performed at the Division of Human Studies of the Max Rubner-Institut in Karlsruhe, Germany, between March 2012 and July 2013. All volunteers visited the study center within a period of 9 days for a total of three visits, in which the second visit was scheduled exactly 1 week after the first, and the third visit was on the day following the second visit (Figure 1). Participants underwent a series of examinations and followed an identical schedule on each of the three examination days (Figure 1). SOPs were developed for any

procedure related to examinations, measurements, sample collection, sample preparation, and storage. Examiners were trained before, and were supervised during, recruitment.

Participants

Healthy, nonsmoking volunteers older than 18 years of age were eligible to participate. Detailed inclusion and exclusion criteria are listed in Textbox 1. Health status examination included the assessment of medical history and a basic physical examination. Women taking hormonal contraceptives or receiving hormonal replacement therapy were not included because of the significant impact of hormone intake on various aspects of human metabolism and physiology. As the phase of the menstrual cycle is known to impact the metabolite profile in women [25], premenopausal women were asked to document their regular menstrual cycle over a period of 3 months. Based on this information, women were scheduled for examinations within their luteal phase. During the anticipated phase before the examinations, they performed an ovulation test (OvuQuick, NanoRepro AG, Marburg, Germany) to verify ovulation and subsequent luteal phase. The status of postmenopausal women was determined by respective anamnestic interview and follicle-stimulating hormone (FSH) measurements (MZV Labor PD Dr Volkmann, Karlsruhe, Germany). We defined postmenopausal status by absence of menstrual bleeding for at least 1 year and FSH >25 IU/L.

Figure 1. Overview of KarMeN study days and examination schedule.



Textbox 1. Inclusion and exclusion criteria for participants of the KarMeN study.

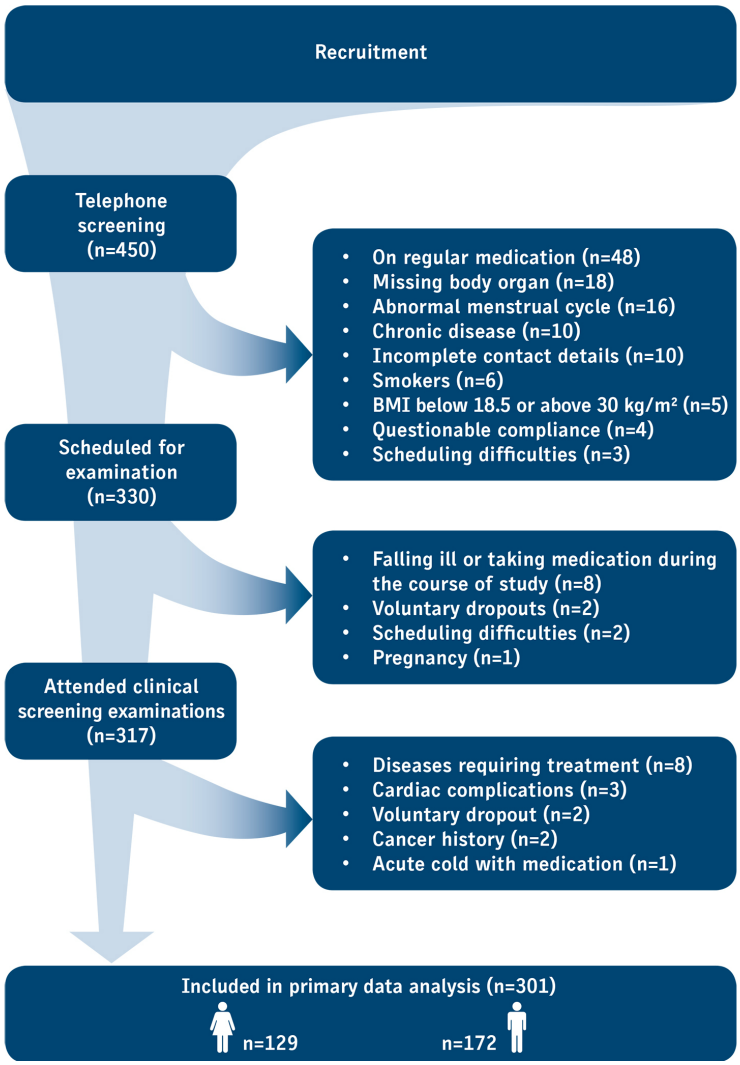
Inclusion criteria

- Healthy men and women
- 18 years of age or older
- Nonsmokers
- Volunteers conducting all examinations and tests
- Participants giving their written and informed consent

Exclusion criteria

- Smokers
- Volunteers on regular medication
- Volunteers taking supplements
- Women using hormonal contraceptives
- Pregnant or breastfeeding women
- Volunteers with diseases of the cardiovascular system, lungs, gastrointestinal tract, metabolism, skin, viscera, nervous system, and infectious or immunological diseases in therapeutic need
- Volunteers with known allergy against *para*-aminobenzoic acid (PABA)
- Volunteers with intolerance against Finalgon
- Volunteers with tumors
- Volunteers with acute or chronic infectious diseases
- Volunteers with drug or alcohol abuse
- Volunteers who may not adhere to the study protocol
- Volunteers who gave no written consent
- Institutionalized patients in psychiatric hospitals

Figure 2. Flowchart describing the recruitment process of the KarMeN study. Along the vertical arrow, the phases of recruitment are shown and the number of volunteers entering each phase. On the right hand side, reasons for exclusion at each stage are given.



Recruitment procedures included direct communication with previous study participants, advertisements in local media (newspapers and radio), flyers, and word of mouth. Initially 450 persons contacted the study center (Figure 2). Those who passed an initial telephone screening done with a checklist were scheduled for a medical examination (n=330). Reasons for exclusion of participants are given in Textbox 1.

Sample Collection

Blood samples were collected after at least 10 hours fasting for the clinical blood profile and hormonal and metabolome analysis. Volunteers were placed on an examination couch in the supine position and blood samples were obtained by an experienced study nurse from an antecubital vein. After cutaneous disinfection, a tourniquet was moderately applied before venipuncture (safety blood collection device: Venofix Safety, Braun AG, Melsungen, Germany). Blood was drawn into S-Monovette tubes (Sarstedt AG & Co, Nümbrecht, Germany). Plasma was obtained by using the EDTA S-Monovette, serum by Serum-Gel S-Monovette; for immunological assays, the Lithium-Heparin S-Monovette was used. After venipuncture, blood- containing ethylenediaminetetraacetic acid (EDTA) tubes for plasma preparation were immediately placed on ice before centrifugation (CR 4.22, Jouan, Saint-Herblain, France).

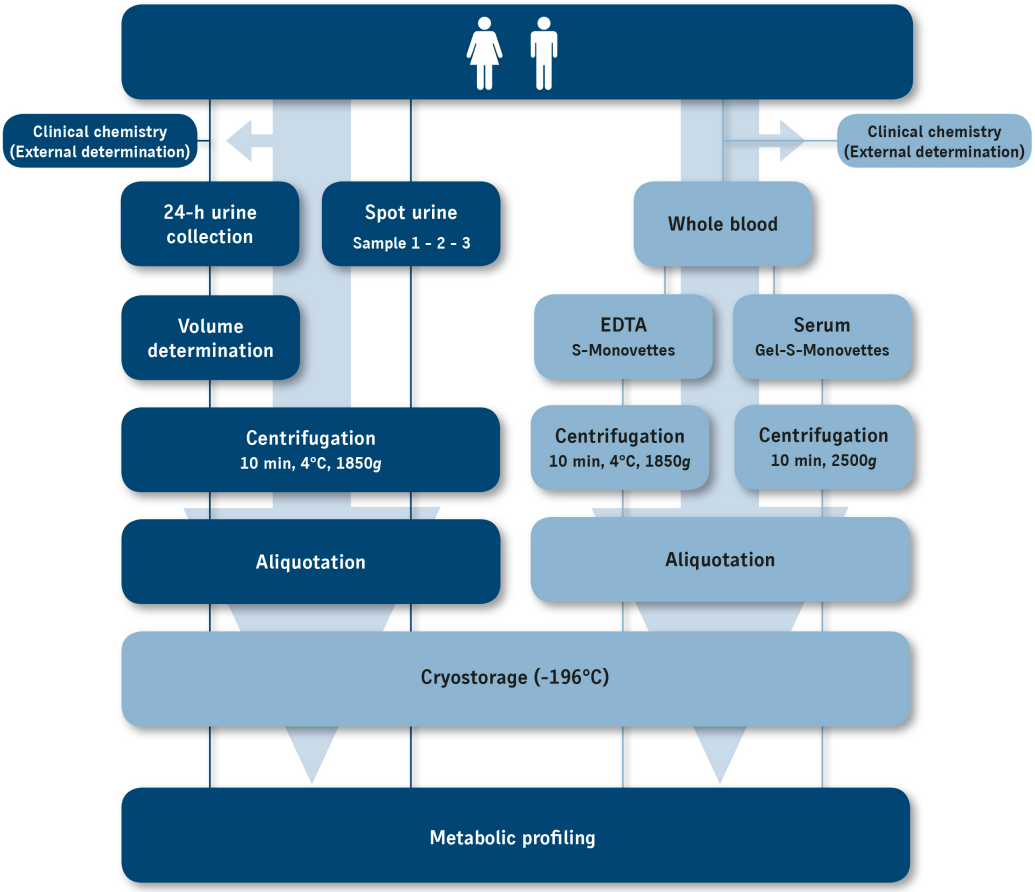
Volunteers collected urine from the morning of the day before blood donation until the morning of the day of blood donation at visit 2 (24-hour urine collection). Completeness of the 24-hour urine was checked with the *para*-aminobenzoic acid (PABA) method [54]. For 24-hour urine collection, volunteers were instructed by a study nurse and received a protocol with written instructions and for documentation. They were provided with two urine containers (volume 2 liters, Sarstedt AG & Co, Nümbrecht, Germany) and were asked to store the urine containers at home in the refrigerator and to place them in a thermal bag containing prechilled thermal packs for transport to the study center. In addition, volunteers provided fasting spot urine at the study center on two consecutive days (visits 2 and 3) (Figure 1). Additional spot urine was collected after cycle ergometry (visit 3). Spot urine samples were collected in 100 mL polypropylene collection cups with screw caps (Sarstedt AG & Co, Nümbrecht, Germany) and immediately placed on ice for a maximum 10 minutes before further processing. Material for sample collection and storage were derived from a single production batch.

Sample Processing and Storage

After collection, samples were processed identically based on a given schedule with defined time intervals between the different preparation steps (see Figure 3). For plasma preparation, EDTA blood was centrifuged (4°C, 10 min, 1850 *g*, CR 4.22, Jouan, Saint-Herblain, France) and supernatants were combined before aliquoting. Serum was obtained after blood clotting for 30 minutes at room temperature and centrifugation (room temperature, 10 min, 2500 *g*). Urine samples were centrifuged at 1850 *g* (4°C, 10 min) to remove cellular particles and debris [55]. Before processing, all urine samples were checked with urine test strips (CombiScreen, CombiScan 100, Analyticon) to exclude samples with pathological aspects.

All samples were transferred into prechilled cryovials (Brand, Germany) by means of electronically regulated pipettes (Eppendorf Multipette Stream, Germany) using disposable tips (Eppendorf Combitips, Germany). Cooling of cryovials during partitioning was achieved by placing them into cooled (–80°C) aluminum racks. For practical handling reasons, samples from each individual generated at visits 2 and 3 were stored in the laboratory at –20°C for up to 2 days and then transferred into the gas phase of the liquid nitrogen (LN_2) storage system until analysis. This procedure has previously been shown not to affect metabolomics results [45].

Figure 3. Schematic representation of the procedures for preanalytical sample handling. After collection, standard parameters in blood and 24-hour urine were analyzed by a certified external clinical chemistry laboratory. All other samples were identically processed at the study center based on a given schedule with defined time intervals between the different preparation steps of centrifugation and aliquotation until cryostorage.



Examinations and Outcome Measurements

Examinations and measurements included anthropometric parameters (weight, height, waist circumference), body composition by dual-energy x-ray absorptiometry (DXA; Lunar iDXA, GE Healthcare, Germany), pulmonary function (FlowScreen, CareFusion, Hoechberg, Germany), electrocardiogram (ECG; Cardioline AR1200, Cavareno, Italy), blood pressure (Boso Carat Professional, Bosch & Sohn, Jungingen, Germany), and arterial stiffness (ARTERIOGraph, Medexpert, Budapest, Hungary).

Food consumption for the day before blood sample drawing and the day of 24-hour urine collection was assessed by the 24-hour recall method using the software EPIC-Soft [56]. In order to differentiate between the impact of acute and long-term diet on the human metabolome, a second 24-hour recall was conducted by telephone at least 2 weeks after the first interview. Additionally, a food frequency questionnaire developed specifically for this study was conducted. It covered food consumption for the last year. Nutrient intake was calculated based on the German Nutrient Database (BLS) version 3.02 [57]. Supplement use was not assessed because participants with supplement use were excluded from the study. To calculate

long-term food consumption and long-term nutrient intake, the Multiple Source Method [58,59] was applied.

Physical activity was assessed for the day before blood sampling and for an average of the study week by combined accelerometry and heart rate measurements (Actiheart, CamNtech, Cambridge, UK). An average of the weekly physical activity for the last 3 months was determined by the standardized International Physical Activity Questionnaire (IPAQ) [60]. Cardiorespiratory fitness was determined by cycle ergometry with combined capillary lactate measurements. Details on physical activity and physical fitness methods will be described elsewhere. Additionally, basal metabolic rate was determined by indirect calorimetry (Vmax Encore, CareFusion, Hoechberg, Germany). During visits at days 2 and 3, volunteers received a breakfast after their examinations. At visit 2, breakfast was given ad libitum, whereas at visit 3, breakfast was adjusted to individual energy requirements and was provided approximately 45 minutes before cycle ergometry. Examinations, blood sampling, 24-hour urine, and spot urine collection were arranged in this setting to ideally combine data from volunteer examinations, food consumption, and physical activity measurement with analytical data from blood and urine metabolite profiling (Figures 1 and 2). Blood and 24-hour urine were analyzed for standard parameters by a certified clinical chemistry laboratory (MZV Labor PD Dr Volkmann, Karlsruhe, Germany).

Metabolomics Analyses

Complementary analytical methods and techniques for targeted and untargeted metabolite profiling of biofluids (GC×GC-MS, GC-MS, LC-MS/MS, and ^{1}H NMR spectroscopy) were applied. All 24-hour urine and fasted plasma samples were analyzed by untargeted GC×GC-MS using a Shimadzu GCMS QP2010 Ultra instrument equipped with a ZOEX ZX2 modulator according to the method established previously [52]. With this method, a wide range of metabolites can be detected, such as amines, amino acids, organic acids, sugars, sugar alcohols, other polyols, etc. Because some isomeric sugar species cannot be sufficiently resolved with the untargeted GC×GC-MS approach, but may play an important role in human metabolism, a complementary targeted GC-MS sugar profiling method was developed for urine samples using a Shimadzu GCMS QP2010 Ultra instrument. Overall, 66 metabolites, consisting of 38 known sugar species, 17 unknown sugar species, and 11 nonsugar compounds, were detected with this method. The chromatographic separation of plasma fatty acids usually requires the application of specialized polar columns and, thus, cannot be done adequately using a standard apolar × medium-polar GC×GC column setup. For this reason, we used a targeted GC-MS analysis method [61] to determine plasma fatty acids as methyl esters, with minor modifications. Using a GC single quadrupole instrument (Shimadzu GCMS QP2010 Ultra) and a BPX90 column (Trajan Scientific), 48 fatty acids could be determined in plasma. LC-MS metabolite profiling using the Absolute IDQ p180 kit developed by Biocrates AG (Innsbruck, Austria) was applied to determine acyl carnitines, amino acids, biogenic amines, phosphatidylcholines, and sphingomyelins in fasted plasma samples. A targeted quantification UPLC-MS/MS method for seven amino compounds in plasma, including L-carnitine, choline, and trimethylamine *N*-oxide (TMAO), was established using an Acquity UPLC H-Class system coupled to a Xevo TQD triple quadrupole MS (both from Waters, Eschborn, Germany). Targeted LC-MS analysis of 14 bile acids was done from fasted plasma using a 1200 series HPLC system (Agilent, Waldbronn, Germany) coupled to a Q-Trap 3200 mass spectrometer (AB Sciex, Darmstadt, Germany) as described elsewhere [62]. All plasma and urine samples were analyzed by untargeted one-dimensional ^{1}H NMR spectroscopy [45]. Typically, metabolites that can be detected include organic acids, amino acids, amines, sugars, sugar alcohols, and others.

Data Processing

The GC×GC-MS raw data files were processed by untargeted alignment by in-house-developed R-modules, as described previously [53]. Signal intensity drift (ie, intra- and interbatch effects) occurring during the 4- to 5-week measurement period were corrected by means of regularly injected quality control (QC) samples. For the data of the semitargeted GC-MS analysis of sugar species in urine, an automatic method for integration was prepared using the Post-run Analysis feature of GCMSSolution (v 4.1.1.). An MS Excel table with integrated peak areas of the chosen substances was made for further data processing.

To analyze the samples of the entire study by LC-MS metabolite profiling (Absolute IDQ p180 kit), five Absolute IDQ well plates were used. To account for possible batch effects between the plates, data normalization as described by the manufacturer's user manual was applied based on the pooled QC samples, which were extracted and measured 10 times on each well plate in-between the study samples.

All NMR spectra were automatically phased with the Bruker AU program apk0.noe without referencing. Using the program AMIX (v 3.9.14.; Bruker, Rheinstetten, Germany) plasma spectra were then referenced to the EDTA signal at 2.5809 ppm and bucketed graphically, such that buckets wherever possible contained only one signal or group of signals and no peaks were split between buckets. Urine spectra were resampled to bring them to a uniform frequency axis. Then, spectra were aligned by "correlation optimized warping" [63] and bucketed using an in-house-developed software based on Python, again trying to define buckets that contain only one signal or group of signals and not splitting peaks between buckets whenever possible. Identification of important metabolites was achieved with Chenomx NMR Suite 8.1 (Chenomx, Edmonton, AB, Canada).

Metabolomic Data Analysis and Statistics

Data for the different analytical platforms were integrated into a common data matrix, consisting of 301 samples and more than 1000 analytes (including knowns and unknowns). Analytes with a detected frequency lower than 75% in the study samples were eliminated from the data matrix before statistical analysis. In the final analysis, 442 plasma analytes and 531 urine analytes were included.

The columns of this common data matrix were mean centered and scaled by standard deviation before analysis. This resulting matrix was used as input for three different prediction models

(support vector machine with linear kernel, generalized linear model, and partial least squares). When the model is used to predict categorially considered variables, the classification accuracy is assessed. For continuous outcomes, the parameters root mean squared error and R^2 are calculated to estimate performance of the predictions. Furthermore, multivariate linear regression models are calculated with standard variables of interest including sex, age, and anthropometric variables. Finally, a ranking of the top metabolites with regard to accordance in the metabolite patterns is created. Therefore, we calculate a rank for every metabolite for each algorithm. For the final ranking, the ranks of categorially considered variables are averaged.

Ethics and Dissemination

The study has been performed in accordance with the Declaration of Helsinki. It was registered at the German Clinical Trials Register (No: DRKS00004890) and approved by the Ethics Committee of the State Medical Chamber of Baden-Württemberg, Stuttgart, Germany (F-2011-051). Approval for DXA measurements in healthy participants was obtained from the Federal Office for Radiation Protection (Z5-22462/2-2011-043). All participants were informed in detail about the examinations, procedures, and measurements, and gave their written consent. Confidentiality of personal data is guaranteed by following the regulations of the State Medical Chamber and the Federal Data Protection Act. Access to data is restricted to project partners, who receive only coded data for analysis.

Results

The project was funded in 2011 and enrollment was carried out between March 2012 and July 2013. Finally, a total of 301 volunteers were eligible to participate in the study and primary analysis. Basic characteristics of the KarMeN study participants are given in Table 1. Metabolite profiling of plasma and urine samples has been completed and data analysis is currently underway.

Table 1. Basic characteristics of the KarMeN study participants.

Characteristics of participants	Total (N=301)	Women (n=129)	Men (n=172)
Postmenopausal women, n	73	73	—
Age (years), mean (SD)	47.5 (17.1)	51.7 (15.0)	44.4 (17.9)
Age (years), range	19-80	19-80	20-80
Height (cm), mean SD	174.4 (9.5)	166.8 (6.5)	180.1 (7.2)
Body weight (kg), mean (SD)	72.9 (12.0)	64.4 (8.3)	79.2 (10.2)
Body mass index (kg/m^2), mean (SD)	23.9 (2.9)	23.2 (2.9)	24.4 (2.7)
Waist circumference (cm), mean (SD)	84.1 (9.7)	79.1 (8.3)	87.8 (8.9)

Discussion

Our main objective was to analyze the human metabolome in blood and in urine by targeted and untargeted metabolite profiling (GC×GC-MS, GC-MS, LC-MS/MS, and ^{1}H NMR spectroscopy) and to determine the impact of sex, age, body composition, diet, and physical activity on metabolite profiles of healthy women and men. Therefore, we performed the KarMeN study and established a strictly scheduled experimental setting with a high degree of experimental standardization. SOPs have been developed and applied on recruitment, examinations, and also on the preanalytical handling of samples. All participants underwent the same procedures according to a specified timeline and all samples were treated identically. This contributed to minimizing variations related to examination, sampling, and data analysis. Because blood and urine samples were taken under defined conditions within a scheduled narrow time frame, the influence of circadian variation [26-29] was minimized. We expanded standardization to issues of data collection, sample preparation, and storage because these also have been reported to be factors of variation [41-46]. In addition to these technical aspects, we aimed to comprehensively characterize the study participants to identify metabolite profiles related to age, sex, body composition, diet, physical activity, fitness, and others. Only healthy nonsmoking male and female participants were included in the study according to our strict inclusion and exclusion criteria and after physical examination. Despite the known influence of smoking on the metabolome [32], this information is often not provided. Participants with acute or chronic diseases or on medication were excluded because we targeted healthy individuals. Associations of distinct metabolite patterns and diseases, such as cardiovascular disease [1-3], cancer [4-7], and others [8,9], have been extensively described and are not the topic of our study. Participant characterization also included a broad set of clinical and physiological examinations covering anthropometry, body composition by DXA, pulmonary function, ECG, blood pressure, and arterial stiffness, which have not been applied in metabolomics studies of healthy subjects so far. An additional strength of our study is the unique assessment of current and long-term diet, as well as current and regular physical activity and cardiorespiratory fitness in this cohort of healthy men and women. The scheduled timing of examinations and sampling allowed us to differentiate between current and long-term effects of diet as well as physical activity on metabolite profiles, while enabling us at the same time to consider confounders such as age and sex in the KarMeN study.

So far, most studies reported data from either plasma/serum [47-49] or from urine [50,51]. In this study, we determined the human metabolome in blood and in urine. Further, we applied

a combined targeted and untargeted multiplatform metabolite profiling (GC×GC-MS, GC-MS, LC-MS/MS, and ^{1}H NMR spectroscopy) for each study participant using only one sample set [48]. This multiplatform approach allows identifying a broader spectrum of metabolites compared to a single-platform metabolomics approach. The cross-sectional design of the KarMeN study does not allow conclusions on metabolite variations over longer periods of time. This is one limitation of our study. Additionally, we did not include smokers and healthy obese individuals. Therefore, results of the KarMeN study cannot be transferred to the general population.

Acknowledgments

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Authors' Contributions

AB and BW developed the study concept and design; IH and SK contributed to the study design. AK, CD, EH, MJR, and SB were responsible for study organization and data acquisition. AB drafted the manuscript and all authors contributed to the final version.

Conflicts of Interest

None declared.

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Abbreviations

DXA: dual-energy x-ray absorptiometry
FSH: follicle-stimulating hormone
GC: gas chromatography
KarMeN: Karlsruhe Metabolomics and Nutrition
LC: liquid chromatography
MS: mass spectrometry
NMR: nuclear magnetic resonance
PABA: para-aminobenzoic acid
QC: quality control
SOP: standard operation procedure

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Protocol

An Exploratory Clinical Trial of a Novel Treatment for Giant Congenital Melanocytic Nevi Combining Inactivated Autologous Nevus Tissue by High Hydrostatic Pressure and a Cultured Epidermal Autograft: Study Protocol

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Abstract

Background: Giant congenital melanocytic nevi (GCMNs) are large brown to black skin lesions that appear at birth and are associated with a risk of malignant transformation. It is often difficult to reconstruct large full-thickness skin defects after the removal of GCMNs.

Objective: To overcome this difficulty we developed a novel treatment to inactivate nevus tissue and reconstruct the skin defect using the nevus tissue itself. For this research, we designed an exploratory clinical study to investigate the safety and efficacy of a novel treatment combining the engraftment of autologous nevus tissue inactivated by high hydrostatic pressurization with a cultured epidermal autograft (CEA).

Methods: Patients with congenital melanocytic nevi that were not expected to be closed by primary closure will be recruited for the present study. The target number of nevi is 10. The full-thickness nevus of the target is removed and pressurized at 200 MPa for 10 minutes. The pressurized and inactivated nevus is sutured to the original site. A small section of the patient's normal skin is taken from around the nevus region and a CEA is prepared after a 3-week culturing process. The CEA is then grafted onto the engrafted inactivated nevus at four weeks after its retransplantation. The primary endpoint is the engraftment of the CEA at 8 weeks after its transplantation and is defined as being engrafted when the engraftment area of the inactivated nevus is 60% or more of the pretransplantation nevus area and when 80% or more of the transplanted inactivated nevus is epithelialized.

Results: The study protocol was approved by the Institutional Review Board of Kansai Medical University (No. 1520-2, January 5, 2016: version 1.3). The study opened for recruitment in February 2016.

Conclusions: This protocol is designed to show feasibility in delivering a novel treatment combining the engraftment of inactivated autologous nevus tissue and CEA. This is the first-in-man clinical trial of this treatment, and it should be a promising treatment of patients suffering from GCMN.

Trial Registration: University Hospital Medical Information Network: UMIN000020732; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000022198 (Archived by WebCite at http://www.webcitation.org/6jLZH2vDN)

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KEYWORDS

giant congenital melanocytic nevi; cultured epidermal autograft; high hydrostatic pressurization; inactivation

Introduction

Giant congenital melanocytic nevi (GCMNs) are large brown to black skin lesions that appear at birth and have a diameter of more than 20 cm [1-5]. GCMNs, which are reported to occur in approximately 1 in 20,000 newborns [1,2], are associated with a risk of transformation that usually results in malignant melanoma. The incidence of malignant transformation into malignant melanoma is reported to be 0.7% to 8.2% [2,5,6]. Histologically, nevus cells are present throughout the entire layer of the dermis and, in some cases, the subcutaneous tissue. Thus, the removal of the full thickness of the nevus tissue is necessary to remove nevus cells completely and to prevent the emergence of melanoma [1-5]. It is often difficult to reconstruct large full-thickness skin defects after the removal of GCMNs. It is also reported that melanoma and aneurocutaneous melanocytosis are most likely in patients with GCMNs that have a final size of more than 40 cm in diameter with numerous satellite nevi [6]. Thus, the skin reconstruction of GCMNs remains a challenge in the field of plastic and reconstructive surgery.

We have already reported that all cells existing in the human skin, porcine skin, and nevus tissue were inactivated completely after high hydrostatic pressurization (HHP) at pressures of more than 200 MPa [7,8]. We also reported that the human-cultured epidermis took and survived on the pressurized skin and nevus after pressurization at 200 MPa [7,9]. Skin consists of the epidermis, which acts as a barrier against infection and water loss, and the dermis, which supports and supplies nutrition to the epidermis. Regarding skin reconstruction, the regeneration of the epidermis by a cultured epidermal autograft (CEA) using Green's method was established in the 1970s [10]. A method of dermal regeneration that achieves sufficient strength and elasticity has not yet been established [11,12].

We designed an exploratory clinical study to investigate the safety and efficacy of a novel treatment combining autologous nevus tissue inactivated by HHP and a CEA. This trial is the first-in-man clinical trial to reuse and apply autologous nevus inactivated by HHP to reconstruct autologous dermis after the removal of the nevus itself without discarding the nevus tissue. JACE (Japan Tissue Engineering Co Ltd, Gamagori, Japan) is a CEA product prepared using Green's method that has been approved for use in Japan since 2007 [13]; CEA products are approved for use in other countries as well. A CEA of sufficient size to cover the total surface area can be produced from an autologous skin specimen of approximately 1 cm × 2 cm in size. This treatment can therefore be expected to overcome the issues of GCMN treatment and prevent the malignant transformation of GCMNs.

Methods

Primary Objective

The objective of this study is to evaluate the safety and efficacy of a novel treatment combining autologous nevus tissue inactivated by HHP with CEA.

Design

This study is an open-label, nonrandomized, single-arm, controlled clinical trial that is a prospective study using historical data as a control. All of the patients will receive a combination treatment consisting of autologous nevus tissue inactivated by HHP with CEA.

The take rate of the CEAs implanted on the inactivated nevus tissue will be estimated at 8 weeks after CEA implantation and compared to the historical data of the take rate of CEAs. This comparison will provide useful information for designing and conducting future trials.

Setting and Participants

Patients with congenital melanocytic nevi will be identified by physicians in Osaka and other prefectures who will refer them to this study, being conducted at Kansai Medical University Hirakata Hospital.

Patients 7 months of age and older who are able to undergo surgery under general or local anesthesia and can give informed consent (proxy consent permitted for pediatric patients only) are included. Patients must have a congenital melanocytic nevi that is not expected to be closed by primary closure (patients require a skin graft or skin flap surgery to close the skin defect after its removal) with a target pigmented nevus area of 0.25% or more of the total body surface area (1/4 of the palmar area, including the fingers, taking the palm including the fingers as 1% of the total body surface area).

Exclusion criteria are extensive scarring from previous therapies (in whom the engraftment of the inactivated nevus is not expected), previous treatment of the target site by CEA in other clinical studies, history of malignant tumors with a disease-free interval of 5 years or less, two previous protocol treatments from this study, or patients who are judged by the investigator or subinvestigator to be inappropriate as study subjects.

Interventions

Removal of the Target Nevus and Its Inactivation by HHP

The full thickness nevus of the target is removed under general or local anesthesia and the subcutaneous adipose tissue is removed by scissors and packed into a polyethylene bag filled with normal saline solution (Otsuka Pharmaceutical Co Ltd, Tokyo, Japan) and sealed. We use a portable HHP device that was developed in collaboration with Kitaoka Iron Works Co Ltd (Osaka, Japan) [14]. The polyethylene bag containing the resected nevus is then placed in the cavity of the cell of this HHP device and the cavity is filled with distilled water (Otsuka

Pharmaceutical Co Ltd, Tokyo, Japan). The pressure is increased up to 200 MPa and maintained for 10 minutes, then decreased to atmospheric pressure over a period of a few seconds.

Retransplantation of the Inactivated Nevus

The pressurized and inactivated nevus is taken from the polyethylene bag and sutured to the original site. The nevus is fixed and stabilized to the wound bed using a tie-over dressing or negative pressure wound dressing for about one week after the retransplantation, as would be performed in a usual skin graft procedure. The graft is then covered by wound dressings or ointment gauze until the application of CEA. The inactivated nevus does not have any cellular components; however, within a few weeks fibroblasts and capillaries will infiltrate the nevus and the engrafted nevus will serve as an autologous dermis without nevus cells and will serve as a recipient floor for the CEA.

Preparation and Application of the CEA

A small section of the patient's normal skin (approximately 1 cm × 2 cm) is taken from around the nevus region for the preparation of the CEA. This skin is transported to a laboratory and the CEA is prepared after a culturing process that usually takes three weeks. The CEA will be grafted on the engrafted inactivated nevus at four weeks after the retransplantation of the inactivated nevus.

Subsequent Therapy

The inactivated nevus and CEA is treated in the same way as a skin graft. The use of ointments and wound dressings are allowed locally and no particular restrictions will be imposed during the study period.

Digital Photography for the Assessment of Healing

A digital camera is used to capture images of the grafts with a calibrator (ColorChecker Passport, X-lite Inc, Michigan, United States) placed on the skin adjacent to the wound. The color and size of the images can be adjusted using the ColorChecker Passport and an image editing software program (Adobe Photoshop, Adobe Systems Inc) to assess the area and color of the target nevus. As with the primary endpoint, the nevus evaluation committee members will assess the original area of the nevus before its removal and the engrafted area of the pressurized nevus and epithelized area on the pressurized nevus at 8 weeks after transplantation of the CEA.

Primary Endpoint

The primary endpoint is engraftment of the CEA at 8 weeks after its transplantation. The CEA is considered to be engrafted when the engraftment area of the inactivated nevus is 60% or more of the pretransplantation nevus area and 80% or more of the transplanted inactivated nevus is epithelialized. The proportion of the engraftment area is referred to as the engraftment rate. The engraftment assessment is carried out by three reviewers of the nevus evaluation committee. Macroscopic pictures of the grafts will be provided to each reviewer without patient information. The reviewers will determine the engraftment area of the inactivated nevus and the epithelized area based on these photographs.

With regard to the cutoff point of 60%, it has been reported that when autologous skin grafting is performed, the area of the skin graft contracts to approximately 80% at 3 months after grafting. Furthermore, in some cases the graft is reported to contract to approximately 60% [15]. We took the above information into consideration and set the cutoff point at 60% or more. Cases in which the engrafted area falls below 60% are not considered to be engrafted even if they are mostly epithelialized. Damage to the inactivated nevus by HHP may lead to such a degree of contracture.

When 80% or more of the CEA is epithelialized, it may be considered to be almost completely epithelized at the macroscopic level. Erosion and blister formation or shedding may occur in the early phase following grafting. The cutoff value for epithelialization was therefore set at 80% or more. This value takes the possibility of erosion and shedding, which may occur in some cases, into consideration [16].

Secondary Endpoints

The event name, grade, and outcome of adverse events and adverse reactions will be assessed according to the Common Terminology Criteria for Adverse Events version 4.0. Adverse events and adverse reactions occurring from the day of the transplantation of the inactivated nevus until the end of follow-up will be assessed.

A secondary endpoint is engraftment of the inactivated nevus at 4 weeks after its transplantation. The inactivated nevus is considered to be engrafted when the pressurized nevus forms a successful recipient floor for the CEA.

Blinding

The baseline nevus area before its removal, the engrafted area of the inactivated nevus, and the epithelized area 8 weeks after CEA transplantation will be independently estimated by blinding the members of the nevus evaluation committee. The patients will be unblinded, and the transplantation of the inactivated nevus and CEA will be performed by unblinded investigators.

Sample Size

The target number of grafted sites of the inactivated nevus is 10 sites. In this study, one patient can receive the study treatment for up to 2 sites, thus a minimum of 5 patients will be included in this study.

The subjects of this study include pigmented nevus patients for whom primary closure is not expected. Regarding the number of newly diagnosed GCMN cases each year, few such cases are diagnosed at Kansai Medical University Hirakata Hospital, while approximately 5 cases are diagnosed at Kyoto University Hospital (which treats more cases). Considering the number of patients with a history of treatment for residual nevi and the need to include 10 sites (at least 5 cases), we determined that the enrollment period should be 1 year and 6 months.

Study Schedule

The schedule of the study assessments and evaluations is shown in Figure 1. The study period will be from the day of informed consent to 12 weeks after the transplantation of the inactivated nevus. The data for evaluating the efficacy and safety of this

study will be collected at enrollment, day 1, weeks 1 and 4 after transplantation of the inactivated nevus, and weeks 1 and 8 after the transplantation of the CEA.

Figure 1. Schedule of the study assessments and evaluations.

Clinical assessments, testing, and investigations	Pre-enrollment exam −24weeks	Pre-operative exam Day -21 to day -1	Graft ①	Graft① Week 1 (±3days)	Graft① Week 4 (±14 days)	Graft ②	Graft② Week 1 (±3days)	Graft② Week 8 (±14 days)	Discontinuation
Patient background	○								
Pigmented nevus exam	○								
Digital photography of the target lesion	○		◎	○	○	◎	○	○	○
Enrollment	○								
Blood tests (Hematological and Biochemical tests)		○						○	○
Inactivated nevus transplant			○						
Normal skin collection			○						
CEA transplant						○			
Adverse events			←	—	—	—	—	—	→

○◎: required

◎: Photographs are taken before and after transplantation.

Statistical Analysis

When CEAs are transplanted on a wound bed without autologous dermal tissue, the engraftment rate is reported to be only 20%. In contrast, the engraftment rate is expected to be 80% when the CEA is transplanted on dermal tissue [17]. In this study, an engraftment rate of 80% can be expected because the autologous dermis is reconstructed using inactivated nevus tissue.

It was considered that the treatment could be deemed effective if it exceeds this engraftment rate. In this case, with an α error (one-sided) of .05 and a statistical power of 90%, the number of sites required was calculated to be 6 sites. Taking into consideration the possibility that some cases may be excluded from the analysis, we considered that there should be 10 target sites.

In our study, a single patient may undergo treatment for up to 2 sites. When two treatments are performed for the same patient, the first and second surgical sites are regarded as independent sites whether they are separated from each other by normal skin or nevus skin. Moreover, when providing simultaneous treatment to multiple sites in one subject, the largest treatment site will be included in the statistical analysis.

The incidences of adverse events and adverse events that can be causally related to the inactivated nevus and CEA application will be evaluated based on the event and severity. An interim analyses and auditing will not be planned; however, the investigators will monitor adverse events and other unintended effects of the trial interventions. A data monitoring committee consisting from three independent clinicians will also monitor patient safety and have the power to recommend termination of the study based on the evaluation of these results.

Ethics

This study is being conducted in compliance with the International Council for Harmonisation Good Clinical Practice and in accordance with the latest revision of the Declaration of Helsinki, Pharmaceutical Affairs Law and all applicable Japanese laws and regulations, as well all local laws and regulations and all applicable guidelines. This protocol and any amendments received Institutional Review Board (IRB) approval from Kansai Medical University (Approval number 1520-2).

Subject Consent

Informed consent will be obtained from all potential study participants using an IRB-approved informed consent form. The clinical investigator will inform the potential study subject about all of the pertinent aspects of the study. The subject must sufficiently understand the content of the information form before providing written consent. The consent form must be dated and signed by both the investigator and the participant. The subjects are also informed that their medical care will not be affected if they do not choose to participate in this study. The consent forms will be retained at Kansai Medical University Hirakata Hospital and the information form and a copy of the consent form are handed to the participant. Whenever the investigator obtains information that may affect the participant's willingness to continue participation in the study, the investigator or subinvestigator will immediately inform the participant and record this observation and subsequently reconfirm the participant's willingness to continue to participate in the study.

Dissemination

The findings of this trial will be disseminated through peer-reviewed journals and national and international scientific meetings as well as to the patients.

Results

The study protocol was approved by the IRB of Kansai Medical University (No. 1520-2, January 5, 2016: version 1.3). The study opened for recruitment in February 2016, and recruitment will continue until August 2017.

Discussion

This study was designed to address the safety and efficacy of the engraftment of nevus tissue inactivated by HHP for dermal reconstruction in combination with CEA. This study is the first-in-man clinical trial to reuse the nevus tissue inactivated by HHP as an autologous dermis for the reconstruction of full-thickness defects after the inactivation of the pigmented nevus. As for the regeneration of the dermal component for the recipient site for the CEA, an allogeneic skin graft is the first line of the treatment. However, the supply of allogeneic skin is limited and constantly insufficient in Japan. Allogeneic skin accelerates the formation of the dermal component, but it does not survive on the recipient site nor does it serve as an autologous dermis [13]. The inactivated nevus is the patient's autologous tissue, and it has the potential to survive and serve as an autologous dermis without inflammation or rejection.

HHP technology can inactivate all of the cells in the nevus tissue, regardless of the thickness of the nevus tissue. According to Pascal's principle, pressure is transmitted, undiminished, in an enclosed static fluid. However, the melanin pigment is not damaged after HHP and it will remain after retransplantation. We think that the melanin pigment will be gradually biodegrade because it is a peptide and the nevus cells that produce the pigment will not be present after HHP. If the pigment does not biodegrade, we will use laser treatment to remove the pigment that remains after the present protocol.

This HHP treatment seeks to inactivate tumor cells in the tumor tissue and reuse the matrix itself after inactivation. This concept could be applied to the treatment of other skin tumors that require extensive safety margins such as malignant melanoma or squamous cell carcinoma. In addition, this could also be used in the treatment of tumors of other types of tissue. If successful, this HHP technology could lead to breakthrough treatments for benign and malignant tumors from the perspective of tissue regeneration.

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Authors' Contributions

NM, MS, NK, KK, and TY designed the study. NM prepared the first draft of the manuscript. NM, NK, and KK will treat patients and conduct the clinical trial. NM will generate the allocation sequence, enroll participants, and assign participants to the interventions. CJ and TY contributed to the engineering of the HHP procedure. NM is a grant holder. All of the authors contributed to refining the study protocol and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CEA: cultured epidermal autograft
GCMN: giant congenital melanocytic nevus
HHP: high hydrostatic pressurization
IRB: institutional review board

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Protocol

A Dyadic Behavioral Intervention to Optimize Same Sex Male Couples' Engagement Across the HIV Care Continuum: Development of and Protocol for an Innovative Couples-based Approach (Partner Steps)

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Abstract

Background: An estimated one- to two-thirds of new human immunodeficiency virus (HIV) infections among US men who have sex with men (MSM) occur within the context of primary partnerships. Thus, HIV interventions that recognize and harness the power of relationships are needed. Increasingly, HIV prevention efforts are being directed toward improving engagement across the HIV care continuum from testing to linkage to care, antiretroviral therapy (ART) adherence, engagement in care, and viral suppression. However, to our knowledge, no behavioral interventions have attempted to address the HIV care continuum using a dyadic approach.

Objective: The objective of this paper is to describe the development of and protocol for an innovative couples-based approach to improving treatment adherence and engagement in care among HIV serodiscordant and concordant HIV-positive same sex male couples in the United States.

Methods: We developed the Partner Steps intervention by drawing from relationship-oriented theory, existing efficacious individual-level ART adherence interventions, couple-focused HIV prevention interventions, and expert consultation. We incorporated new content to address all aspects of the HIV care continuum (eg, linkage to and retention in care) and to draw on relationship strengths through interactive activities.

Results: The resulting theory-based Partner Steps intervention is delivered by a trained bachelors-level counselor (interventionist) over 2 in-person sessions with male-male dyads in which at least 1 partner has recent suboptimal engagement in HIV care. Each session is designed to use relationship strengths to increase motivation for HIV care and treatment, and cover sequential intervention "steps" relating to specific challenges in HIV care engagement and barriers to ART adherence. For each step, couples work with a trained interventionist to identify their unique challenges, actively problem-solve with the interventionist, and articulate and commit to working together to implement a plan in which each partner agrees to complete specific tasks.

Conclusions: We drew on theory and evidence to develop novel intervention strategies that leverage strengths of relationships to address engagement across the entire HIV care continuum. We provide details on intervention development and content that may be of use to researchers as well as medical and mental health professionals for whom a dyadic approach to HIV prevention and care may best suit their patient population.

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KEYWORDS

HIV prevention; interventions; men who have sex with men; HIV cascade; HIV care continuum; ART adherence; engagement in care; couples-based interventions; intervention development

Introduction

Men who have sex with men (MSM) experience the highest risk for human immunodeficiency virus (HIV) acquisition in the United States [1], accounting for 64% of new infections in 2012 [2], up from 53% in 2006 [3]. Substantial evidence supports the role of primary partnerships in increasing HIV transmission risk among MSM, with an estimated one- to two-thirds of incident HIV infections among MSM attributed to sexual behavior with main partners [1,4-9]. Increased HIV risk within primary partnerships has been attributed to greater frequency of unprotected anal sex with main versus casual partners, lowered perceived risk within relationships and reduced HIV testing [10-18], and desires to demonstrate intimacy, trust, and commitment [7,8,19-23]. These relationship dynamics are associated with lower self-perceived HIV risk and suboptimal HIV testing among MSM in committed relationships [24,25], potentiating the prevalence of undiagnosed infections among male-male couples [26]. In addition to reducing morbidity and mortality from HIV infection, diagnosing HIV and linking HIV-infected individuals to care and initiating antiretroviral therapy (ART) greatly reduces the risk of onward transmission to their partners [27,28]. Despite the increasing interest in a couples-focused approach to HIV prevention among MSM [29-32], to date, no theory-based behavioral interventions exist to promote male-male couples' engagement in the HIV care continuum from linkage to retention in HIV care. This paper describes the development of a novel theory- and evidence-based intervention, Partner Steps, designed to promote and sustain engagement across the HIV care continuum among HIV serodiscordant and concordant HIV-positive male-male couples.

The HIV care continuum is a model for describing progression from HIV diagnosis to the achievement of controlled viremia in the body known as viral suppression [33,34]. Four stages are generally recognized in this continuum, including (1) diagnosis with HIV infection, (2) engagement in HIV medical care, (3) prescription of ART medications, and (4) achieving viral suppression (viral load <200 copies/mL) [35-37]. Individuals progress through these stages at different rates and may experience multiple challenges along the way (eg, transportation, communicating with providers, maintaining a Daily Medication Schedule; see Table 1 for a comprehensive list). The significance of these challenges is apparent in the observed percentage drops at each successive stage of this continuum. In 2011, an estimated 86% of all HIV-infected individuals in the United States had been tested and were aware of their HIV status [35,37]. Among those diagnosed with HIV, approximately 40% were engaged in HIV medical care. Of those engaged in HIV care, only 37% had been prescribed ART [35,37]. Although detailed national data on ART adherence are not available, studies in a variety of populations have documented a wide range of adherence (53-89%) [38-48], with an estimated national average of 70% [49]. With high ART adherence recommended for achieving viral suppression, the suboptimal levels observed may help explain why viral suppression, the ultimate end point of the HIV care continuum, is believed to be achieved by only 30% of the HIV-infected population [35,37]. It is also important to note that while the continuum is presented as a linear stage progression, it in fact represents a series of dynamic states. For example, some individuals may achieve and then lose viral suppression while others may experience periods in which they are retained and then absent from HIV care.

With viral suppression improving the health of HIV-infected individuals and reducing the likelihood of further transmission to partners, improving outcomes along the entire HIV care continuum has been identified as an important HIV prevention priority [50]. Recommendations from the US Preventive Services Task Force include screening all patients aged 15 to

65 for HIV. Moreover, in light of conclusive evidence that viral load suppression via ART helps prevent onward transmission to sex partners, the US Department of Health and Human Services guidelines now recommend prescribing ART medications to every adolescent and adult diagnosed with HIV regardless of disease progression status [50]. This shift away from the previous use of CD4 levels as a criteria for starting ART–in conjunction with expanded access to health care through the Affordable Care Act–has changed the climate in HIV prevention [51-53]. Increasing efforts are now being directed toward the development of innovative approaches to improving engagement along the HIV care continuum, particularly for populations most affected by HIV, including MSM, transgender women who have sex with men, and racial/ethnic minorities [35,50]. As main partner transmission accounts for an estimated one- to two-thirds of incident HIV infections among MSM, main-partner dyads could benefit greatly from an intervention centered on improving their engagement across the HIV care continuum [1,4-9].

Most prior interventions with male couples focused on the first stage of the HIV care continuum, getting couples tested, have been largely successful. For example, couples HIV testing and counseling (CHTC) is a particularly promising intervention for the earliest stage of the continuum, HIV diagnoses through testing. CHTC has been used as an HIV prevention intervention in Africa and other regions for over 20 years [54] and is considered by the US Centers for Disease Control and Prevention (CDC) to be a "high leverage HIV prevention intervention" [55]. The critical difference between the CHTC model and the conventional model of individual HIV testing and counseling is that partners receive HIV testing together and combined counseling and prevention messaging based on the characteristics of their relationships and their joint HIV status. CHTC has been adapted for US MSM and has been found to be highly acceptable [54,56]. Qualitative data from MSM in 3 US cities shows strong support among MSM for CHTC, including its use in forming sexual agreements (ie, rules regarding outside sexual partners) and communicating about sexual risk behaviors and condom use [57]. Recent work has both shown CHTC is highly acceptable to male-male couples [58] and demonstrated CHTC's safety, with safety measured as no increases in relationship dissolution or intimate partner violence among male couples undergoing CHTC [59]. CHTC is now endorsed by the CDC, and has been rolled out in over 40 US states [60]. Until now, few interventions have delved further into the HIV care continuum (eg, engagement in care). Instead, most of the limited number of dyadic interventions emphasize a single stage in the HIV care continuum or are not tailored to the specific needs of male-male couples. In particular, the handful of intervention studies that have worked with couples to improve ART adherence [61] were not specifically designed for male-male couples and did not address important issues upstream in the HIV care continuum [31,61,62].

Partner Steps is a counseling intervention designed to address multiple stages of the HIV care continuum within the male-male dyad [32,62]. Recent findings indicate that such an intervention would be acceptable among same-sex male couples. Findings from focus groups conducted by Goldenberg et al [32] suggest male-male couples may be interested in more comprehensive care at the level of the dyad. Many couples indicated that comprehensive dyadic care had the potential to strengthen positive relationship dynamics [32]. In addition, there is evidence that dyadic interventions result in better ART adherence when compared with individual adherence counseling interventions. For example, in a randomized controlled trial of 215 couples, including male-male couples, HIV-infected persons receiving ART adherence counseling with their partners had significantly higher levels of ART adherence compared with those who did not [61]. Similarly, among a cohort of 210 male-male HIV-serodiscordant couples, both the patient's positive appraisal of his relationship and his partner's positive beliefs regarding treatment self-efficacy were linked to greater self-reported ART adherence; although, in this study, participants did not receive counseling as a dyad [63]. Working with couples offers unique advantages for designing an intervention: couples can cope together to reduce stress burden; work in tandem to remember routine responsibilities; problem solve more effectively; pool resources; and navigate social environments as a unit. These advantages in addition to reported interest in couples-based interventions serve as the impetus behind Partner Steps.

With no interventions to date attempting to address every stage of the continuum for broadly defined male-male couples (in which at least one partner is HIV positive) and evidence that such an intervention would be acceptable among male-male couples [31,32,62], we developed Partner Steps for HIV serodiscordant and concordant HIV-positive male-male couples by adapting selected content from efficacious adherence interventions at the individual level. We also developed entirely new content and approaches for working with male dyads. The aim of this article is to describe our intervention development process in order to inform other investigators and provide recommendations for programs in HIV prevention and treatment.

Methods

Overview and Specific Aims

Partner Steps is designed to increase couples' motivations, behavioral and problem-solving skills, mutual support, and collaboration with the ultimate goal of promoting engagement in HIV care and ART adherence. We developed this theory-based intervention with attention toward leveraging relationship strengths within a diverse community of HIV serodiscordant and concordant HIV-positive male-male couples at any stage of engagement in HIV care, including those who are HIV care–naive. The intervention development process involved drawing from both theoretical and evidence bases to consider men's relationship dynamics throughout all components of the resulting Partner Steps program. All of the research described in this multisite project received ethics approval from the institutional review boards of Emory University in Atlanta, GA, Fenway Health in Boston, MA, and the Ann & Robert H. Lurie Children's Hospital in Chicago, IL.

Theoretical and Evidence Base

Several promising models for addressing particular components of the HIV care continuum have been developed and tested in

other contexts and populations. To identify and develop an intervention relevant to improving couples' HIV care outcomes, we critically assessed prior ART adherence interventions for HIV-infected individuals including Safren and colleagues' [64] influential Life-Steps intervention. Over the past decade, Life-Steps has been adapted for diverse settings and populations leading to content and structure that differs with respect to target behaviors, dose (eg, length, number of sessions), interventionist background and training, and assessment and follow-up techniques [65,66]. Notably, members of our study team recently adapted Life-Steps for HIV-infected adolescents, which required greater emphasis on the role of family, peer, and other interpersonal relationships and social contexts [65]. Building on this work we developed content and structure appropriate for HIV serodiscordant and concordant HIV-positive male-male couples.

Life-Steps integrates general principles of cognitive behavioral therapy, motivational interviewing, and problem-solving [67] to help patients solve "blocks" of adherence problems through a step-by-step approach [64]. To the extent possible and relevant, we preserved the overall structure of this efficacious intervention, in which a trained interventionist engages participants in a series of educational, problem-solving, and rehearsal strategies to identify specific barriers to ART adherence and develop solutions through a series of small, manageable problem-solving "steps." This process was designed to train individual patients to identify and address complex and stressful challenges of medication adherence into simplified, proximal steps addressed in a checklist format [64]. For the unique social and relationship contexts that characterize male-male couples' experiences, we adapted, reorganized, and expanded the original 10 steps to involve both partners in identifying barriers to and developing solutions for improved ART adherence and engagement in HIV care.

We subsequently reviewed the existing literature's evidence from observational and intervention studies focusing on medication adherence and engagement in HIV care separately and for individuals. Absent from these programs was a focus on social and relationship dynamics; we thus drew from multilevel frameworks [68,69] and theories of interpersonal interaction to help conceptualize adaptions that would be necessary given the unique social experiences and relationship dynamics of male-male couples. Lewis et al's [69] conceptual model of couple's health behavior change incorporates theories of communal coping and interdependence to understand how relational and dyadic processes determine behavior change, particularly in the uptake of risk-reducing behaviors. This model posits that the couple's interdependence influences behavior as motivations shift from what is best for each partner's wellbeing to what is best for the relationship. Using this construct, the adaptations or additional steps centered on building communal social skills by harnessing a couple's motivation to keep their relationship healthy, thereby increasing the likelihood of adopting positive health behavior change and sustaining this change as they work together. When adapting and enhancing the original 10 steps to a dyadic context, we drew from these two perspectives in order to infuse Partner Steps with adequate consideration of how interpersonal interactions could be used to increase couples' motivation for engagement in HIV care. We also reviewed the counseling principles that inform existing couples-based sexual health and primary HIV prevention interventions [70-72], including CHTC [50,54,56]. This relationship-oriented theoretical framework guided our review and adaptation of existing individual-based intervention components.

Adaptation of Existing Evidence-Based Interventions for Couples

We adapted existing steps for a context in which a trained interventionist meets with both partners jointly, equally engaging both partners in the session despite the desired outcome of the curriculum being optimal ART adherence for the HIV-infected partner. For example, the first original step of Life-Steps provided information to individual patients on the importance of ART adherence for improved individual health outcomes (eg, through reduced viral load) via a video followed by discussion with the interventionist [73]. To increase the relevance of this background information and motivation for HIV-negative partners to help their HIV-positive partners with adherence, we updated and revised the content of this step to emphasize how optimal adherence and engagement in care can reduce transmission, simultaneously protecting the HIV-negative partner from transmission and improving the health of the HIV-positive partner [27,28]. Rather than employ the original video format, we elected to deliver the information through an engaging conversation, which required each partner to interact with the interventionist and with one another (eg, after delivering a key message, the interventionist asks one partner to explain, in his own words, to the other partner).

While increasing dyadic interaction and collaboration, these adaptations to leverage interpersonal dynamics and strengths are still in line with Life-Steps' utilization of effective approaches that increase motivation for behavior change [64] and encourage participants to take an active role in developing, practicing, and planning to implement their own solutions to specific adherence problems [73]. One particularly useful method from Life-Steps that we preserved throughout our adaptation is based on problem solving methods [67]. For example, for each adherence barrier, individuals are encouraged to articulate their goal, identify potential barriers to reaching the goal, and develop a plan to overcome the barriers [64]. We preserved the structure of this method but reframed activities and language such that interventionists encourage both partners to work together to articulate a particular goal, identify barriers to reaching that goal, and develop plans to overcome those barriers that recognizes potential stumbling blocks and includes "backup" plans [64]. For example, for the original Life-Steps topic of communicating with providers, we encourage both partners to identify barriers and develop and practice communication strategies together. Partners are also encouraged to attend health care visits together, if possible and appropriate (discussions can be tailored to couples' unique relationship dynamics, which are explored by the interventionist in the introductory "getting to know your relationship" module).

Reorganizing Existing Intervention Content to Enhance Focus on Relationship Contexts

We reorganized some of the original Life-Steps content given that we would need to save time to cover additional (new) content covering relationship and social topics, mental health and substance abuse, and linkage to and engagement in HIV care, as described below (see Multimedia Appendix 1). Due to the increased amount of content, we planned a two-session intervention instead of the original single-session format of Life-Steps. For the first "adherence steps" session, we grouped six steps that related to logistical considerations, including getting to appointments (transportation), obtaining medications, communicating with providers, storing and transporting medications, coping with side effects, and developing a concrete daily medication schedule. The overall objective for each of these steps is to enable couples to jointly identify related adherence barriers and, if barriers exist, develop solutions and make specific plans for overcoming the logistical barriers together. For each specific step, we also adapted content and interventionist scripts to better engage HIV-negative partners and facilitate collaboration within couples in the problem solving process.

Based on the literature on male couples and expertise within our team [32,74], we recognized a need to expand upon the original Life-Steps content in order to better address the social contexts and relationship dynamics experienced by male-male couples and created several new, more social-oriented steps. We grouped these four new relationship and social steps into a second "adherence steps" session covering self-care and relationships, communicating within relationships, managing social lives and other interpersonal relationships, and dealing with privacy and disclosure. The objectives for these steps vary from the objectives of the previous set of more logistical steps to focus on and require more nuanced discussion of barriers within these interpersonal domains [32,69,74,75]. Similar to the first session, if couples jointly identify adherence barriers relating to any of these steps (eg, having a social network unaware of the couples' serodiscordant status), the interventionist then works with the couple to develop solutions and make specific plans that partners can implement together. These modules explore social and relationship influences on adherence and provide partners with a safe space to problem-solve and develop plans for achieving progress toward the ultimate goal of viral load suppression. One exception is the topic of disclosure, for which the interventionist emphasizes respect for individual preferences and works with couples to ensure that they leave with a "shared vision" even if that requires a compromise between partners.

Expansion of Existing Intervention Content to Promote Engagement in HIV Care

In addition to logistical and social/relationship-focused adherence "steps" described above, we developed new content to address other stages of the HIV care continuum, recognizing that some couples in this population require additional motivation and problem-solving around linkage to care and retention in care over time (see Multimedia Appendix 2). While initial linkage to care (including connecting with a provider for the first time) and sustained engagement in care over time represent two different components of the HIV care continuum, the underlying motivation, potential barriers, and skills necessary to achieve linkage and engagement overlap significantly. We thus combined these two components of the HIV care continuum into the resulting "preadherence steps" session through which partners are counseled together. The overall format of this session (which can stretch over two sessions as necessary) involves new content focused on increasing motivation (ie, background information), problem-solving around a set of identified barriers (ie, steps), and developing a long-term plan for improved engagement in HIV care.

To develop this new content, we first reviewed the literature on HIV care engagement as well as previous quality improvement projects to identify potential barriers and existing efficacious methods for facilitating engagement in HIV care [33,35-37,76-87]. We adapted these previous interventions and recommendations to fit the foundational "steps" structure and the social and relationship context of male-male couples. First, to increase motivation for initial linkage to care and engagement in care over time, we reviewed recent literature on seeing a provider regularly and the impact on long term health outcomes [33,86,88,89]. The resulting motivational background information, similar to the "psycho-education" content included in the original Life-Steps [64] and our updated adherence background information (as described above), explain the importance of connecting with providers to receive information about treatment options, monitoring viral load levels, assessing for possible comorbidities and coinfections requiring additional treatment, and ultimately keeping one's partner and relationship safe [33,86,88,89]. As all couples could benefit from this motivational information, regardless of progression along the HIV care continuum [33], the study team elected to offer this information to all couples as a core element of the intervention.

Next, we reviewed the literature on recommendations to increase engagement in HIV care as well as barriers to achieving this (eg, housing [90-92]) to develop a set of problem-solving steps for engagement in the HIV care continuum [78-81,83,85,87]. In particular, the International Association of Providers of AIDS Care guidelines for improving entry into and retention in care and ART adherence were central to the development process of the "preadherence steps" [85]. Topics identified in the literature for these steps were carefully considered and adapted for relationship contexts, including coping with HIV diagnosis (or serodiscordant status), obtaining health insurance/coverage, navigating the health care system, scheduling and getting to appointments, increasing comfort with providers, anticipating and coping with medication side effects, and increasing interest in HIV care. To be responsive to couples' unique situations and allow partners sufficient time to work together to generate and plan for implementing solutions to the problems of most relevance to them, this portion of the session begins with an interventionist-administered checklist in which both partners are asked if they endorse particular engagement challenges. Interventionists then initiate problem solving around only the identified challenges, and partners are encouraged to develop solutions and plans together.

Additional Content and Structure Considerations

In addition to adapting, reorganizing, and expanding upon existing interventions, we developed new content to be covered at various points during Partner Steps to make it more comprehensive and relevant to diverse male-male couples. First, we incorporated brief background information on antiretroviral pre-exposure prophylaxis (PrEP) for HIV prevention. Given the evidence on PrEP for preventing transmission within serodiscordant couples, we incorporated an explanation of PrEP, using simplified language, into the background (motivational) information portion of the adherence and engagement steps sessions. Second, we incorporated an enhanced focus on mental health and substance use within dyadic contexts as acknowledged, but not explicitly addressed, by the original Life-Steps intervention [64]. Extensive research has shown that substance use behaviors are highly interdependent within intimate couples [75,93,94] and are associated with high risk sexual behaviors [95] including breaking sexual agreements among male couples [96]. Third, we adapted and refined framing, content, language, and structure of all Partner Steps modules to make them relevant for concordant HIV-positive couples. The overall aim of the concordant positive intervention is to move both partners through the HIV care continuum toward viral suppression. The intervention leverages relationship strengths, fosters a spirit of team-based care, and encourages each partner to practice self-care while at the same time supporting the needs and preferences of their partner. Similarly, skill-building activities aim to transform both men into engaged patients and supportive partners: each partner cultivates skills for engaging in HIV care and maintaining adherence while also supporting their partner in doing the same thing. The manual also de-emphasizes background information on primary transmission of HIV infection within relationships to instead place greater emphasis on explaining the importance of treatment for the health of both partners and their overall relationship.

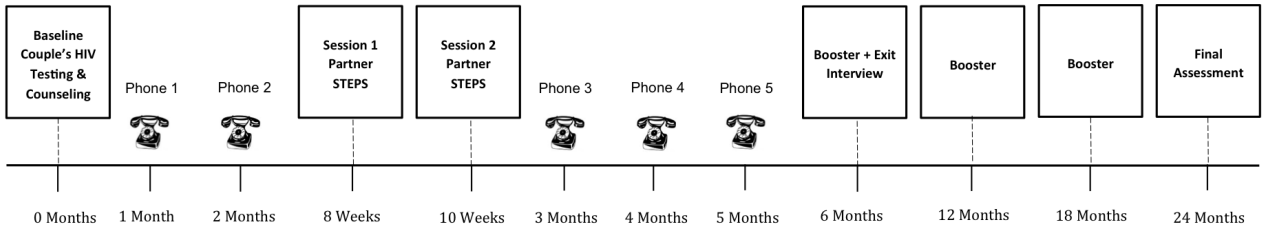
Finally, in order to increase cohesion throughout the comprehensive Partner Steps intervention for any couple, regardless of dyadic HIV status or stage along the HIV care continuum, we streamlined the numerous intervention modules using a singular format which used common language, session elements, and styles (eg, for introductions, check-ins, background information, review/planning sessions at the end, and encouragement of interaction throughout all modules). To increase ease of intervention delivery, which could ideally occur through community health centers (where it has been designed by our team), and HIV testing sites, all content was compiled into a single theory-based intervention (one for serodiscordant couples and another for concordant HIV-positive couples). An interactive, 2-day training was developed to ensure that interventionists understood the program rationale and objectives, mastered the methods involved, and had ample opportunity to practice delivering the intervention components and receive feedback and make improvements in counseling styles and techniques. The training was designed for interventionists who could be HIV counselors, community health workers, social workers, or other health care professionals who have been trained in the protocol. Experts on our team and in the broader antiretroviral adherence field carefully reviewed the manual and related training materials.

Results

Overview of Partner Steps Content and Delivery

The resulting theory-based intervention consists of two in-person, manualized intervention sessions delivered to both partners at the same time approximately 2 weeks apart (Figure 1).

Figure 1. Partner Steps intervention structure and timing.



Men in the intended target population are ≥18 years of age, biologically male, report being in a "committed" relationship for ≥1 month, and are not experiencing intimate partner violence or coercion to participate. Periodic check-in phone calls are conducted with both partners to assess linkage to care, retention in care, medication uptake and adherence, and relationship dissolution. A trained bachelors-level counselor (interventionist; described below) delivers each intervention session using a Partner Steps manual that structures each session, provides example prose, indicates probing questions and problem-solving approaches, and provides specific activities designed to facilitate active participation from the couple (eg, use of notecards or smartphones; see Table 1). Each session is comprised of a specific topic (eg, background information, communicating with providers) and ends with interactive activities and discussions designed to create a participant-driven plan in which each partner takes ownership and agrees to be responsible for specific tasks (eg, the HIV-negative partner may agree to help with specific activities, as detailed in Table 1).

Table 1. Content of the partner steps intervention.

Step	Objectives[a]	Problem Solving	Activities
1. Transportation to appointments	Objective A (if barriers are identified through Objective A, then: Objectives B, C)	Encourage the couple to travel together Encourage the couple to combine medical visits with other errands on the same trip Encourage the couple to ask friends and family for support with transportation Refer the couple to a case manager to assist with transportation discounts or vouchers	Transportation mapping: facilitate an interactive transportation planning session using free, public-access mapping software
2. Obtaining medications	Objective A (if barriers are identified through Objective A, then: Objectives B, C)	Provide couple with medication delivery service options Suggest couple take turns picking up medications Encourage couple to set up auto-refills Encourage couple to set reminders to go to the pharmacy	Facilitated discussion: have each partner turn to each other and work together to come up with a plan to pick up medications regularly
3. Communicating with providers	Objective A (if barriers are identified through Objective A, then: Objectives B, C)	Encourage both partners to attend the visit. Discuss the merits of having 2 people asking questions and 2 people listening to answers Encourage both partners to come up with questions for the provider ahead of time	Writing exercise: have each partner write down questions for the provider on a 3×5 notecard or on their smartphone during the session
4. Storing and transporting medications	Objective A (if barriers are identified through Objective A, then: Objectives B, C)	Encourage the couple to bring a spare dose with them regularly or to store a dose in a strategic location (eg, in a car, work desk, or partner's house) Suggest the couple plan ahead for long nights out or staying somewhere other than regular residence (traveling) by bringing the appropriate number of doses along	Summarization: solicit opinions on strategies discussed from both partners
5. Coping with side effects	Objective A (if barriers are identified through Objective A, then: Objectives B, C)	Encourage the couple to discuss experiences with side effects with their provider Encourage partners to be open with each other about experiences with side effects Suggest potential routine adjustments (eg, getting more sleep, drinking fluids, exercise, or relaxation practices)	Couples coping brainstorm: facilitate a brainstorming session where couples come up with and reflect upon fun activities they do at home that could be used when side effects are pressing (eg, movie night, game night, staying in)
6. Having a daily medication schedule	Objective A (if barriers are identified through Objective A, then: Objectives B, C)	Suggest other partner take a multivitamin or similar routine to taking medications Suggest the couple combine and integrate pill taking routine with other routines (eg, morning routines, regular schedules) to develop associations between the activities Encourage the couple to use pill boxes Encourage the couple to use alarms	Dot stickers: hand out dot stickers to the couple and explain how they place these in strategic locations around the house to help remind them about taking their medications; Phone reminders: have couple schedule in a recurring reminder on their phones (discretely) to take medications while they are in the session
7. Adherence, self-care, and your relationship	Objectives D, E, F, G, and H	Encourage couple to identify relationship strengths that could be useful for adherence If applicable, promote collective coping mechanisms in place that help alleviate mood considerations If applicable, promote teamwork in reducing the influence of substances on adherence	Reflection: have the couple reflect on self-care concerns (eg, mood, substance use, etc) and relationship-care concerns (eg, collective mood, routines, behaviors, etc) and how these might impact medication adherence

Step	Objectives[a]	Problem Solving	Activities
8. Communicating within your relationship	Objectives D, E, F, G, and H	Suggest couples write down discussion topics before discussing with each other Facilitate a discussion about signs and signals that each person feels they are "heard" Facilitate a discussion about each partner's ideal communication style	Role play: have each partner turn to the other and identify when, where, and how it will be appropriate to discuss adherence. Then have each model an adherence discussion opener.
9. Managing your social life and other relationships	Objectives D, E, F, G, and H	Encourage couple to pool collective knowledge about people in their life to create a plan to cope with social support concerns Create an adherence plan for going out to parties or traveling on weekends Facilitate a discussion about how each partner could balance the various social support systems available to them	(No activity)
10. Dealing with privacy and disclosure	Facilitate discussion of the couples' privacy and disclosure plan	Facilitate a detailed discussion about who the couple is willing to disclose to or not disclose to	(No activity)
	Facilitate the couples' ability to problem-solve around privacy and disclosure concerns that serve as barriers to adherence	Provide storage and transportation ideas (eg, secret locations, containers, etc)	
	Create a participant-driven plan and a backup plan to implement in the future to ensure couple leaves session two with a common vision for dealing with privacy and disclosure		

[a]Objectives: A: To identify "step"-relevant barriers to successfully executing "steps" 1-6; B: To facilitate the couples' ability to overcome "step"-relevant barriers through participant-driven problem-solving; C: To create a participant-driven plan and a backup plan to implement in the future in order to overcome "step"-relevant barriers; D: To identify "step"-relevant strengths; E: To identify "step"-relevant concerns and problems; F: To promote "step"-relevant strengths for the purpose of improving medication adherence; G: To facilitate the couples' ability to work together and problem-solve regarding "step"-relevant concerns that serve as barriers to adherence; H: To create a participant-driven plan and a backup plan to implement in the future to leverage "step"-relevant strengths for adherence.

The intervention sessions are structured to cover the following topics: introduction and background, preadherence or adherence steps (specific modules), and review and planning. The manual is also "tracked," allowing the interventionist to do a quick inventory at baseline (Figure 2; Table 2) to determine where the couple needs to begin. Depending on how far couples have progressed along the HIV care continuum, couples either receive preadherence or adherence steps, and the interventionist can also administer "booster sessions" at 6-month interval follow-up visits to quickly review all material covered in the first session, allowing the couple to receive as many needed "steps" as possible (eg, the dyad needs to cover more than six steps in one session). The manual uses simplified language (ie, layman's terms) to relate to the broadest audience possible and to avoid distracting or confusing language and unnecessary detail. Lastly, the manual includes worksheets or "takeaways" where participants write down solutions to their adherence blocks and can reference these, facilitating the usage of Partner Steps material outside of the sessions.

Figure 2. Partner Steps intervention content for the HIV care continuum.

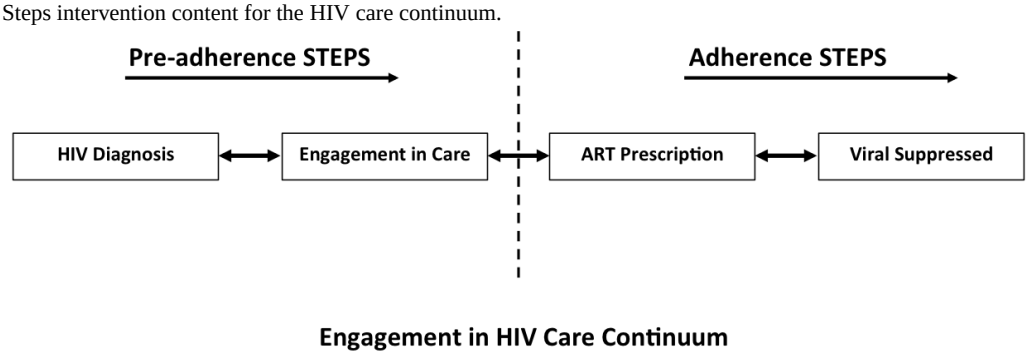


Table 2. Assessment tool for partner steps preadherence content.

Preadherence steps	Screening and assessment questions	Yes or No?			
		HIV-infected partner		HIV-uninfected partner	
1. Coping with HIV	Do either of you feel that you are having trouble or difficulty coping with your HIV diagnosis?	Yes	No	Yes	No
	Are either of you worried about other people learning about your HIV diagnosis and/or treating you differently?	Yes	No	Yes	No
2. Health insurance	Are you/your partner having any trouble getting health insurance or are you worried about medical costs?	Yes	No	Yes	No
3. Health care navigation	Are you unsure who to call or how to navigate the health care system?	Yes	No	Yes	No
4. Getting to appointments	Is making and remembering appointments difficult?	Yes	No	Yes	No
5. Transport	Is transportation a challenge?	Yes	No	Yes	No
6. Housing	Do you not have stable housing right now?	Yes	No	Yes	No
7. Comfort with providers	Are either of you worried about unfriendly health care providers or staff or how you might be treated?	Yes	No	Yes	No
8. Provider communication	Are either of you concerned that it might be difficult to talk with health care providers?	Yes	No	Yes	No
9. Side effects	Are either you concerned about medication side effects?	Yes	No	Yes	No
10. Lack of interest	Do you feel it's not necessary to see a doctor or start treatment right now?	Yes	No	Yes	No
11. Mood management	Do either of you feel that your mood has gotten in the way of seeking HIV care?	Yes	No	Yes	No
12. Substance use	Has drinking or using drugs gotten in the way of seeking HIV care?	Yes	No	Yes	No

Training of Interventionists

Partner Steps interventionists complete a 2-day training comprised of seven training "modules" covering background information, couples counseling skills, intervention content, and opportunities to practice counseling through role-playing scenarios. The first two modules are designed to impart an understanding of the intervention, aims, theoretical framework, and counseling skills. After mastering these concepts and skills, the training modules guide interventionists through all Partner Steps content, including the preadherence and adherence problem-solving "steps." This phase of the training is discussion-based, interactive, and requires participants to practice newly acquired counseling skills in a series of role-playing scenarios that are observed by trainers. An important emphasis throughout the entire intervention manual and interventionist training protocol is a focus on increasing interaction within dyads, with the ultimate goal of engaging both HIV-negative and HIV-positive partners. Throughout Partner Steps, interventionists work to identify and leverage relationship strengths that can be applied toward helping the couple better problem solve together. The training emphasizes motivational interviewing techniques adapted for a couple's context, such as both partners completing motivation scales, sharing these with one another, and then discussing their results together to create a unified plan.

Fidelity Monitoring

In order to monitor fidelity to the Partner Steps manual, we created a two-part system: (1) interventionists complete a checklist immediately following intervention delivery, and (2) all intervention visits are audio-recorded and reviewed by an outside monitor (eg, any intervention-trained study staff member who was not present during the intervention). Both the interventionist checklist and the outside monitoring form contain specific directions to standardize the information reported. The forms asks detailed questions about which required and recommended intervention elements were performed by the interventionist. Required and optional elements that are not performed must be explained and/or justified in the notes section. As the success of the previous Life-Steps intervention hinged on successful problem solving and planning on the part of the interventionist as well as from the participant, the fidelity monitoring plan accounts for these interactions. Thus, for each of the counseling "steps," the forms require the interventionist to report on a scale with three responses (0 = not sufficiently covered; 1 = somewhat covered; and 2 = sufficiently covered) the level of problem solving and the level of planning that occurred during the visit. The forms also assess the level of engagement from each participant individually and the couple as a whole. This fidelity monitoring plan will enable study staff to improve upon and adapt the intervention based on participant feedback and results from the quality assurance of the outside monitor.

Discussion

Summary of Key Innovations

This paper describes the development of Partner Steps, a theory-based intervention to improve engagement in HIV care and ART adherence among HIV serodiscordant and concordant HIV-positive male-male couples. We drew on theory and evidence to develop Partner Steps, which leverages the strengths of men's relationships to address engagement in the entire HIV care continuum, extending beyond previous individual- and couples-based interventions focusing on HIV treatment adherence alone. In order to address the unique needs of male-male couples in which at least one partner is HIV positive, we innovated new content and counseling approaches to better accomplish the aims of this intervention. After describing the content and methods of Partner Steps, which is delivered by trained interventionists to couples through two in-person sessions, several brief phone calls, and booster sessions, we highlight several key innovations and provide recommendations for other researchers interested in using a dyadic approach to HIV prevention.

First, the intervention was designed to be adaptable and applicable for couples at any stage along the HIV care continuum. This flexible design recognizes the necessity of passing through each stage of the continuum in sequence in the current health care system, but also the reality that HIV-positive individuals can regress, cycling through struggles with ART adherence, and falling out of care. As a result, the intervention triages the most important problem solving "steps" according to the couples' recent HIV care experience. This adaptability is achieved through subdividing the intervention into "preadherence" steps and "adherence" steps and by casting a wide net as to the potential barriers to engaging in HIV care. Although prior couples interventions have focused on one element of the HIV care continuum, this intervention empowers couples to work together in all aspects of HIV care [31,97].

Second, we integrated couples counseling approaches and relationship strength-building exercises to increase the capacity of these couples to work together on problem-solving strategies [32]. The intervention promotes pre-existing and established abilities to accomplish the following: work together as a united team; support each other emotionally and otherwise; cope with hardships; and problem-solve together through challenges. These pre-established skills are then harnessed for the purpose of achieving goals that progress the couple across the HIV care continuum in the direction of the target aim, viral suppression. Though past interventions have worked with couples in similar ways [98], few have tailored the intervention to male-male couples or accounted for a diverse set of aims that relate to the HIV care continuum.

As a third point of innovation, we used a broad definition of "couples" to be inclusive of a more diverse array of male-male couples. Rather than the longer-term inclusion criteria of relationship durations of ≥6 months used in many existing intervention studies, we developed an intervention that would be inclusive of shorter-term couples in which partners felt "committed" to each other "above all others" with relationship duration of at least 1 month. We used this relatively open inclusion criterion, in which couples are not required to be monogamous, legally committed, or in a relationship for a significant amount of time, in order to engage a broad range of couples who could benefit from the intervention. Our study team intentionally limited any assumptions about signifiers of love, trust, intimacy, and relationship strength based upon sexual agreements or relationship duration. We believe that this approach will help maximize accessibility to Partner Steps for many couples who could benefit from the intervention. Prior studies with couples have had narrower eligibility criteria, overlooking partnerships in need of assistance with the HIV care continuum [62].

Finally, Partner Steps is innovative in its accommodation of both HIV serodiscordant and concordant HIV-positive male couples. Two manuals were developed, 1 for each combination of serostatuses. This decision is based upon a large number of considerations related to the elements within the intervention that promote better engagement across the HIV care continuum that concordant HIV-positive couples stand to benefit from as well. Very few interventions in the United States to date have worked with couples in which both partners are HIV-positive and struggling with different aspects of HIV care and treatment [31,97].

Limitations and Conclusions

This protocol description is limited by several factors. First, we lack of data on the feasibility, acceptability, and efficacy of the Partner Steps intervention. However, we are currently assessing these factors in 3 sites; thus, the processes and outcomes of the program will be assessed in a diverse population of male couples and by trained staff with slightly different background experiences and qualifications. We acknowledge that future research is needed to identify ideal intervention delivery settings, potential organizational challenges, and interventionists with the capacity to successfully engage and retain couples in the intervention over time. Exploring these aspects of intervention implementation in future research will be critical to the ultimate uptake and success of our intervention. Another limitation is that our preliminary intervention design centered on a target population ≥18 years of age and biologically male; intervention research is urgently needed for younger and transgender populations at risk for HIV acquisition who may benefit from dyad-focused interventions to promote their involvement in the HIV care continuum. Finally, many of the innovations of Partner Steps have the potential to inform a diverse array of ongoing and novel couples-based intervention structures and delivery formats (eg, using online social media) among key populations in diverse geographical settings [98,99]. Despite these limitations, we believe that Partner Steps has high policy relevance, particularly given new recommendations to prescribe ART medications to all adults and adolescents with HIV and a call from the White House Office of National AIDS Policy for innovative strategies to improve progression through the HIV care continuum [50].

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Sources for development of Partner Steps adherence content.

[PDF File (Adobe PDF File), 34KB - resprot_v5i3e168_app1.pdf]

Multimedia Appendix 2

Sources for development of Partner Steps preadherence content.

[PDF File (Adobe PDF File), 31KB - resprot_v5i3e168_app2.pdf]

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Abbreviations

ART: antiretroviral therapy
CDC: US Centers for Disease Control and Prevention
CHTC: couples HIV testing and counseling
HIV: human immunodeficiency virus
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis

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Protocol

Single-Incision Multiport/Single Port Laparoscopic Abdominal Surgery (SILAP): A Prospective Multicenter Observational Quality Study

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Abstract

Background: Increasing experience with minimally invasive surgery and the development of new instruments has resulted in a tendency toward reducing the number of abdominal skin incisions. Retrospective and randomized prospective studies could show the feasibility of single-incision surgery without any increased risk to the patient. However, large prospective multicenter observational datasets do not currently exist.

Objective: This prospective multicenter observational quality study will provide a relevant dataset reflecting the feasibility and safety of single-incision surgery. This study focuses on external validity, clinical relevance, and the patients' perspective. Accordingly, the single-incision multiport/single port laparoscopic abdominal surgery (SILAP) study will supplement the existing evidence, which does not currently allow evidence-based surgical decision making.

Methods: The SILAP study is an international prospective multicenter observational quality study. Mortality, morbidity, complications during surgery, complications postoperatively, patient characteristics, and technical aspects will be monitored. We expect more than 100 surgical centers to participate with 5000 patients with abdominal single-incision surgery during the study period.

Results: Funding was obtained in 2012. Enrollment began on January 01, 2013, and will be completed on December 31, 2018. As of January 2016, 2119 patients have been included, 106 German centers are registered, and 27 centers are very active (>5 patients per year).

Conclusions: This prospective multicenter observational quality study will provide a relevant dataset reflecting the feasibility and safety of single-incision surgery. An international enlargement and recruitment of centers outside of Germany is meaningful.

Trial Registration: German Clinical Trials Register: DRKS00004594; https://drks-neu.uniklinik-freiburg.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00004594 (Archived by WebCite at http://www.webcitation.org/6jK6ZVyUs)

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KEYWORDS

single-incision; quality study; minimally invasive

Introduction

The surgical standard for many abdominal diseases is changing. Traditionally, operative treatments meant open resection with laparotomy. However, over the last two decades, laparoscopic surgery has become a valuable alternative to many procedures, for example, cholecystectomy, appendectomy, or colon resection [1-6].

Conventional laparoscopic surgery requires a number of ports and a specimen extraction incision. Increasing experience with minimally invasive surgery and the development of new instruments has resulted in a tendency toward reducing the number of skin incisions. Natural orifice transluminal endoscopic surgery (NOTES) is the closest we have come to scar-free surgery because it does not leave any visible scars on the surface of the body. But NOTES is still an experimental approach [7]. For that reason, single-incision laparoscopic surgery could represent an attractive approach to minimally invasive abdominal surgery [8]. Several recently published retrospective and randomized prospective studies could demonstrate that the single-incision single port/multiport technique is not associated with a higher rate of morbidity or mortality compared with conventional laparoscopic surgery [9-21]. The majority of the relevant literature documents single-incision cholecystectomy. Single-incision appendectomy, liver surgery, colon surgery, and gastric surgery have also been described [22-28].

The determination of differences in the safety of classic multitrocar techniques compared to the single-incision techniques in prospective randomized studies is still difficult because of the rarity of some relevant complications. For example, injury to the major bile duct during surgery, with a frequency of about 0.5%, is a rare but severe complication. Large prospective randomized studies with many thousands of subjects are necessary to answer some of these clinically relevant questions; however, such large prospective randomized studies are not necessarily feasible. Prospective multicenter observational quality studies should support the data of published prospective randomized studies on this subject.

While surgeons develop new techniques for entering the abdominal cavity, patient safety should remain important. This prospective multicenter observational quality study will provide a relevant dataset reflecting the feasibility and safety of single-incision surgery. This study focuses on external validity, clinical relevance, and the patient perspective. Accordingly, the single-incision multiport/single port laparoscopic abdominal surgery (SILAP) study will supplement the existing evidence, which is currently too sparse to allow evidence-based surgical decision making.

Methods

Trial Objectives

The aim of the trial is to collect data about indications, technical aspects, mortality, and morbidity of single-incision multiport or single port abdominal surgery in daily use. All types of single-incision multiport or single port abdominal surgery will be included in the study. Every participating center will receive a quality report every year (online in real time for the individual center and in a print version once a year for the complete study). The analysis time period for the annual quality report is one calendar year. This quality report will be available for each center by May of the ongoing year and will include data from the previous year.

Trial Design

SILAP is a prospective nonrandomized multicenter observational quality study with no intervention.

Trial Duration and Schedule

The duration of the trial for each patient is limited to the hospital stay. The trial duration itself is from January 2013 to December 2018 (see Figure 1). The actual overall duration or recruitment may vary.

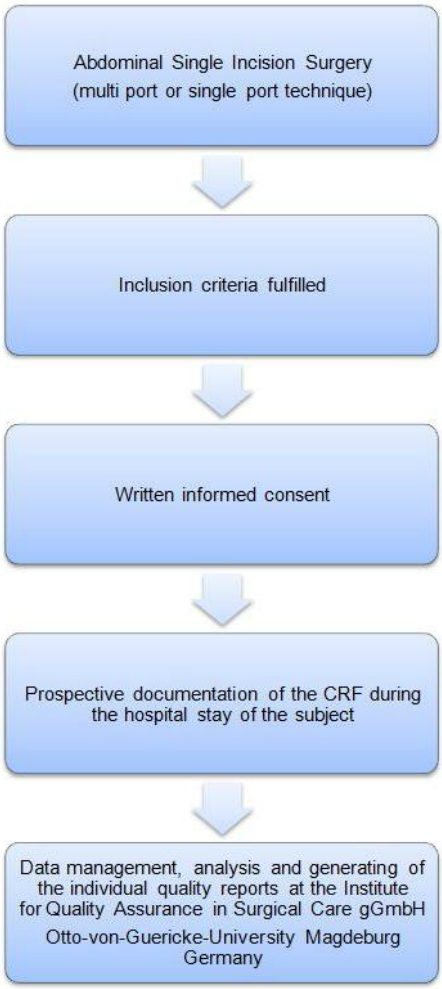
Figure 1. Trial duration.

Inclusion of first subject (FSI):	January 2013
Inclusion of last subject (LSI):	December 2018
End of trial last subject (LSO):	February 2019
Database closure:	Second quarter 2019
Final statistical analysis:	Third quarter 2019
Final report:	Fourth quarter 2019
First annual report:	Second quarter 2014

Study Population

All patients at the participating centers who are scheduled for single-incision multiport or single port abdominal surgery will be informed about the purpose of the observational trial. All types of abdominal surgery can be included. After being screened for the inclusion and exclusion criteria, eligible patients will be included in the trial (informed consent necessary) (see Figure 2). Surgery, examinations, and measures are not influenced by this observational trial.

Figure 2. Trial flow chart.



Number of Subjects and Trial Centers

A sample size calculation is not relevant for this observational quality study. A minimum of 100 surgical centers is expected. The participating centers will include a maximum of their patients fulfilling the inclusion criteria and not meeting an exclusion criterion. The data are documented using an Internet database including a self-plausibility control function.

Inclusion Criteria

Subjects meeting all of the following criteria will be considered for admission to the trial: (1) patients (≥18 years) scheduled for elective or emergency single-incision multiport or single port abdominal surgery (all types of abdominal surgery), (2) ability of subject to understand character of the clinical trial, and (3) able and willing to provide written informed consent.

Exclusion Criteria

Subjects presenting with the following criteria will not be included in the trial: participation in another intervention trial that interferes with the intervention and outcome of this study.

Outcome Variables

The following endpoints will be used to answer the trial goals: (1) Mortality (hospital mortality), (2) Morbidity, which includes complications during surgery (eg, bleeding during surgery or injury of small or large bowel, common bile duct, urine bladder, ureter, solid organs, or other intraabdominal structures) and post-operative complications (eg, wound infection according to Centers for Disease Control and Prevention [CDC] criteria, intraabdominal infections, urinary tract infection, pneumonia, cardiac complications, pulmonary complications, intraabdominal bleeding after surgery, ileus, insufficiency of an anastomosis, reoperation, burst abdomen, or other complications), (3) Patient characteristics (sex, age, height in cm, weight in kg, duration of hospital stay, duration of hospital stay after surgery, routine or emergency surgery, date of surgery, American Society of Anesthesiologists classification [29], indication only for cholecystectomy), and (4) Technical aspects, such as type of surgery (ie, appendectomy or cholecystectomy), type of single-incision procedure (multiport or single port), location of the single incision (umbilical or other position), used port device or size and number of the trocars for single-incision surgery, success rate of the single-incision procedure (procedure finished in single-incision technique), incision to closure time (operation time), conversion rate, device for closing the cystic duct, use of holding sutures or other holding devices, and type of sutures for closing the fascia incision.

The assessment of outcome variables comprises (1) mortality, that is, death due to any cause at any time during the hospital stay, and (2) morbidity (during the hospital stay), including:

- surgical site infections (SSIs) will be assessed at discharge and divided into superficial and deep incisional SSIs according to the CDC definition [30] (see Figure 3)
- post-op pulmonary infection (pneumonia) will be assessed at discharge and is defined as infection of the lung with either evidence of increased infection parameters (C-reactive protein/CRP >2mg/dl and/or leukocytes >10 0000/ml), which are not caused by a different pathologic process, or evidence of pulmonary infiltration in the chest x-ray, requiring antibiotic therapy
- lesion of small or large bowel (any unplanned complete lesion of bowel)
- bleeding during surgery (any bleeding during surgery that required conversion to an open approach or to an multiple trocar approach or required transfusion)
- intraabdominal bleeding after surgery (requiring transfusion or surgery)
- intraabdominal infections (any kind of peritonitis, intraperitoneal abscess, infected bilioma requiring medication, drainage, or surgery)
- ileus (any kind of postoperative intestine passage disturbance requiring medication or surgery)
- insufficiency of an anastomosis (every anastomotic leak clinical or radiographic proven)
- burst abdomen (postoperative dehiscence of the fascia/peritoneum with or without dehiscence of the skin)

Other aspects for assessment are operation time (from skin incision to closure of wound), conversion rate (conversion from single incision to an open approach), and need for additional trocars.

Statistical Procedures

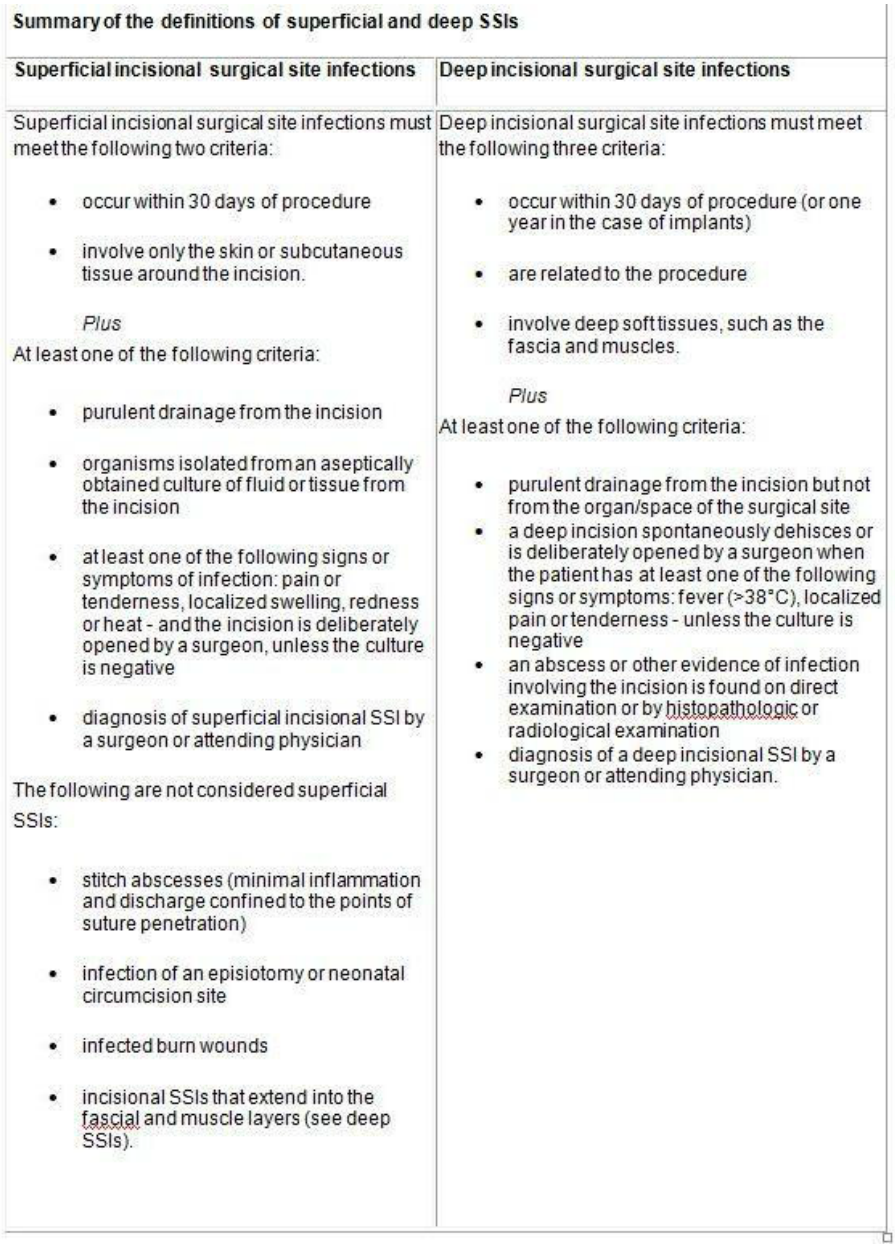
Every participating center will get an annual report detailing their cases. The documented case report form data will be described in relationship to the study population. Continuous variables will be represented with the usual international metrics: mean, standard aberration, minimum, lower quartile, mean, median, higher quartile, and maximum. Categorical variables will be represented with absolute and relative frequencies.

The overall description of the whole study population will be completed with subgroup analyses according to important patient characteristics (eg, gender and age) or technical aspects (eg, type of surgery). The influence of potential prognostic factors on the outcome variables will be studied in logistic regression analyses at an exploratory level.

Ethics

The procedures set out in a trial protocol pertaining to the conduct, evaluation, and documentation of this trial are designed to ensure that all persons involved in the trial abide by good clinical practice and the ethical principles described in the current revision of the Declaration of Helsinki. The trial will be carried out in accordance with local legal and regulatory requirements. The trial protocol, the informed consent document, and any other appropriate documents were accepted by the Ethics Committee of the Otto von Guericke University of Magdeburg (#148/12). Since all surgical procedures examined in this trial are well established and in current daily use, no increased medical risks are expected for the participating patients. This study is registered with the German Clinical Trials Register (DRKS00004594).

Figure 3. Definitions of superficial and deep SSIS (adapted from Horan TC et al).



Summary of the definitions of superficial and deep SSIs

Superficial incisional surgical site infections	Deep incisional surgical site infections
Superficial incisional surgical site infections must meet the following two criteria: • occur within 30 days of procedure • involve only the skin or subcutaneous tissue around the incision. *Plus* At least one of the following criteria: • purulent drainage from the incision • organisms isolated from an aseptically obtained culture of fluid or tissue from the incision • at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness or heat - and the incision is deliberately opened by a surgeon, unless the culture is negative • diagnosis of superficial incisional SSI by a surgeon or attending physician The following are not considered superficial SSIs: • stitch abscesses (minimal inflammation and discharge confined to the points of suture penetration) • infection of an episiotomy or neonatal circumcision site • infected burn wounds • incisional SSIs that extend into the fascial and muscle layers (see deep SSIs).	Deep incisional surgical site infections must meet the following three criteria: • occur within 30 days of procedure (or one year in the case of implants) • are related to the procedure • involve deep soft tissues, such as the fascia and muscles. *Plus* At least one of the following criteria: • purulent drainage from the incision but not from the organ/space of the surgical site • a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain or tenderness - unless the culture is negative • an abscess or other evidence of infection involving the incision is found on direct examination or by histopathologic or radiological examination • diagnosis of a deep incisional SSI by a surgeon or attending physician.

Results

Funding was obtained in 2012; enrollment began on January 01, 2013 and will be completed on December 31, 2018. As of January 2016, 2119 patients have been included, 106 German centers are registered, and 27 centers are very active (>5 patients per year).

Discussion

Principle Considerations

Extensive literature exists on laparoscopic abdominal surgery. Conventional laparoscopic surgery requires a number of ports and a specimen extraction incision. Surgeons all over the world try to minimize abdominal wall trauma by using single-incision surgery. Single-incision surgery can use a single port system or a single-incision multiport approach [31-34]. Retrospective and randomized prospective studies could show the feasibility of this type of surgery without any increased risk to the patient. Of course, patients are usually selected and surgeons are very experienced. This limits the power of these studies. Some studies show advantages for single-incision surgery in postoperative pain, cosmetics, and patient satisfaction [35-39]. However, studies focused on pain were not blinded, which could lead to a relevant bias. Operative time was usually longer for the single-incision single port/multiport techniques [40]. Advantages of single-incision laparoscopic surgery, for example, reduced risk of hemorrhage or hernia, are intuitive at this time. The previous randomized prospective studies have too few patients to answer important questions in this area because of the low frequency of some relevant complications. For instance, it is still unclear if single-incision surgery leads to an increase in common bile duct injuries. To answer this question in a prospective randomized study is not easy or feasible, because there would be a need for thousands of patients to be included.

Conclusion

The endpoints of this study will allow a comprehensive evaluation of the surgical technique of single-incision abdominal laparoscopic surgery and its results. The results of this prospective trial will be compared with available evidence (ie, data from prospective randomized studies or reviews of single-incision surgery and classic multiple trocar techniques) in order to substantiate the current knowledge in this area.

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Authors' Contributions

RM and HL designed, managed, and conducted the trial together with the Institute for Quality Assurance in Surgical Care in Magdeburg, Germany. RM wrote the manuscript together with HL and MKD. SK and RO are the biostatisticians. TM is a member of the data quality monitoring board. BV, LM, and GW are active in patient recruitment and participated in the study design. All authors have read and approved this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention
NOTES: natural orifice transluminal endoscopic surgery
SILAP: single-incision multiport/single port laparoscopic abdominal surgery study
SSI: surgical site infection

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Protocol

Family-Centered Care in Juvenile Justice Institutions: A Mixed Methods Study Protocol

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Abstract

Background: Treatment and rehabilitation interventions in juvenile justice institutions aim to prevent criminal reoffending by adolescents and to enhance their prospects of successful social reintegration. There is evidence that these goals are best achieved when the institution adopts a family-centered approach, involving the parents of the adolescents. The Academic Workplace Forensic Care for Youth has developed two programs for family-centered care for youth detained in groups for short-term and long-term stay, respectively.

Objective: The overall aim of our study is to evaluate the family-centered care program in the first two years after the first steps of its implementation in short-term stay groups of two juvenile justice institutions in the Netherlands. The current paper discusses our study design.

Methods: Based on a quantitative pilot study, we opted for a study with an explanatory sequential mixed methods design. This pilot is considered the first stage of our study. The second stage of our study includes concurrent quantitative and qualitative approaches. The quantitative part of our study is a pre-post quasi-experimental comparison of family-centered care with usual care in short-term stay groups. The qualitative part of our study involves in-depth interviews with adolescents, parents, and group workers to elaborate on the preceding quantitative pilot study and to help interpret the outcomes of the quasi-experimental quantitative part of the study.

Results: We believe that our study will result in the following findings. In the quantitative comparison of usual care with family-centered care, we assume that in the latter group, parents will be more involved with their child and with the institution, and that parents and adolescents will be more motivated to take part in therapy. In addition, we expect family-centered care to improve family interactions, to decrease parenting stress, and to reduce problem behavior among the adolescents. Finally, we assume that adolescents, parents, and the staff of the institutions will be more satisfied with family-centered care than with usual care. In the qualitative part of our study, we will identify the needs and expectations in family-centered care as well as factors influencing parental participation. Insight in these factors will help to further improve our program of family-centered care and its implementation in practice. Our study results will be published over the coming years.

Conclusions: A juvenile justice institution is a difficult setting to evaluate care programs. A combination of practice-based research methods is needed to address all major implementation issues. The study described here takes on the challenge by means of practice-based research. We expect the results of our study to contribute to the improvement of care for adolescents detained in juvenile justice institutions, and for their families.

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KEYWORDS

adolescents; delinquency; juvenile offenders; family-centered care

Introduction

Delinquent youths often come from malfunctioning families. The problems of these families vary from disturbed mutual relationships, to drug abuse, delinquency, and poor mental health among family members [1,2]. In adolescents, the risk of committing criminal offenses is related to family factors such as poor parenting skills, lack of emotional support from parents, neglect and physical abuse, and criminal behavior of family members [3]. Family therapy reduces criminal behavior of adolescents [4], and also improves family functioning [5-7]. Therefore, intervention programs for delinquent adolescents should focus not only on the youth but also on the family in order to have the adolescent abstain from criminal activities [3,8-10]. Such family-centered intervention programs could include family therapy [11].

Whereas family problems are related to youth delinquency, the protective effects of positive parenting should not be ignored [10]. Involving parents during their child's detention is important for improved outcomes for youth [12]. Parental engagement and emotional support help to improve outcomes for youth in terms of treatment engagement, well-being, behavior, and recidivism [10,13]. Additionally, recidivism rates decline if parents are more involved with their children in juvenile court [14].

Until the start of the project that led to the current paper, care in youth detention centers in the Netherlands, called juvenile justice institutions (JJIs), has been mainly youth-focused, with little attention for the family. Realizing the importance of family factors, the Netherlands Government decided to encourage JJIs to adopt a family-centered approach. This has resulted in incorporating a few family-centered actions in all JJIs' usual care (UC) programs, such as staff calling parents once a week or inviting parents to key meetings where the intervention plan for their child is being discussed [15]. However, JJIs were found to not properly adhere to this rather modest way of involving parents [16], and methods to involve parents have not been systematically implemented in practice [17]. The need for programs stimulating family involvement during a child's detention is not only of concern in the Netherlands, but is internationally recognized [18,19]. Families need to be heard, empowered, supported, and the ties between adolescents and their parents need to be strengthened by improving communication [18].

Previous studies have elaborated on the challenges to involve parents in juvenile justice services. Characteristics from parents and from the juvenile justice system can negatively influence parental involvement [12,14]. These parent characteristics include lack of resources for transportation, time constraints, fear of losing a job because of the time-consuming process, competing demands, and lack of child care for other children. Also, there may be medical concerns, and parents may feel failed and tired after years of struggle with their child's problem behavior. Parents may mistrust the institution because of previous negative experiences with service providers. Characteristics of the justice system that could hamper parental involvement include staff's lack of respect towards parents, their unwillingness to work with parents, confusing communication with parents, time-consuming and not family-friendly processes, the lack of a cultural competent system, and the lack of communication in parents' native language [12,14]. Additionally, staff's negative attitudes can give parents the impression that they are seen as the problem instead of part of the solution [14]. Other factors are able to both facilitate and hinder parental involvement, such as availability of staff and flexibility of the system [12]. A positive relationship between parents and their child prior to detention can positively influence parental engagement during their child's detention [20].

Dissatisfied with the underdeveloped level of family-centered care in the Netherlands, two JJIs participated in the Academic Workplace Forensic Care for Youth (AWFZJ) to develop and evaluate a program for family-centered care (FC) [21]. The AWFZJ is a practice-based research collaboration between two JJIs, two universities, two colleges of applied sciences, and two centers for child and adolescent psychiatry. The AWFZJ developed two versions of the FC program, one for youth detained in short-term stay groups and one for youth detained in long-term stay groups.

We decided to examine if FC is beneficial for detained youths and their parents. We report here on the design of a study to evaluate FC in the first two years after the first steps of its implementation in short-term stay groups. Each short-term stay group has room for 10 adolescents. The groups are supported and monitored by JJI staff, so-called group workers (mostly social workers). The aim of the current paper is to describe the study protocol and to stress the potential of research studies in a challenging setting such as a JJI with its ethical dilemmas, the unfamiliarity of staff with research methodology, and with a difficult population with low treatment motivation [22-24].

Methods

Design

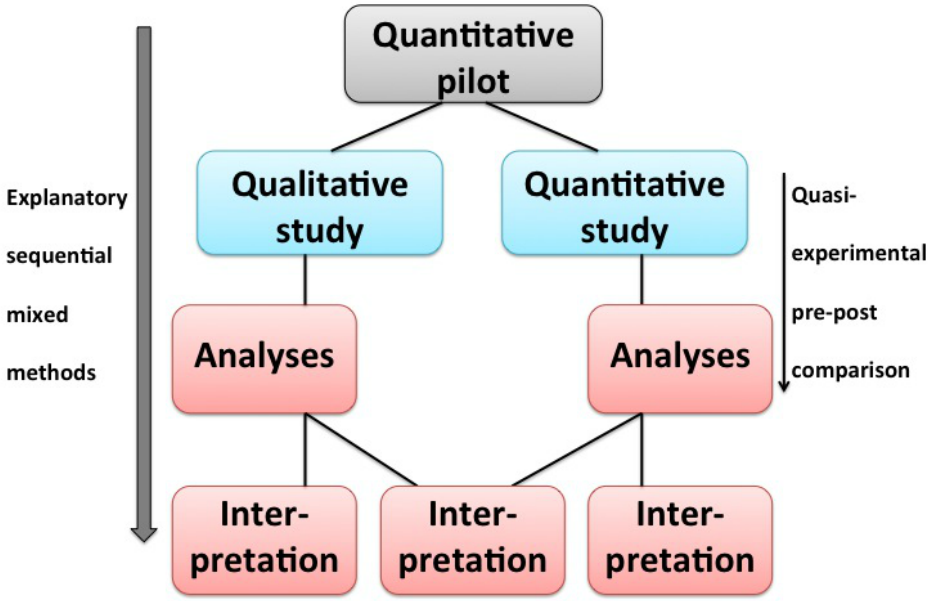
Our study has a practice-based nature. Carrying out research in a setting such as a JJI is challenging, as it is in most practice-based studies [25]. It is virtually impossible to organize a randomized controlled trial in a JJI. First, judges are not likely to agree with randomizing adjudicated adolescents to different detention conditions. Second, JJIs struggle with relative instability of staff due to high turnover and high rates of absenteeism [26]. Another barrier for conducting research in JJIs is the unfamiliarity among most of the institution's staff with the principles and benefits of research studies [23]. To prepare JJI personnel for implementing and evaluating FC, we trained them to internalize FC rationale and FC practice and we organized a seven-month pilot stage. In the remainder of the pilot stage, we found FC short-term stay groups to differ in number and nature of family-oriented actions, although all group

workers had received the same training. Also, we noticed that not every parent visited their child or attended every kind of family activity organized by the JJI. Additionally, the preliminary analyses of the pilot data showed the surprising finding that most parents and youths report few family problems, while at the same time they report motivation for family therapy.

In setting up the actual study, we used feedback from staff and the results of monitoring the groups during the pilot stage to improve the FC program.

Evaluating the pilot stage gave rise to our final study design, in which the pilot is considered as the first stage, see Figure 1.

Figure 1. Study design.



In our study, we employ a mixed methods design in which quantitative and qualitative research methods are combined [27]. In mixed methods studies, qualitative and quantitative stages of data collection can occur concurrently or sequentially and can be nested in each other [28,29]. We utilize an explanatory sequential mixed methods design [30] with a large concurrent stage. The first stage of the sequence consists of the quantitative pilot. The second stage of the sequence involves concurrent qualitative and quantitative components. In the third stage, which is integral part of the study, we distinguish data analyses and interpretation. Part of the interpretation concerns the integration of qualitative and quantitative outcomes.

The qualitative part of our study is used to elaborate on the preceding quantitative pilot outcomes and to discuss further interpretations of the quantitative quasi-experimental pre-post study outcomes. This qualitative part can help to gain insight into underlying mechanisms influencing parent participation and is therefore considered explanatory [31]. Understanding these mechanisms can contribute to overcoming possible obstacles in organizing family-oriented activities and can therefore improve FC.

The quantitative part in the second stage of our study will be carried out parallel to the qualitative part. This quantitative part is a pre-post comparison of two programs–FC and UC–for adolescents placed in short-term stay groups of two JJIs. This comparison is quasi-experimental, as no randomization will take place in assigning youth to either a FC or a UC group.

The details about the stages and the contents of our study were discussed and detailed in workgroups of JJI staff and research staff, in an attempt to render FC study activities attainable in daily practice and to prepare staff for the requirements of our study. Over the course of our study, we will regularly discuss the study's progress and its practical impact on staff in these workgroups. Additionally, registered information of staff's family-oriented actions will be shared during team meetings, which offers insight into the success of implementing FC and its program integrity. This feedback can stimulate family-centered activities. These overviews will also be provided on a regular basis to the managements of the two JJIs, enabling them to monitor and direct the organization of family-centered activities in the institutions as outlines in the program manual.

Study Objectives and Research Questions

The overall aim of our study is to evaluate FC in the first two years after the first steps of its implementation in short-term stay groups in JJIs. The key question to be answered in the quantitative part in the second stage of the study is if FC has additional value compared to UC. We will test the following hypotheses comparing FC with UC during detention: (1) FC increases parents' involvement with their detained child; (2) FC increases the motivation of the adolescent and his parents for accepting treatment and guidance by JJI staff and for taking part in family meetings; (3) FC adolescents show less problem behavior; (4) FC improves family interactions; (5) FC parents experience less parenting stress; (6) FC youth more often return to their families' home upon discharge; (7) FC enhances

adolescents' and parents' satisfaction with the JJI; (8) In FC groups, JJI staff members are more satisfied, feel more confident in their contact with parents, and more often incorporate the family perspective in their thinking.

Finally, we will study if parents who participate in family-centered activities, differ from parents who do not participate based on characteristics such as proximity to the JJI, age of their child, duration of his stay, and baseline outcomes in other demographics, family functioning, parenting stress, treatment motivation, and satisfaction.

The aim of the qualitative part of the study is to trace which factors influence parental involvement. We will interview adolescents, parents, and group workers from short-term stay groups based on the following research questions: (1) How do adolescents, parents, and group workers feel about the current involvement of parents in FC and UC? (2) What are the attitudes of FC and UC group workers towards working with parents? (3) What are the needs, wishes, and expectations of adolescents, parents, and group workers concerning FC?

Setting

This study will be carried out in two JJIs in the Netherlands. A juvenile judge can refer an adolescent to a short-term stay group in a JJI for pre-trial detention. Depending on the interim ruling of the juvenile judge, the time spent in pre-trial detention can last for a few days up to a maximum of customarily 90 days. As a rule, the juvenile judge refers the adolescent to a JJI close to the home of the youth. The JJI's secretarial office monitors a group's capacity and decides on which group the adolescent is placed.

One of the JJIs has three short-term stay groups. The management of this institution chose two of these groups for a step-by-step implementation of the FC program, while the third group will continue to offer UC. Of the two short-term stay groups in the other JJI, the management chose one to offer FC, and the other UC. The managements of the two JJIs based their choices for the groups starting with the implementation of FC on pragmatic considerations. Because the JJIs are required to fill free slots in the living groups if new adolescents are referred to the institutions, the assignment of adolescents to groups is not dependent on characteristics of youths and is therefore without bias.

Each team of about 10 group workers is headed by a team leader and collaborates with a psychologist or pedagogue (hereafter jointly referred to as psychologist), who is responsible for coordinating the treatment the adolescent will receive.

Participants

Adolescents and Their Parents

All adolescents in our study will be boys, as girls are not referred to the two JJIs concerned. The boys will be between 12 and 18 years old at the time of placement. All youth placed in a FC group will be offered FC, but not all of them will be included in our study. An adolescent will be excluded (1) if his stay in the short-term stay group lasts less than 14 days (we need a minimum of two weeks to complete all assessments for the study); (2) if he does not have a parent or a parent figure; (3) if he already participated in our study during a previous stay; (4) if he does not understand Dutch; (5) if he and his parents refuse to take part in the assessments; (6) if he is already sentenced by the juvenile judge to a so-called PIJ order (Placement in an Institution for Juveniles for mandatory treatment) which implies long-term detention with treatment, or (7) if he is temporarily transferred from another institution.

As our assessments will be part of the Routine Outcome Monitoring (ROM) and of the standard screening and diagnostic procedures, psychologists can withhold the adolescent or his family from assessments, for example in case of severe psychiatric disorders. Reasons for excluding participants from the study will be noted. Consequently, we will first consult psychologists before approaching adolescents and their parents for the interviews. In general, following the psychologists' advice, we will not approach them in case of an alleged sex crime or when severe psychiatric disorders such as mental retardation, psychosis, autism, or acute suicidal behaviors are present.

Because the questionnaires in the quantitative part of our study are embedded in the standard procedures in the institutions, no incentives will be used for youth and parents. For the interviews, however, youths will receive extra television time in their rooms and parents will receive a small incentive such as a mug filled with chocolates and a personal thank you note.

Staff

All staff allocated to the short-term stay groups in our study will be included in the quantitative part. In order to promote program integrity and to avoid contamination, group workers who work at the FC groups will preferably not work in the UC groups, and vice versa. The JJIs agreed to ensure as much staff-stability in the teams as possible, and to make an effort to keep staff consistent per group.

In addition, we will interview the group workers from the first two FC groups for the qualitative part of our study, as well as all group workers from the two UC groups. In each JJI, we will interview group workers from one FC and from one UC group.

At certain milestones during the study, we will bring a cake to the team meeting as an incentive for group workers for their family-centered activities or research-related activities. Team leaders will also discuss these activities in evaluation meetings with the group workers. For group workers' participation with the interviews, they will receive the same incentive as parents.

Recruitment and Sample Size

Adolescents and parents are informed of the JJI's research activities by a flyer in the information leaflets from the JJI. The flyer informs that the data will be used anonymously in research studies and that parents can address their questions concerning these activities to their child's mentor (one of the group workers) or to the psychologist.

The JJIs in the Netherlands jointly apply ROM and standard screening and diagnostic procedures for detained adolescents and their parents. As our assessments will be embedded in these procedures, the quantitative part of our study will use data collected in the two participating JJIs by these means.

Recruitment of adolescents and their parents in the quantitative part of our study will last 21 months, including the pilot stage of 7 months. Based on records from 2011, the year prior to the pilot stage, we estimate that in 21 months, 300 adolescents will be placed in the groups concerned. Taking into account the exclusion criteria, we expect to recruit 160 adolescents and parents for the present study. Based on previous research, this number suffices for establishing statistically significant differences on quantitative measures between the two conditions [9].

As for qualitative studies, 10 interviews are generally sufficient to achieve saturation (ie, the point where additional interviews do not yield new essential information regarding the research question) [32]. Once an eligible adolescent is placed in a short-term stay group (either FC or UC), he and his parents will be invited to participate in the qualitative part of the study. If they are willing to participate, an appointment will be made for the interview. We will interview 10 boys (5 aged < 16 years and 5 aged > 16 years) in each JJI (N=20). We will also interview 20 parents (10 in in each JJI, 10 fathers and 10 mothers, 10 with a detained child aged < 16 years, and 10 with a detained child aged > 16 years). Finally, we will interview 20 FC group workers and 20 UC group workers.

Programs

Family-Oriented Activities in Usual Care

According to the Dutch guidelines for UC, the adolescent's mentor calls the parents within the first 10 days of placement of the youth to agree on weekly moments of telephone contact and to invite them for a meeting in the group, including a tour of the institution and its intramural school. The adolescent's psychologist is invited to join part of that meeting as well. After the first 10 days, the mentor discusses which goals the adolescent wants to achieve and asks parents to sign for agreement. After three weeks, the mentor informs parents about the treatment plan and provides them with the opportunity to give feedback. Parents are invited for a meeting to discuss the second treatment plan after 12 weeks. If family-evenings are organized and if adolescents receive diplomas, parents are invited. Finally, parents may possibly be involved in treatment interventions for their child and in family therapy. All this is UC as outlined on paper; however, in practice these family-centered activities are barely translated into daily routine [16].

Family-Centered Care

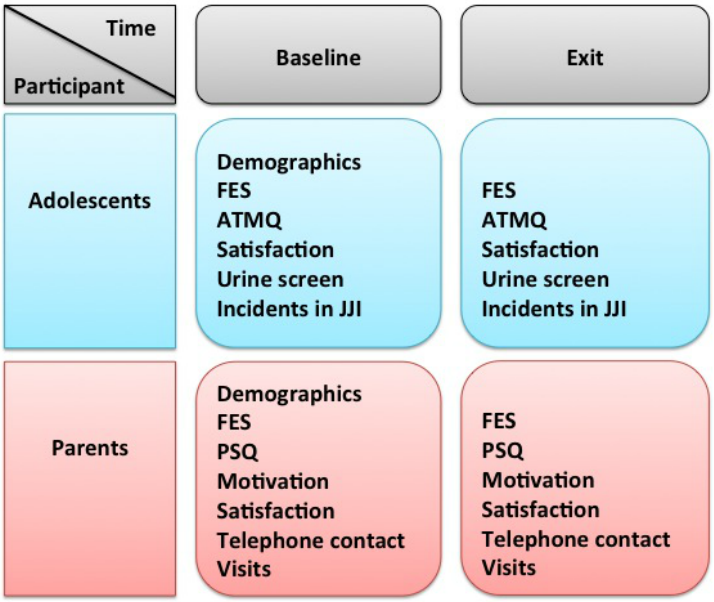
An important aspect of FC is the training, ongoing coaching, and yearly booster sessions that JJI staff receive in working with parents. This training enables staff to adhere to the FC program with its more comprehensive and more structured family-oriented activities. In FC, staff members actively motivate parents to visit their detained child frequently and to take an interest in their child's progress. Staff members also encourage parents to visit their child's group and to join group activities such as cooking, sports, and playing games. The first phase of a youth's detention is considered important in FC as the existing crisis is seen as an opportunity to establish engagement and build alliance with parents. A lot of emphasis is placed on the meeting in the third week of a child's detention. During this meeting, the psychologist first meets the parents alone to learn about the family. Later, the adolescent and his mentor join the meeting. Parents are also invited for a variety of other meetings with staff, other parents, and youths where particular themes of general interest are being highlighted. Further, staff members actively and urgently invite parents to attend and have a say in all the meetings where the goals and the progress of the treatment plan for their child are being discussed. FC staff members are constantly in touch with the parents and give them regular (at least once a week) feedback on how their child is doing. If desired, parents can sign up for family therapy together with their child. This therapy–multidimensional family therapy (MDFT) or functional family therapy (FFT)–may already start when the adolescent is detained and will then be continued on an outpatient basis upon discharge of the adolescent from the JJI.

Procedure and Instruments of the Quantitative Part of the Study

Assessments

The baseline assessment for adolescents and parents will take place in the third week of detention. The second (exit) assessment will be held in the week of the adolescent's departure from the short-term stay group. Although our assessments will be embedded in ROM and in the standard screening and diagnostic procedures of JJIs, we will assist in scheduling assessments and we will help to interpret the scores of family-oriented questionnaires so that they are usable in clinical practice. The assessments will be carried out by trained research assistants or by trained students enrolled in one of the social sciences Master's program, under supervision of the first author. Figure 2 presents an overview of the measures used for adolescents and parents.

Figure 2. Overview of the quantitative measures for adolescents and parents; (FES) Family Environment Scale, (ATMQ) Adolescent Treatment Motivation Questionnaire, (JJI) Juvenile Justice Institution, (PSQ) Parenting Stress Questionnaire.



Demographics

Demographic data on age, place of birth, and ethnic background will be retrieved from the individual JJI database and from the joint ROM-JJI database. Because these databases do not contain information on family background, housing, past treatment, school careers, and jobs, we will use a short questionnaire to gather these data.

Family Interactions

The Family Environment Scale [33] (FES, in Dutch: Gezins Klimaat Schaal, GKS [34]) will be administered to adolescents and parents. This questionnaire consists of the subscales Cohesion, Expressiveness, Conflict, Organization, Control, Moral Standards, and Social Orientation. Each subscale contains 11 items. Questions are answered with “yes” or “no”. The FES has two underlying dimensions, Family Relationship and System Maintenance. The FES has adequate psychometric properties [35]. For example, regarding the internal consistency, the Cronbach alphas for the total group of mothers, fathers, and children differ between .63 (Social Orientation) to .70 (Cohesion). The Cronbach alphas for the System Maintenance and the Family Relationship dimensions are .78 and .82 respectively. The Cronbach alphas for the subgroups are higher than .60 for all subscales, except for Social Orientation for children (alpha=.38) [36].

Parenting Stress

We will use the Parenting Stress Questionnaire (PSQ, in Dutch: Opvoedingsbelasting Vragenlijst, OBVL) [37] for assessing the level of parenting stress experienced by parents. The PSQ targets individual characteristics of parents in relation to parenting and to the quality of the parent-child interaction. The questionnaire consists of 34 items to be scored on a four-point scale. Its five subscales are Parent-child relationship problems, Parenting problems, Depressive mood, Parental role restriction, and Physical health problems. The PSQ is shown to be reliable and valid. The Cronbach alphas for the five subscales are .84, .83, .83, .79, and .78 respectively. The total scale was also found reliable (alpha=.90) [38].

Satisfaction

We devised a questionnaire based on the Satisfaction Scale [39] and the Client-test (C-test, in Dutch: C-toets [40]), which we will use to determine how satisfied the adolescents and parents are with the JJI. These two questionnaires are shown to be reliable and valid [39,41]. Regarding the Satisfaction Scale for parents, all subscales for the inpatient/residential treatment center population demonstrate good internal consistency, with Cronbach alphas ranging from .76 to .94. For children, all subscales for the inpatient/residential treatment center population show good internal consistency, with Cronbach alphas ranging from .78 to .91, except subscale Access and convenience (alpha=.63) [39]. Cronbach alphas for the four subscales of the parent versions of the Client-test demonstrate good internal consistency, ranging from .77 to .90. The total questionnaire is found to be reliable (alpha=.94). The children version only has a total scale, which is found to be reliable (alpha=.91) [41]. Our satisfaction questionnaire has two parts, part A and part B. Part A contains 14 items to be rated on a three-point scale. It includes items such as “The staff members are friendly”, “I feel that the staff members are interested in me”, “The staff members treat me with respect”, and “The staff members help me dealing with problems”. Part B contains one question, “All things considered, which grade would you give to the service provided by the JJI?”, to be rated on a scale of 1-10.

Treatment Motivation

We will apply the Adolescent Treatment Motivation Questionnaire (ATMQ) to measure treatment motivation for adolescents. The ATMQ consists of 11 items to be rated on a three-point scale, adding up to a total score. The construct validity and internal consistency reliability are adequate (alpha=.84) [42]. We added three questions with a three-point scale to the ATMQ about adolescents’ motivation to take part in family therapy during their stay in the short-term stay group

and about motivation for continued individual and family therapy after leaving the JJI. We also added four motivation questions to the Satisfaction questionnaire for parents (eg, "I am willing to participate in family therapy during my son's stay in the JJI", "I feel that my son needs treatment after his stay in the JJI").

Parents' Involvement During Their Child's Detention

To examine to which extent parents are involved with their sons, we will record the number of visits by parents and the purpose of each visit to the JJI. Group workers, team leaders, and psychologists will note when they have had contact via telephone with the parents.

Incidents in JJIs

We will gather data on problem behavior as shown by the adolescents from routine daily reports and from JJI database input. JJIs record incidents such as verbal fights, physical fights, quarrels, rule breaking behavior, and possession of contrabands.

Cannabis Use

We will gather data on cannabis use from the JJI database. Routinely, JJIs collect a urine sample from the adolescent to check for traces of cannabis use as soon as he is placed in a short-term stay group. Later on during the stay, JJIs regularly perform urine screens, both at scheduled times and at random.

JJI Staff

We devised questionnaires for JJI staff (group workers, team leaders, psychologists) about working with families and about using the family perspective in their thinking and in day-to-day interventions. The questionnaire has two parts, part A and part B. Part A contains 12 items to be rated on a five-point scale and includes questions such as "Do you invite parents of every mentor-child for a meeting?", "Do you invite parents of every mentor-child for a tour through the facility?", "Do you inform parents on the same day when their child was involved in an incident?", and "If parents are divorced, do you involve both parents in the same way?". Part B contains 17 items to be rated on a scale of 1-10. This part includes questions such as "How satisfied are you with the course of the contact with the parents?", "How satisfied are you with the way in which you involve parents during their son's stay?", and it includes statements such as "Parents are difficult to work with", "Parents are indispensable for reducing recidivism", and "Parents are a source of support for staff".

These questionnaires will be filled out every three months. On an additional form, psychologists will note where the adolescent is going to live after leaving the short-term stay group.

To assess if staff members adhere to the guidelines of the FC program, they will use logbooks and will fill out short forms on family-centered activities undertaken. This will enable us to assess program integrity. The overviews of these logs are shared during team meetings and with the managements, enabling managers and team leaders to monitor and direct the organization of family-centered activities.

Procedure and Instruments of the Qualitative Part of the Study

Before the interview, the participant will complete a short demographic questionnaire. The interview will be about 60 to 90 minutes and will be audio recorded. The recording will be stopped during the interview if so requested by the participant. The semi-structured interviews will be conducted by qualified trained students enrolled in the last year of either a Bachelor's or a Master's program of Social Work or another social science.

The interviews are structured using a topic list [43]. We drafted a topic list for each group of participants (adolescents, parents, FC group workers, and UC group workers). The topic lists were devised following deductive and inductive strategies. Deductively, topics were derived from a review of literature of factors that contribute to the success of family-centered work in institutions similar to JJIs. Inductively, experiences from group workers, parents, and adolescents were used to supplement the topic list. Additionally, each interview can influence the construction of the topic list as new themes may arise. The themes of the final topic lists are represented by questions and are displayed in Table 1 and Table 2. Although the topics follow a logical order in themes, the topic lists will be used in the order as the interviewer sees appropriate, based on the answers of the respondents. Based on further subtopics and keywords the interviewer will probe for more information on each main theme as specified in Tables 1 and 2.

Table 1. Main themes of the topic lists for interviewing adolescents and parents.

Adolescents and parents	Adolescents only	Parents only
To what extent are parents currently involved?	Do you consider the involvement of your parents as being important?	To what extent and in which way do you wish to be involved?
How can parents be motivated for involvement?	How should the JJI involve parents?	
What are your expectations of staff in involvement and contact?	How can the JJI motivate adolescents for FC?	
Which factors influence involvement and in which ways?	Which reasons do adolescents have to object to FC?	
How can we explain the surprising preliminary finding in the quantitative pilot stage that parents and youths report few family problems while they also report to be motivated for family therapy?		

Table 2. Main themes of the topic lists for interviewing group workers.

Group workers FC and UC	Group workers FC only	Group workers UC only
How do you feel about the involvement of parents?	What is Family-centered Care?	What is parental participation?
What do you think about the following elements in parental participation: knowing, discussing, activities, and deciding?	Which changes in practice did you notice since the implementation of FC?	What do you expect of FC when it will be implemented in your group in the future?
How is the atmosphere in your team?	How has FC been implemented in your team?	Which changes are necessary before your team is ready for the implementation of FC?
What is your role within your team?	How do you feel about the FC training?	
Do you have sufficient skills for involving parents?		
Do your colleagues have sufficient skills for involving parents?		
To what extent do managers support you in involving parents?		
What pros and cons of FC do you see?		
Do you have tips for involving parents?		

Analyses

Quantitative Analyses

All statistical analyses will be performed using SPSS 23. In a future paper, we will provide a flowchart of participants in our study, including reasons for exclusion. Descriptive statistics will be presented as means and standard deviations for all continuous variables and subscales. Additionally, frequency distributions or qualitative descriptions of all categorical variables will be presented for each group. The groups will be defined as FC or UC. We will test if these groups differ on demographic factors. If these differences exist, we will use these factors as covariates in our analyses. If necessary, we will also include the JJI in which an adolescent is placed as a covariate.

We will perform within-group pre-post comparisons, between-group comparisons (FC vs UC), and repeated measures analyses. The selection of a specific test will depend on which hypothesis is tested and on the characteristics of the corresponding data (eg, categorical, ordinal, or interval level and normally or non-normally distributed). Table 3 shows the planned analyses to test our hypotheses for comparing FC with UC in case of normally distributed data. For combining the within-group pre-post comparisons and the between-group comparisons in our analyses, we will use the repeated measures ANOVA. Because the normality of the distribution of the data cannot be determined beforehand, the final analyses will be selected after the data is gathered. In analyzing the hypotheses, two-tailed analyses will be performed and we will correct for multiple testing.

Table 3. Planned analysis for between-group hypotheses.

Hypothesis	Data source	Analysis
FC increases parents' involvement with their detained child	Registration logs visits	Unpaired *t* test
FC increases the motivation of the adolescents and parents for accepting treatment and guidance by JJI staff and for taking part in family meetings	ATMQ youth total score	Unpaired *t* test
	Motivation items youth	Pearson's Chi-square test
	Motivation items parents	Pearson's Chi-square test
FC adolescents show less problem behavior	Incidents in JJI	Unpaired *t* test
	Cannabis database	Unpaired *t* test
FC improves family interactions	FES	Unpaired *t* test
FC parents experience less parenting stress	PSQ	Pearson's Chi-square test
FC youth more often return to their families' home upon discharge	Registrations logs living situation after discharge	Pearson's Chi-square test
FC enhances adolescents' and parents' satisfaction with the JJI	Satisfaction questionnaire-A	Pearson's Chi-square test
	Satisfaction questionnaire-B	Unpaired *t* test
In FC groups, JJI staff members are more satisfied, feel more confident in their contact with parents, and more often incorporate the family perspective in thinking	Questionnaire staff-A	Generalized estimating equations
	Questionnaire staff-B	General linear model repeated measures

Qualitative Analyses

The recordings of the interviews will be transcribed verbatim and imported into ATLAS.ti, a computer program facilitating the analysis of qualitative data. The students will be trained to code the data using a code tree representing the topic list. This first draft of the deductively developed code tree will be complemented with codes inductively derived during the coding process, as new themes will appear in the answers of participants [44]. The first author and the students will work in a cyclic process. This first phase of open coding will be followed by a second phase of axial coding. During axial coding, codes will be further interpreted and reorganized based on the interview fragments they refer to. Codes can get split, merged, and joined into more abstract central themes. Code families will be constructed enabling further analysis of the data. The third and last phase of the analytic process, selective coding, will enable theoretical interpretations aimed at finding more general patterns [43]. Finally, this analytic process enables us to explain the underlying mechanisms influencing parental involvement during their child's detention.

Ethics

The medical ethical board of the Leiden University Medical Center reviewed our study. The board ruled that our study falls outside the realm of the WMO (Dutch Medical Research in Human Subjects Act) and that it conforms to Dutch law, including ethical standards.

Discussion

Until recently, care for adolescents detained in a juvenile justice institution (JJI) has been mainly youth-centered with interventions targeting a youth's problem behavior without much regard for the youth's social environment, in particular the family. The Dutch government and the JJIs are convinced that outcomes for detained adolescents are more improved if their parents are allowed to meet and to talk with their child more often, to have direct and extensive contact with JJI staff, to join parent meetings organized by the JJI, and to have a say in decisions regarding their child. As research supports these notions [3,8-10,13,45], this calls for drastically revising current JJI programs [12,18,19]. Two JJIs in the Netherlands combined efforts with universities, colleges, and mental health centers within the Academic Workplace Forensic Care for Youth (AWFZJ) to introduce family-oriented care in their institutions. The AWFZJ developed two programs for family-centered care (FC), for youths detained in groups for short-term and long-term stay, respectively. In FC, staff members receive training, ongoing coaching, and yearly booster sessions on working with parents. The current paper reports on the design of a study evaluating FC in the first two years after the first steps of its implementation in short-term stay groups. After the pilot stage in 2012, the second stage of the study started in 2013 and we completed the data collection procedures in 2015. Currently, we are analyzing the first sets of outcomes and we expect to report on them over the coming years.

Our study has an explanatory sequential mixed methods design, combining quantitative and qualitative approaches in a practice-based study. In order to overcome the challenge of conducting practice-based research with possible tension between practice and science [25,46], we established good working relationships with the staff, collaborating with the same goal in mind: evaluating and eventually improving FC. Over the course of our study, we kept in mind the need to be flexible in carrying out practice-based research [25], possibly resulting in changes in practical ways of collecting data while adhering to our study's methods.

During our study, we undertook a few actions as discussed in the Methods section to ensure that staff members benefit from our study. First, we discussed our research design in a workgroup with staff in each institution. We enabled staff members to provide feedback on our original design and we incorporated their suggestions in our final study. The workgroups supported our study by serving as a bridge between practice and science. Second, we helped scheduling the assessments and interpreting the scores so that they were usable in clinical practice. Third, we provided feedback on the registered information of staff's family-oriented actions during team meetings and to the managements of the two JJIs. Using research information as feedback for practice helps staff members to understand the benefits of conducting research. While our study is useful for practice, this advantage also has a down side. Along the course of our study, practice can evolve as staff might improve in the way of working with parents. Nevertheless, by directly using results of our study in practice, we meet an important requirement of practice-based research [25,47].

Close collaboration with the JJI managements is necessary to overcome possible bottlenecks during our practice-based study. Since the wish to develop and evaluate FC originates from the institutions themselves, the joint goal to improve parental participation is emphasized. JJIs are also interested in more distal outcomes such as recidivism rates. We recognize the importance of studying the long-term effects of implementing FC and therefore suggest future research to incorporate distal outcomes.

In conclusion, we expect the results of our study to contribute to practice by showing how to organize FC and by providing suggestions for improving the FC program, which consequently can lead to improved care for detained adolescents and their families.

Acknowledgments

This study is funded in 2010 by ZonMW, the Netherlands Organization for Scientific Research (NWO). Its ZonMW project number is 159010002. The managements of the two participating JJIs decided to implement family-centered care and to let us carry out the study as described here, for which we are grateful. We gratefully acknowledge the staff members in the workgroups

for their suggestions regarding the attainability of research activities in daily practice. We also would like to thank Kees Mos for sharing with us his experience with family-centered work and for his help during the study. Finally, thanks are gratefully extended to Winneke Ekkel for helping improve the interviews in the study.

Conflicts of Interest

The managements of the JJIs assigned RB and IS to the AWFZJ. RB works as a consulting psychiatrist in one of the JJIs and IS works as a licensed psychologist in the other JJI, both one day a week. Other than that, the authors declare that they have no competing interests. In order to minimize possible bias occurring from the two authors working in the JJIs, we will reassure staff, adolescents, and parents that all data is handled confidentially and anonymously. Additionally, RB will not be involved in the process of data collection and analyses. IS will not be involved in her clinical work as part of the present study. Data collection will be carried out by trained research assistants or by trained students, under supervision of IS.

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Abbreviations

AWFZJ: Academic Workplace Forensic Care for Youth
ATMQ: Adolescent Treatment Motivation Questionnaire
FC: family-centered care
FES: Family Environment Scale
FFT: functional family therapy
GKS: Gezins Klimaat Schaal
JJI: juvenile justice institute
MDFT: multidimensional family therapy
OBVL: Opvoedingsbelasting Vragenlijst
PIJ: Placement in an Institution for Juveniles for mandatory treatment
PSQ: Parenting Stress Questionnaire
ROM: Routine Outcome Monitoring
UC: usual care
WMO: Dutch Medical Research in Human Subjects Act

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Protocol

Protocol Outlines for Parts 1 and 2 of the Prospective Endoscopy III Study for the Early Detection of Colorectal Cancer: Validation of a Concept Based on Blood Biomarkers

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Abstract

Background: Programs for population screening of colorectal cancer (CRC) have been implemented in several countries with fecal immunochemical testing (FIT) as the preferred platform. However, the major obstacle for a feces-based testing method is the limited compliance that reduces the clinical sensitivity for detection of participants with non-symptomatic CRC. Therefore, research approaches have been initiated to develop screening concepts based on biomarkers in blood. Preliminary results show that protein, genetic, epigenetic, and metabolomic components may be valuable in blood-based screening concepts, particularly when combinations of the various components appear to lead to significant improvements.

Objectives: The protocol described in this paper focuses on the validation of concepts based on biomarkers in blood in a major population screened by FIT.

Methods: In Part 1, participants will be identified and included through the Danish CRC Screening Program comprising initial FIT and subsequent colonoscopy to those with a positive result. Blood samples will be collected from 8000 FIT-positive participants, who are offered subsequent colonoscopy. Findings and interventions at colonoscopy together with personal data including

co-morbidity will be recorded. Blood samples and data will also be collected from 6000 arbitrarily chosen participants with negative FIT. In Part 2, blood samples and data will be collected from 30,000 FIT-negative participants three times within 4 years. The blood samples will be analyzed using various in-house and commercially available manual and automated analysis platforms.

Results: We anticipate Part 1 to terminate late August 2016 and Part 2 to terminate late September 2022. The results from Parts 1 and 2 will be presented within 12 to 18 months from termination.

Conclusions: The purpose of this study is to improve the efficacy of identifying participants with neoplastic bowel lesions, to identify false negative participants, to identify participants at risk of interval neoplastic lesions, to improve the compliance in screening sessions, and to establish guidelines for out-patient follow-up of at-risk participants based on combinations of blood-based biomarkers.

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KEYWORDS

colorectal neoplasms; genomics; epigenomics; transcriptome; proteomics; metabolomics; early detection of cancer

Introduction

Colorectal cancer (CRC) represents the second leading cause of cancer-related death in Europe with a high social and economic impact on human health [1,2]. Population-based screening has been shown to reduce the incidence of CRC and lead to improved overall survival, presumably because the disease is diagnosed in precursor or early stages [3,4].

Direct colonoscopy is considered the gold standard for CRC screening: sensitivity and specificity are higher than 95% for diagnosing neoplastic lesions if performed by experienced colonoscopists [5]. However, the feasibility of direct colonoscopy as a screening method is challenged by capacity requirements, costs, and side-effects such as bleeding, arrhythmia episodes, and bowel perforation. Consequently, a focus has been on the development of methods to identify participants having increased risk of CRC in order to selectively offer colonoscopy. At present, fecal immunochemical testing (FIT) is probably the optimal test for identifying high-risk participants as it outperforms other fecal-based tests when it comes to usability, sensitivity, compliance, and costs [6]. FIT has some limitations, however; the positive predictive value of FIT for diagnosing CRC is in the range of 6% to 10% [7-9], and consequently greater than 10 colonoscopies have to be performed in order to diagnose one case of CRC. An additional drawback is the risk of interval cancer - CRC diagnosed in the timeframe between screening rounds mostly due to false negative FIT results. The predominant challenge is the association with low patient compliance in the range of 33% to 64% which reduces the clinical sensitivity significantly [9,10], resulting in a large proportion of undiagnosed CRC among participants who have not taken the test in addition to participants with a false negative result of FIT. An urgent need has therefore emerged to develop improved methods for early detection of CRC with high performance regarding sensitivity and improved compliance.

Major efforts have been invested in research making use of biological markers in blood to identify high-risk participants who should be offered subsequent colonoscopy. A blood sample is easy to retrieve and is far more acceptable for a screening population consisting mostly of healthy participants compared with fecal samples required for FIT [11,12]. Blood-based biological markers of interest are a heterogeneous group consisting of various proteins, nucleosomes, transcriptomes, metabolomes, circulating tumor-derived DNA, and microRNAs having shown association with early stages of CRC [13-17]. In particular, a combination of biomarkers, which results in a complementing performance, has shown promising results [13,14,18-21].

It has been shown that the presence of various benign diseases including diabetes, liver fibrosis, asthma, and chronic obstructive lung disease may cause elevated levels of specific biological protein and methylated gene markers associated with CRC [13]. Such associations with epigenetics, transcriptomics, and metabolomics have not yet been evaluated, but particular results will be presented shortly. Statistical and mathematical analyses have shown that such associations may be taken into account and thereby blood-based biomarkers may still identify participants at risk of CRC [17]. In addition, an individualized risk assessment evaluation (RAE) can be performed in order to identify participants with high risk of having CRC. This is done by combining subject-based data (ie, age, gender, body mass index, the presence of other specific diseases, etc) with the results of the biological marker analyses [17]. The mathematical model of the RAE is dynamic and can be improved by adapting data according to new findings of potential biological markers or other individualized data found to be relevant for the risk of having CRC.

At present, the established RAE model is undergoing validation in a major multicenter study (the Endoscopy II Project) [22]. In collaboration with academic and industrial partners various genetic and epigenetic molecules, proteins, and metabolites are presently being analyzed in collected blood samples. Based on results achieved from that study, a specific profile will be constructed consisting of the combination of analyzed biomarkers selected according to the statistical association with early stage CRC and high-risk adenomas. This panel will then be used to validate the designed RAE model.

The population of the Endoscopy II Project consists of participants undergoing diagnostic colonoscopy due to symptoms attributable to CRC; hence the validated RAE model found in the Endoscopy II Project is only applicable to such

populations. However, if the RAE is to be implemented in future programs the screening population will comprise asymptomatic participants. Hence, it is an absolute requirement that the RAE model is validated in an asymptomatic population. The aim of the present Endoscopy III Project is to validate the RAE model in a population consisting of participants of the Danish screening program.

Methods

Part 1

Eligible participants are identified through the Danish CRC Screening Program that is based on an outreach FIT and subsequent offer of colonoscopy to participants with positive test results. The screening program was initiated in March 2014 and is offered to Danish citizens of 50 to 74 years of age. Screening is to be repeated every second year after the initial implementation period of 4 years. The study population consists of two sub-groups, in accordance with the FIT result; FIT-positive participants (hemoglobin [hgb] ≥ 100 ng/mL; OC-Sensor platform) and FIT-negative participants (hgb < 100 ng/mL: OC-Sensor platform).

Participants undergoing subsequent screening colonoscopies at Amager/Hvidovre, Bispebjerg, Herlev, Herning, Hillerød, Holstebro, Horsens, Randers, Silkeborg, and Viborg hospitals will be invited to participate in the project. The result of the positive FIT and booking information for colonoscopy will be forwarded to the screening participants. Simultaneously, an electronic letter with study information and an invitation to attend the Endoscopy III Project will be forwarded to the participants. The inclusion was initiated May 2014 and is planned to terminate by late August 2016. The scheduled number of participating FIT positive participants is set to 8000.

At the day of the colonoscopy an informed consent must be signed by the participants before inclusion into the project; specifically, the study participants also sign that they allow access to health and pathology files according to the Danish Health Act §43,1-3. An interview will be conducted to obtain personal and possible concurrent disease data, followed by blood collection prior to colonoscopy.

Blood samples of 90 mL will be collected from an antecubital vein with light stasis and subsequently handled and stored according to a validated standard operating procedure including pre-analytical and analytical aspects such as blood sampling, handling, storage, and the effects of freeze/thaw on biomarkers of interest (Multimedia Appendix 1). Specifically, the blood samples for plasma are centrifuged twice to reduce the contaminating effects of leucocyte- and platelet-derived granule proteins. All collection and storage tubes are marked with unique barcodes, which by 8 digits identify the hospital where the sample is collected (2 digits), identification of the subject (4 digits), and identification of the specific tube content (2 digits; serum, plasma or buffy-coat). The Freezer Works PC-based storage handling system is used to track every sample in the -80^{o}C freezers, which are electronically surveyed and monitored 24 hours a day, 7 days a week.

Data including findings and interventions at colonoscopy will be registered in a locked Web-based database and continuous audit of the database will be performed ensuring correct data recordings. At the end of the study on-site audit sessions will be performed as well.

The FIT-negative participants are arbitrarily selected from the database of the Danish CRC Screening Program and will be invited to blood collection at the nearest participating hospital. The inclusion started August 2014 and is planned to terminate by late August 2016. A total of 6000 participants will be recruited. The informed consent, data collection, and blood collection, handling, and storage will be carried out according to the procedure for the FIT-positive participants.

The emerging results from the Endoscopy II Project will be used to identify the specific biomarker profile subsequently used in analyzing data for Part 1 of the Endoscopy III Project. The analysis will be carried out as shown in Table 1.

Part 2

Limitations of FIT screening include suboptimal sensitivity that leads to false negative results, and thereby some participants with CRC or high-risk or medium-risk adenomas (Textbox 1) are not identified.

Due to the prolonged implementation of FIT screening in Denmark, the period between the first and second screening rounds is estimated to be 4 years; limited colonoscopy capacity will, however, extend the implementation period to about 5 years. Therefore, even low-risk adenoma participants, who far from always are identified by the FIT test, may develop either high-risk/medium-risk adenoma or even early CRC in that prolonged period. Therefore, Part 2 of the Endoscopy III protocol, initiated in March 2016, will include blood samples and data from 30,000 participants screened negative by the FIT testing. The 10 participating hospitals have the capacity to include these participants within 24 to 30 months. Similar to Part 1 FIT-negatives (hgb<100 ng/mL; OC-Sensor platform) the participants are identified and arbitrarily selected from the database of the Danish CRC Screening Program and will be invited to blood collection at the nearest participating hospital. Informed consent, data collection, and blood collection, handling, and storage will be carried out according to the procedure for Part 1 of the project.

At inclusion the participants accept to have blood and data collections after 2 and 4 years, respectively. The third blood and data collection will be approximated to the period just after the second FIT screening testing. All participants will be advised by electronic mail (e-boks in Denmark) 1 month before data and blood collections after 2 and 4 years, respectively.

Table 1. Determination of the following biomarkers is in progress or planned in samples from the Endoscopy II Project with national and international academic and biotech laboratories.

Biomarker	Technique or platform
Profile of 8-15 plasma proteins	The Architect Automated platform, Abbott, Chicago, IL, USA
Soluble urokinase plasminogen activator receptor-I (suPAR-I), suPAR-II, suPAR-III, total suPAR	In-house ELISA platforms, Finsen Laboratory, Copenhagen, Denmark
Galectin ligands	In-house ELISA platforms, MD Anderson Cancer Center, Houston, TX, USA
Cathepsins	In-house ELISA platforms, University of Slovenia, Ljubljana, Slovenia
Cell-free DNA	inhouse PCR Platform, Roskilde Hospital, Roskilde, Denmark
Cell-free, tumor-derived DNA	Platform under development, Skejby Hospital, Skejby, Denmark
Nucleosomes	Tecan-based in-house ELISA platforms, Volition, Namur, Belgium
Proteomes	Mass-spectrometry-based platform, primarily tandem LCMS, Applied Proteomics Inc., San Diego, CA, USA
Metabolomes	Raman Hyperspectral Imaging, ChemImage INC., Pittsburg, PA,USA
YKL-40	Manual commercially available ELISA platform, Herlev Hospital, Herlev, Denmark
Profile of 4 soluble coagulation proteins	Luminex platform, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
Nuclear magnetic resonance (NMR)	NMR profiles, University of Copenhagen, Copenhagen, Denmark
Gas chromatography-mass spectrometry (GC-MS)	GC-MS profiles, University of Copenhagen, Copenhagen, Denmark

Textbox 1. Categories of the identified adenomas.

Adenoma characteristics

- High-risk adenoma
  - Lesion ≥ 20 mm or
  - ≥ 4 lesions or
  - Resection by piece-meal
- Medium-risk adenoma
  - Lesion ≥ 10 mm, but ≤ 20 mm or
  - 3-4 lesions independent of size or
  - Tubulovillous or villous lesion or
  - High-grade neoplasia
- Low-risk adenoma
  - < 3 lesions (< 10 mm) or
  - Tubular lesion or
  - Low-grade neoplasia

Parts 1 and 2

Intensified follow-up of all included participants will be performed electronically via existing health databases and/or participant-specific health files using the unique 10-digit computerized Central Personal Registration number given to all Danish citizens. Thereby no-one is lost to follow-up. Among the aims are evaluations of the risk of developing intra-bowel as well as extra-bowel neoplasia among those diagnosed with adenomas, other benign bowel lesions, and those without any lesions in relation to the biomarkers determined in the project. It has previously been indicated that blood-based biomarkers may be useful to identify such at risk participants [23]. Specifically, the 30,000 FIT-negative participants will be followed-up according to the same aims to identify those with presence of bowel neoplasia although the FIT result was <100 ng/mL and those at risk of developing interval bowel neoplasia during the 4 to 5 years between the two first screening rounds.

Based on a number of approved addendums to the protocol the exact FIT hemoglobin concentrations will, among other parameters, be included for everyone participating in the project. Thereby combinations of blood- and feces-based screening platforms may improve the entire screening concept [24].

Among the aims is the ability to evaluate associations between hemoglobin concentrations and CRC or high-risk adenoma, medium risk-adenoma, low-risk adenoma, non-neoplastic bowel lesions or clean colorectum. Thereby, the amount of screen colonoscopies may be reduced significantly and independently of the cut-point hgb level of 100 ng/mL restricted to those who are in urgent need.

Statistical Analysis

Sample size calculations are based on results from previous published pre-screening studies [8]. It is expected that a total of 8000 participants with a positive FIT test will be included in the study. This sample size results in a coverage probability (exact) of more than 90% for a half width less than 5% in the determination of the sensitivity. It is estimated that 450 to 500 participants will be identified with CRC, 2200 to 2500 with adenomas separated into high-risk, medium-risk and low-risk (Textbox 1); the estimation is that 15% to 20% of these will be identified with high-risk adenomas.

In addition, 6000 FIT-negative patients will be included as controls; the aim is to evaluate a possible difference in biomarker levels and/or presence between FIT-positive and FIT-negative participants. The specific inclusion of 30,000 participants with FIT-negative results will be performed without pre-protocol calculation; presumably, the amount is sufficient to perform the calculations outlined above, in particular because blood and data collections are performed trice in 4 years.

The primary endpoint is the detection of CRC. Secondary endpoints are high-risk adenomas and other non-bowel cancers [23]. The model determined in the Endoscopy II Project will be assessed in this study, in particular with emphasis on the sensitivities, specificities, and the predictive value of the risk. In addition, statistical modeling will be considered using logistic regression analyses, with biomarkers log transformed (base 2); all analyses will be adjusted for age and gender, hospitals will be considered as a random effect. The biomarkers included in the final model will be restricted to combinations of specific biomarkers with the highest likelihood score. Results will be presented by the odds ratios with 95% confidence intervals and area under of the receiver operating characteristic curve. Model validation will be assessed using 10-fold cross-validation. The chosen model will be applied to the FIT-negative samples and compared to the FIT-positive samples using a linear model. A secondary analysis of the FIT-positive samples will be done using decision tree analysis (Adaptive Index Model) [25]. Database management will be done by a locked Web-based database and the statistical calculations will be performed using SAS (v9.4) and R (R Development Core Team, Vienna, Austria).

Ethical Approval

All planned procedures are in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The protocol for the Endoscopy III Project has been approved by the Regional Ethics Committee (H-4-2013-050) and the Danish Data Protection Agency (2007-58-0015/HVH-2013-022).

Results

We anticipate Part 1 to terminate late August 2016 and Part 2 to terminate late September 2022. The results from Parts 1 and 2 will be presented within 12 to 18 months from termination.

Discussion

The primary purpose of Part I of the prospective Endoscopy III Project is to validate the RAE model in an asymptomatic population undergoing FIT screening for CRC. While the study is not a direct comparison between FIT and RAE because the population is selected from the Danish CRC Screening Program, and the included participants have either a positive or a negative FIT result, the results may indicate performance status of the RAE model. Another possible outcome is an indication of a complementary performance of the RAE model and FIT. The outcome may lead to future changes in the structure of implemented screening concepts to include a blood test with a possible supplementary feces test or visa-versa, or to offer the participant a choice between the two test modalities.

Most of the included participants in the present study are healthy and asymptomatic but achieved results are not directly referable to a possible screening population because of selection based on positive or negative FIT; hence, a higher or lower prevalence, respectively, of premalignant and malignant large bowel lesions in the two sub-populations is expected compared to the actual prevalence in the Danish population. The benefit of including the two sub-populations in the study leads to the possibility of comparing biomarker levels and/or the presence in high and low prevalence populations.

In Part 2 of the project, blood samples and data from the participants with negative FIT result may lead to information of how to identify those who either have a present or are at risk of developing interval neoplastic lesions. These participants are currently offered a second screening within a scheduled 4-year period according to the Danish CRC Screening Program. Inclusion of blood collection three times within that period may lead to detailed information on the biomarker levels and/or presence compared with the determination at the first screening and the association to risk of having or developing a neoplastic lesion. In addition, the information on velocity of biomarkers in bowel neoplasia may be specifically valuable to establish a basis for future directions of out-patient visits offered to participants at certain risk of developing bowel neoplasia.

At present, FIT is probably the most commonly used screening test for CRC in Europe, and is also in the implementation phase in some American states and Canada, but the test is challenged by low compliance. The compliance to blood sampling in the included participants in the present study is expected to be high due to expectations of a general acceptability in the population to a blood sample compared to a stool sample [11,12]. A previous study has shown compliance to blood sampling among participants with symptoms of CRC referred to colonoscopy of 96% [13]. Participants enrolled in the present Endoscopy III Project have already committed to screening in performing FIT and have accepted a subsequent colonoscopy. Hence,

compliance found in the present study may not be directly comparable to the Danish population in general, but can give an indication of compliance to a blood sample in a healthy, screen-relevant population.

The amount of 90 mL blood collected and processed is not necessary for the planned analyses (Table 1). The repository of blood samples may, however, form a solid basis for future projects on new and potentially improved biomarkers of the growth, invasion, and/or dissemination processes of CRC; some of these may either stand alone or be integrated in the RAE model resulting in an improved RAE. The Ethics Committee of the Capital Region of Denmark has approved an amendment to the primary protocol (amendment #43062) to take care of the bio-bank.

The personal information, including information about concurrent diseases collected at the time of inclusion, is registered in the locked database. This provides the opportunity to perform follow-up on the future course of participants diagnosed with CRC or other benign or malignant diseases. The Ethics Committee has approved the follow-up opportunity according to The Danish Health Act §43.1-3, which subsequently is granted by participant signatures at the Consent Declaration. This could lead to hypotheses regarding an association between the analyzed biomarkers in this study and the course/prognosis of CRC. It could also lead to an indication of association between the analyzed biomarkers and presence/course of other malignant diseases; maybe even malignant diseases outside the large bowel [23].

We are aware that the ideal and definite study for validating the RAE would be a study including the background population of Denmark with randomization to outreach FIT or blood collection with subsequent colonoscopy in order to compare the value of the two screening tests. The logistic requirements and cost of such a study would be a major task, and is at present not feasible based on local research opportunities. However, the Endoscopy III Project will contribute to evidence for the use of blood-based biomarkers in the RAE model for CRC screening. The performance of FIT and the blood-based RAE will be compared in both the FIT-positive and FIT-negative cohort with colonoscopy considered as the gold standard. A comparable and/or better performance of the blood-based RAE could ultimately contribute to the argument of planning and financing a comparative, nationwide clinical trial of RAE versus FIT. In recent years, molecular pathological epidemiology has evolved describing premalignant adenomas as a heterogeneous group of various subtypes composed of different combinations of genetic and epigenetic variations in close interaction with non-genetic exposures [26]. Through cellular and extracellular interactions, genetic and epigenetic variants of premalignant adenomas and/or CRC could possibly influence levels of blood-based biological markers in the RAE model. However, collection and pathological evaluation of tissue samples from participants undergoing polypectomy/biopsy of tumor in Part 1 of the study is at present not feasible.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

[PDF File (Adobe PDF File), 70KB - resprot_v5i3e182_app1.pdf]

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Abbreviations

CRC: colorectal cancer
FIT: fecal immunochemical test
hgb: hemoglobin
RAE: risk assessment evaluation
suPAR: soluble urokinase plasminogen activator receptor

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Protocol

Nutritional Strategies Facing an Older Demographic: The Nutrition UP 65 Study Protocol

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Abstract

Background: The population of Portugal is aging. The lack of data on older adults' nutritional status and the lack of nutrition knowledge amongst health professionals, caregivers, and older adults themselves, remains a challenge.

Objective: The Nutrition UP 65 study aims to reduce nutritional inequalities in the older Portuguese adult population and improve knowledge regarding older Portuguese adults' nutritional status, specifically relating to undernutrition, obesity, sarcopenia, frailty, hydration, sodium, and vitamin D statuses.

Methods: A representative sample of older Portuguese adults was selected. Sociodemographic, lifestyle, anthropometric, functional, and clinical data were collected. Sodium excretion, hydration, and vitamin D statuses were assessed.

Results: Data collection (n=1500) took place between December, 2015 and June, 2016. Results will be disseminated in national and international scientific journals, and via Portuguese media.

Conclusions: Nutrition UP 65 results will provide evidence for the design and implementation of effective preventive public health strategies regarding the elderly. These insights may represent relevant health gains and costs savings.

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KEYWORDS

older adults; nutritional inequalities; Portugal

Introduction

Demographic projections for the 28 member states of the European Union show that as the population continues to age, the population aged >65 years is estimated to increase from 17% in 2008 to over 25% in 2035, and to 30% in 2060 [1]. As this older population ages, it is expected that the proportion of people aged >80 years will increase from 4.4% in 2008 to 12.1% in 2060 [1]. Accordingly, the Portuguese population is also getting older. Data from the most recent national census in 2011 revealed that 19% of the population was >65 years, and there was an increase of 18.7% in the older population between 2001 and 2011 [2].

These projections are of major concern, due to the links between aging and cognitive and functional decline, emotional changes, and depressive symptoms (all of which may directly influence general health) and, in particular, nutritional status. Furthermore, the scarce national data that is available in Portugal reveals that older adults' nutritional inequalities are present in an accentuated way [3]. The majority of older Portuguese adults have economic

constraints, which directly impact on food security [3]. The current socioeconomic situation in countries experiencing an economic crisis (such as Portugal) leads us to predict that the frequency and consequences of nutritional status-related disabilities will increase in the coming years.

Frail elders living in the community, institutionalized in nursing homes, or admitted to hospitals have increased risks associated with nutritional disorders [4]. In many instances the existing nutritional disorders of these patients go unrecognized and adversely affect their clinical outcomes. Nutritional status impairment in older adults is a serious public health problem [5,6]. Despite the alarming data released during the last decade relating to the negative influence of nutritional disorders on the health status of older populations, undernutrition occurrence is still very common in Europe [7,8]. Data from a systematic sample of patients admitted to six Portuguese hospitals showed that undernutrition is prevalent, affecting approximately one in three patients upon admission [9]. Undernutrition is a relevant factor for disease prognosis and is linked to higher odds of morbidity, premature mortality, and higher costs of care [10]. In addition, older age is an established risk factor for undernutrition [9]. Data regarding the prevalence of undernutrition and general nutritional status of older Portuguese adults living in communities are scarce and limited to a small number of geographic areas in Portugal [11]. Additional knowledge about the dimensions of undernutrition frequency in different regions, as well as the identification of the main factors associated with this problem, will allow for a better design and implementation of preventive strategies.

In addition to undernutrition, other priority areas will be addressed in this project. Nutritional status of fat-soluble vitamins in subjects aged >65 years is highly variable and determined by season, nutritional status, inflammation, renal function, and hospitalization [12]. The skin of elderly people produces less vitamin D than the skin of younger people; moreover, older adults also spend less time in the sun, and this population has an increased risk of vitamin D deficiency [13]. Data from a European report revealed a prevalence of vitamin D deficiency of up to 40% [14], and vitamin D deficiency among institutionalized and/or hip fracture patients is a major concern [15]. However, there is a lack of knowledge regarding the burden of vitamin D deficiency in Portugal.

Dehydration is a common condition among older people, and likely contributes to a number of medical conditions that lead to higher morbidity and mortality in these individuals [16]. Despite the scarcity of data pertaining to the hydration status of the Portuguese population, the assessment of fluid intake in a representative sample of Portuguese adults revealed a low intake of fluids by older subjects, particularly elderly men that reported to have consumed 51% less fluids than the recommended intake [17].

The World Health Organization recommends no more than 2 grams of sodium (5 grams of salt) per day for adults, in order to reduce the burden of noncommunicable diseases [18]; however, in all countries with recent data available, salt intake is much higher than recommended [19]. Excessive sodium intake is strongly associated with high blood pressure [20] and approximately 75% of the Portuguese elderly have been classified as hypertensive [21]. To our knowledge, the estimated amount of sodium ingested by this Portuguese subpopulation has not been published.

Current trends also indicate that the prevalence of obesity and sarcopenic obesity in this age group is increasing [22,23]. These conditions also have implications for the frailty of the elderly, which is strongly associated with higher mortality in older adults [24]. Nevertheless, Portuguese data concerning the dimensions of these conditions is scarce.

Together with the aforementioned trends and data, the absence of adequate nutritional data in Portugal (particularly in settings such as community and care institutions) reinforces the relevance of this study. The main objective of the Nutrition UP 65 study is to expand the knowledge of older Portuguese adults' nutritional status. More specifically, the study aims to improve the information regarding undernutrition, obesity, sarcopenia, frailty, hydration, sodium and vitamin D statuses. These data will be a basis for the development of public health guidelines, with the goal of reducing nutritional inequalities in the older Portuguese population.

Methods

Study Design and Setting

A cross-sectional observational study was conducted in Portugal in a cluster sample of 1500 older adults (≥65 years old), which was representative of the older Portuguese population in terms of age, sex, education, and regional area. Data from the most recent national census in 2011 showed that the number of Portuguese residents was 10,562,178 and a total of 2,010,064 older Portuguese adults were identified, corresponding to 19% of the Portuguese population [2]. Thus, the recruited study sample (n=1500) corresponds to 0.075% of the Portuguese older population. Data for this study were collected between December, 2015 and June, 2016.

Ethics

This research was conducted according to the guidelines established by the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the department of Ciências Sociais e Saúde (Social Sciences and Health) from the Faculdade de Medicina da Universidade do Porto (PCEDCSS – FMUP 15/2015) and by the Portuguese National Commission of Data Protection (9427/2015).

Sampling and Recruitment

To achieve a nationally representative sample of older Portuguese adults aged ≥65 years, a quota sampling approach was adopted using data from Census 2011 regarding sex, age, educational level, and residence area.

Individuals were considered to be Portuguese if they had only Portuguese nationality and if their current tax residence was in Portugal, and were eligible to participate in the study if they were aged ≥65 years. The following age categories were considered: 65-69, 70-74, 75-79, 80-84, 85-89, and >90 years old [25]. Educational level was determined by the number of school years completed, and the following categories were used:

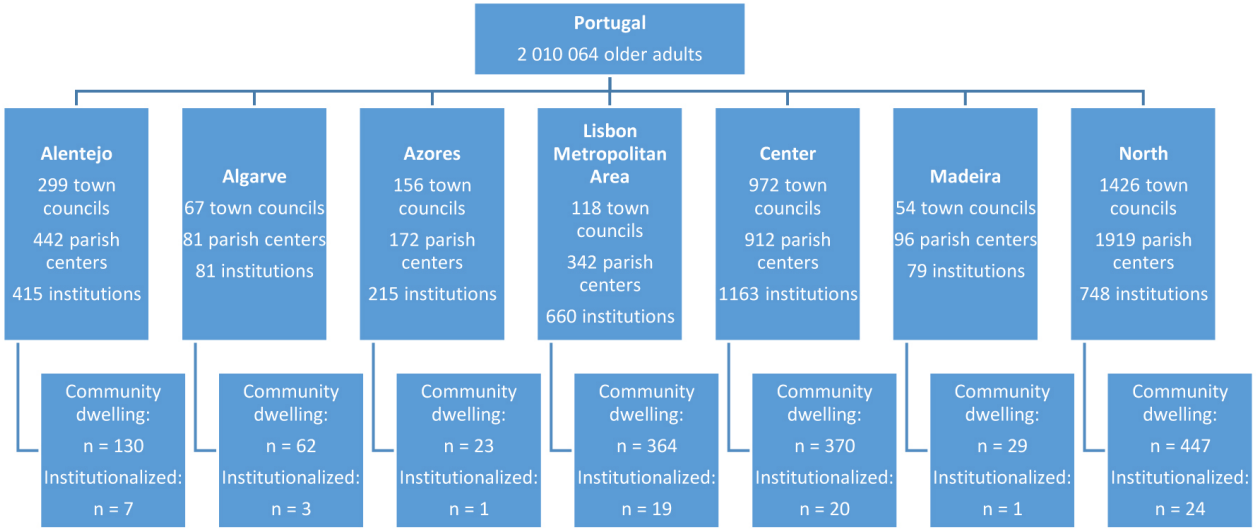
<4 years of schooling, first cycle (4 years of schooling), second cycle (6 years of schooling), third cycle (9 years of schooling), secondary (12 years of schooling), post-secondary (>12 years of schooling but no higher education), and higher education (academic, vocational, and advanced professional education) [25]. The regional areas used were defined in the Nomenclature of Territorial Units for Statistics: Alentejo, Algarve, Azores, Lisbon Metropolitan Area, Center, Madeira, and North (Multimedia Appendix 1) [26].

A random, stratified, and clustered sampling method was applied. In each regional area, three or more town councils with >250 inhabitants were randomly selected. Potential community-dwelling participants were contacted via home approach, telephone, or via institutions, such as town councils and parish centers.

The study sample was composed of community-dwelling older adults and individuals institutionalized in retirement homes, representing the 5% proportionality of older Portuguese individuals [2]. Participants were considered to be community-dwelling individuals if she/he slept in their own house, or in the house of a family member or friend, more than half of the days of the preceding month. Individuals institutionalized in retirement homes were contacted through the individual institutions (Figure 1).

Potential participants were contacted by the interviewer, who provided information about the study purposes and methodology, and invited them to participate. A document entitled *Information for the participant* was prepared and read by each potential participant or by a surrogate. In cases of acceptance, all participants (or two representatives if the participant was deemed to be cognitively impaired) were asked to read and sign a duplicated *Informed consent* form. Individuals presenting any condition that precluded the collection of venous blood samples or urine (eg, dementia or urinary incontinence) were excluded from the study.

Figure 1. Sample composition and distribution.



Sociodemographic, Anthropometric, Lifestyle, and Clinical Data

Demographic data, cognitive performance, current and former professional occupation, lifestyle practices, health status and clinical history, nutritional status, cohabitation, skin phenotype, and household income were collected using a structured questionnaire applied by means of an interview. The interview was conducted by eight previously trained registered nutritionists, who were also responsible for anthropometric data collection.

Demographic data included sex, date of birth, marital status, and education. Cognitive performance was assessed by the Portuguese version of the Mini Mental State Examination [27]. This test consists of 30 questions (each scored one point if correct) and examines the functions of orientation, registration, attention and calculation, recall, language, and ability to follow simple commands. The cutoff scores for cognitive impairment are as follows: individuals with no education, ≦15 points; 1 to 11 years of years of school completed, ≦22 points; and ≦11 years of school completed, ≦27 points. For individuals identified as presenting cognitive impairment, the *Informed consent* form was signed by two representatives and all data was provided by a person close to the participant, such as a family member or caregiver.

Lifestyle was evaluated via involvement in physical activities during the past seven days, current and former tobacco use, consumption of alcoholic beverages, and adherence to the Mediterranean diet, as described below.

Physical activity was assessed by the short form of the International Physical Activity Questionnaire [28]. This questionnaire gathers information regarding the previous seven days, namely how many days and how much time the participant spent: walking or hiking (at home or at work, moving from place to place, for recreation or sport), sitting (at a desk, visiting friends, reading, studying, or watching television), moderate activities (carrying light objects, hunting, carpentry, gardening, cycling at a normal pace, or tennis with two pairs), and vigorous activities (lifting heavy objects, agriculture, digging, aerobics, swimming, playing football, or cycling at a fast pace).

Adherence to the Mediterranean diet was evaluated with the Portuguese version of the Prevention with Mediterranean Diet tool [29]. This tool was developed with the purpose of testing the effectiveness of the Mediterranean diet on the primary prevention of cardiovascular disease, and consists of 14 questions, each scored with zero or one point. The criteria for assigning one point are established and a final score ≥10 indicates a good adherence to the Mediterranean diet.

Data regarding subjective general health were collected using questions drawn from the Portuguese National Health Survey 2005-2006. These questions concerned: self-reported diagnosis of chronic diseases in the past 12 months, namely the presence of asthma; chronic bronchitis, chronic obstructive pulmonary disease, or emphysema; myocardial infarction or chronic consequences of myocardial infarction; coronary heart disease or angina pectoris; hypertension; stroke or chronic consequences of a stroke; arthrosis; lumbar pain or other chronic lumbar problems; neck pain or other chronic neck problems; diabetes; hepatic cirrhosis; allergies; chronic renal disease, including renal failure; urinary incontinence or bladder control problems; depression and other diseases; and pharmacological treatment and use of nutritional supplements, including the name and number of daily doses.

Detailed information regarding each participant's nutritional status encompassed the assessment of the following anthropometric measurements: body weight; standing height; mid-upper arm, waist, and calf circumferences; triceps skinfold thickness; and the functional status indicators of hand grip strength and walking speed [30,31].

Anthropometric measurements were collected following standard procedures [32]. Standing height was obtained with a calibrated stadiometer (Seca 213) with 0.1-centimeter resolution. For participants with visible kyphosis, or when it was impossible to measure standing height due to the participant's paralysis, mobility, or balance limitations, height was obtained indirectly from nondominant hand length (in centimeters) [33], measured with a calibrated paquimeter (Fervi Equipment) with 0.1-centimeter resolution. Body weight (in kilograms) was measured with a calibrated portable electronic scale (Seca 803) with 0.1-kilogram resolution, with the participants wearing light clothing. When it was not possible to weigh a patient (for the same reasons described for standing height measurement) body weight was estimated from mid-upper arm and calf circumferences [34]. Mid-upper arm, waist, and calf circumferences were measured with a metal tape measure (Lufkin) with 0.1-centimeter resolution. Triceps skinfold thickness was obtained using a Holtain Tanner/Whitehouse skinfold caliper with 0.2-millimeter resolution.

Nondominant hand grip strength was measured with a calibrated Jamar Hand Dynamometer (Sammons Preston), as recommended by the American Society of Hand Therapists [35]. Each participant performed three measurements with a one-minute pause between measurements [36]. When the individual was unable to perform the measurement with the nondominant hand, the dominant hand was used.

The MNA-SF consists of six questions targeting food intake, weight loss, physical and mental status, and anthropometry through body mass index (BMI) assessment. BMI was calculated using the standard formula (weight in kilograms/height^2 in meters). A participant scoring ≦7 out of 14 points was classified as undernourished, one that scored between 8 and 11 was at risk of undernutrition, and one scoring between 12 and 14 points was considered well-nourished [30].

Frailty, according to the frailty phenotype described by Fried et al [37], encompasses the assessment of five criteria: unintentional weight loss in the previous year, weakness evaluated as low hand grip strength (adjusted for gender and BMI), poor endurance and energy evaluated as exhaustion, slowness (gait speed measurement adjusted for gender and standing height), and low activity (kilocalories expended per week, adjusted for gender). If one or two of these criteria were present, the individual was characterized as prefrail. Frailty was defined as the presence of three or more criteria [37].

According to the European Working Group on Sarcopenia in Older People [38], sarcopenia was defined as the combined presence of low muscle mass and low muscle strength, or diminished physical performance. Muscle mass was assessed based on the two compartment model (body muscle mass = body weight - body fat mass). Body density was estimated based on triceps skinfold thickness [39] and body density was converted to fat mass through the Brozek equation [40]. Muscle strength was evaluated by hand grip strength (adjusted for gender and BMI) and physical performance by gait speed. Presarcopenia occurs when only muscle mass is diminished. Sarcopenia is characterized by low muscle mass plus one of the other two criteria. All three criteria are present in an individual with severe sarcopenia.

Information on cohabitation, skin phenotype (as measured by the Fitzpatrick classification [41]), and household income were also collected.

Laboratory Procedures and Biological Samples

A sample of blood and the volume of urine in a 24-hour period were collected for each participant. The study interviewers gave the participants oral and written instructions detailing the collection and storage procedures for the volume of 24-hour urine. Participants were instructed to refrain from collecting the first urine of the day, but to record the time of the first urine, and collect all excreted urine during the day and evening. The following day, participants collected the morning urine until the time they recorded the first urine the day before. A 24-hour urine container was also provided, and participants were instructed to keep the container in the refrigerator until it was delivered for analysis. A certified laboratory (Labco Portugal) was responsible for blood and urine sample collection and analyses.

Vitamin D status was evaluated by dosing the plasmatic levels of 25-hydroxycholecalciferol or calcidiol through the electrochemiluminescence immunoassay using Roche Cobas Vitamin D total assay reagent (Roche Diagnostics GmbH, Mannheim, Germany). Blood samples for these analyses were collected by qualified nurses within four days of the application of the questionnaire, and preferentially after a 12-hour fasting period.

The following urinary markers were quantified: urine volume (milliliters), urinary creatinine (milligrams/day), urine osmolality (milliosmoles/kg), and urine density for 24 hours. Urinary creatinine was measured by the Jaffe method.

Hydration status was evaluated by free water reserve (milliliters/24 hours [42-47]) calculated by subtracting 24-hour urine volume from obligatory urine volume (solutes in urine 24 hours [milliosmoles/day] / 830 - 3.4 x [age - 20]), allowing for the classification of the 24-hour hydration status (euhydrated vs hypohydrated subjects, or at risk of hypohydration [43,48]). Urine samples were also analyzed for urinary sodium (milliequivalents/day); however, for comparative purposes, these values were converted to milligrams/day by using the molecular weight of sodium (23 milligrams sodium = 1 millimole sodium or 1 milliequivalents sodium).

Results

Data collection (n=1500) took place between December, 2015 and June, 2016 and results are being analyzed. Final results will be disseminated by scientific journals and via the media throughout Portugal.

Discussion

Nutrition UP 65 will provide an innovative and important contribution to overcome the lack of data regarding nutritional conditions in Portugal. These data will also generate information to define public health interventions and guidelines tailored to Portugal's health realities.

This project also expects to bridge the gap in knowledge regarding the country's regional differences with respect to the prevalence of inadequate nutritional status, particularly in rural areas, by the gathering of nationwide nutritional information (including rural areas and the interior region). Nutrition UP 65 includes a sample of older adults that are widely distributed in different geographical regions, thus allowing for a *picture* of the country's situation. This study will first describe the nutritional status of older populations according to regional area, and using the same methodology, provide a better understanding on nutritional risk contrasts. This baseline nutritional status description will support the development of evidence-based public action that considers regional discrepancies and contrasts. This study will make it possible to define the main regional priorities for nutritional intervention at the level of primary health care, hospitals, and community.

The data from this project will reveal a nationwide description of the burden of major nutritional health problems affecting older Portuguese adults, identify vulnerable target groups for public health interventions, and allow for the implementation of an evidence-based nutritional surveillance system. Nutrition UP 65 will guide the design and implementation of preventive public health strategies at all levels of dependence, with unequivocal health gains for this population group. These strategies have been proven to be economically effective, and increase the awareness of health professionals with regards to nutrition-related issues.

Furthermore, information regarding the main nutritional problems that affect older populations will empower older adults with knowledge to recognize nutritional imbalances, and to have better nutrition, which should help to prevent major nutritional problems and nutrition-related disabilities.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Sample size and constitution.

[XLSX File (Microsoft Excel File), 64KB - resprot_v5i3e184_app1.xlsx]

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Abbreviations

BMI: body mass index
MNA-SF: Mini-Nutritional Assessment - Short Form

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Original Paper

Young Adult Utilization of a Smoking Cessation Website: An Observational Study Comparing Young and Older Adult Patterns of Use

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Abstract

Background: There is little research on how young adults or young adult subgroups utilize and engage with Web-based cessation interventions when trying to quit smoking. Addressing this knowledge gap is important to identify opportunities to optimize the effectiveness of online cessation programs across diverse young adult users.

Objective: This study examines utilization of the BecomeAnEX.org smoking cessation website among young adults and young adult subgroups compared with older adults to identify patterns of use by age, gender, and race/ethnicity.

Methods: Study participants were 5983 new registered users on a free smoking cessation website who were aged 18 to 70 years. Website utilization was tracked for 6 months; metrics of use included website visits, pages per visit, length of visit, and interaction with specific website features. Differences in website use by age were examined via bivariate analyses and multivariate logistic regression adjusted for age, gender, and race/ethnicity. Interactions were examined to determine differences by gender and race/ethnicity within young (18- to 24-year-olds and 25- to 34-year-olds) and older (35 years and older) adult segments.

Results: A greater percentage of young adults aged 18 to 34 years visited the site only once compared with older adults aged 35 years and older (72.05% vs 56.59%, respectively; *P*<.001). Young adults also spent less time on the site and viewed fewer pages than older adults. In adjusted analyses, young adults were significantly less likely than older adults to visit the site more than once (18-24 years: adjusted odds ratio [AOR] 0.58, 95% CI 0.49-0.68, *P*<.001; 25-34 years: AOR 0.56, 95% CI 0.50-0.64, *P*<.001), spend more than 3 minutes on the site (18-24 years: AOR 0.67, 95% CI 0.57-0.79, *P*<.001; 25-34 years: AOR 0.56, 95% CI 0.49-0.64, *P*<.001), view 12 or more pages (18-24 years: AOR 0.72, 95% CI 0.61-0.83; *P*<.001; 25-34 years: AOR 0.67,

95% CI 0.59-0.76, *P*<.001), utilize the BecomeAnEX.org community (18-24 years: AOR 0.61, 95% CI 0.48-0.79, *P*<.001; 25-34 years: AOR 0.73, 95% CI 0.60-0.88, *P*<.001), or utilize Separation Exercises (18-24 years: AOR 0.68, 95% CI 0.51-0.89, *P*<.01; 25-34 years: AOR 0.77, 95% CI 0.63-0.94, *P*<.01). Gender differences in utilization were more pronounced among young adults compared with older adults, with lower levels of utilization among young men than young women. For all age groups, utilization was higher among whites and African Americans than among Hispanics and other racial minorities, with one exception—BecomeAnEX.org community utilization was significantly higher among Hispanic young adults compared with white and African American young adults.

Conclusions: Results point to important areas of inquiry for future research and development efforts. Research should focus on enhancing demand and increasing engagement among younger adults and men, examining strategies for capitalizing on young adult developmental needs, and increasing utilization of effective site features among diverse young adult users.

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KEYWORDS

young adults, smoking cessation, Internet, utilization

Introduction

Tobacco smoking remains the leading cause of preventable disease and death in the United States, with 16.8% of US adults (40 million individuals) reporting current cigarette smoking in 2014 [1,2]. The adult smoking rate has declined significantly in the last decade from 20.9% in 2005 to 16.8% in 2014 [2], and further reductions require continued comprehensive tobacco control efforts of which cessation interventions are a key component [3,4]. Helping young adult smokers quit in particular is critical to ensure continued reductions in population-level cessation.

Young adulthood is a critical developmental period for tobacco use and cessation. Substance use–related risk behavior peaks during young adulthood [5]. As individuals age into this time of life, they gain the ability to purchase tobacco legally in the United States and may enter a phase of transition from experimental to regular tobacco use [6]. Smoking often becomes entrenched during these years, and young adults are increasingly a prime target for tobacco marketing [7,8]. Critically, research indicates quitting before age 35 can result in a life expectancy on par with that of never smokers [9].

Young adults are more likely than older adults to make a quit attempt [10] but less likely to use assistance when trying to quit [10,11]. Curry et al [10] analyzed data from the 2005 National Health Interview Survey to examine use of evidence-based treatment by young adults (18-24 years) compared to older adults (25 years and older). Young adults reported very low levels of cessation treatment with only 4% using any behavioral treatment (eg, telephone quit line, class/clinic/group, one-on-one counseling). Young adults were also much less likely to report using any pharmacotherapy (eg, nicotine replacement therapy, bupropion) as compared with older adults (18% vs 33%, respectively). Less than 5% of these young adults reported using other types of cessation such as printed self-help materials, Internet, or hypnosis/acupuncture [10].

Comprehensive reviews have documented promising evidence for the efficacy of online interventions for smoking cessation [12-28]. Web-based interventions can promote cessation among adults, particularly if they are tailored to individuals and maximize interactivity to engage users [12,14]. Given the increasing utilization of the Internet among US adults, online interventions have the potential for substantial reach and population-level impact in reducing smoking [4]. A majority of adults across all age, race/ethnicity, income, and educational groups are Internet users [30]. The greatest increases in Internet adoption in recent years have occurred among those with the lowest rates of cessation [30,31], suggesting the Internet may be an increasingly feasible channel for intervention among these groups. With users of all ages having expanded access to the Internet, online interventions become more convenient [14]. Further, low costs per user make online interventions cost effective given sufficient reach [14,15].

While Web interventions may be important for reaching adults across all age groups, this channel may be especially relevant for reaching younger smokers. Young adults aged 18 to 29 years have demonstrated consistently higher levels of Internet adoption than older groups in the past 15 years and currently report Internet use at a nearly ubiquitous rate of 96% [30]. Young adults also use social networking sites at high rates, with 89% of young adult Internet users reporting social network site use in contrast to only 74% of adult Internet users overall [32].

Further, young adult smokers have indicated interest in using technology-based interventions [33], and Web-based resources have been identified as a potentially promising intervention for younger smokers [27,28,34-39]. Although An et al [40] reported very low levels of participation in a Web-based cessation intervention among college students during the beta phase of development, utilization increased sharply as the site was changed from a stop-smoking website to an online college life magazine and proactive peer email support and directed activities were added. Age did not moderate treatment effects in the formal outcome evaluation [36]. In a 3-group randomized trial, An et al [27] found high rates of 30-day abstinence and intervention engagement among 18- to 30-year-old smokers in a personally tailored online intervention that utilized an avatar host for individual personal health “makeovers” plus video-based online peer coaching. An additional study by Berg et al [4] found higher rates of intervention engagement and fewer cigarettes smoked per day among participants randomized to an intervention with online health behavior monitoring and targeted messages compared with those randomized to the online American Cancer Society Guide to Quitting Smoking. In one

of the few studies of an open-access smoking cessation website, Richardson et al [17] found no differences between young and older adults on overall number of visits to the website or use of the community forum but did find that young adults were more likely to access an interactive feature about managing smoking triggers. Together, these studies along with research on media utilization demonstrate that young adults are extensive users of digital and social media and suggest that online interventions may play an important role in reaching and engaging a young adult audience.

There is little research focused on examining patterns of engagement on cessation websites among specific populations. While metrics used to capture engagement differ somewhat across studies, common metrics generally include some measures of website "dose" to capture potential exposure to or use of the content of the website intervention [41-43]. Such metrics commonly include number of visits or log-ins [16,17,19-21,23,26,28,43-46], average session length in minutes and/or total minutes on the site [16,17,23,28,43], and total number of pages viewed [16,17,23,28] or Web sections opened or read [16,18,47]. Other engagement metrics capture utilization of specific website components, including use of interactive tools such as setting a quit date [17,43,47], identifying triggers [17,43], tracking or monitoring one's smoking behaviors [17,28,40,47], and watching videos [27,28,43]. Additional program components often captured include use of or participation in an online community in some form, which may involve accessing the community and/or reading posts [16,17,36,43], posting messages [16,23,36,43,48], and sending or receiving personal messages [23,36,43,45].

Only a few of these studies provide details on how users engage with website interventions or examine utilization outside of a controlled trial setting [17,23,26,36,45,46]. Fewer still focus on young adults or young adult subgroups [27,28,39,40]. Understanding how young adult smokers utilize cessation websites in a real-world setting is a necessary first step in optimizing interventions for engagement and ensuring they are effective for youth audiences and diverse groups of users. This observational study was conducted to identify patterns of website engagement among young adults compared with older adults and among subgroups defined by gender and race/ethnicity, with a focus on young adults. This study adds to a relatively small body of literature specifically focused on the role of digital and social media interventions in promoting cessation among young adults.

Methods

BecomeAnEX.org Intervention

BecomeAnEX.org is an evidence-based smoking cessation website developed by Truth Initiative (formerly American Legacy Foundation), a national nonprofit organization that, in partnership with the Mayo Clinic's Nicotine Dependence Center, focuses on smoking prevention and cessation. Launched in 2008, the website was designed for a target audience broadly defined as smokers between the ages of 25 and 49 years who were open to quitting smoking [49]. Promotional activities and the voice of the site were designed to appeal to blue-collar smokers of low to moderate incomes because of their higher smoking rates. The site was developed in accordance with the 2008 US Department of Health and Human Services Public Health Service Clinical Practice Guidelines for Treating Tobacco Dependence (PHS Guideline) [50] and focuses on educating and supporting smokers throughout their quitting efforts. The site is available on multiple platforms, including mobile, and is designed to engage smokers through the following core elements: (1) My Quit Plan, a checklist that helps smokers set a quit date and tracks their progress through the steps of the quit plan; (2) Beat Your Smoking Triggers, a list of common triggers with tips for dissociating cigarettes from them; (3) a Cigarette Tracker to help smokers identify and track their smoking triggers; (4) Separation Exercises to teach smokers how to separate smoking a cigarette from the activities that trigger cravings (ie, drinking coffee or alcohol); (5) a Support Exercise to help smokers identify who they can turn to for support when quitting smoking; (6) Quit Smoking Resources, a list of national organizations, state quitlines, and websites that smokers can turn to for additional information and help to quit smoking; (7) texts and videos detailing the importance of medication and the different types available; and (8) the BecomeAnEx.org community, a large online network of current and former smokers.

BecomeAnEX has been promoted through a national multimedia campaign since 2008 [49]. During the study period, registration on BecomeAnEX.org required users to indicate age, gender, and race/ethnicity. Registration also required users to agree to the site's Terms of Use and Privacy Policy which state that (1) Truth Initiative collects information about its users and their use of the site, (2) information is used for research and quality improvement purposes only, and (3) personal information is kept confidential. Informed consent was not required given the availability of website utilization data and the observational nature of the study.

Study Participants

Study participants were 5983 users aged 18 to 70 years who registered on BecomeAnEX.org between May 7, 2012, and November 18, 2012. We excluded new registered users that were recruited to other research studies being conducted within BecomeAnEX at the time (n=3800) and those without a valid email address (n=3566).

Data Collection and Measures

Demographic data (age, gender, race/ethnicity) gathered during site registration were extracted from the BecomeAnEX database. Website utilization data were collected using Adobe Analytics, a customizable Web analytics product. Every page view by a participant is recorded into a relational database, and page views are grouped into sessions. The duration of a session is defined as the time elapsed between the first page view and the last page view in a given session. If a user does not view a new page for over 30 minutes, the system marks them as inactive and their next return visit creates a new session. We focused on 6-month metrics of utilization given prior research that has shown that the majority of utilization occurs during this time frame [51]. Two types of measures here were utilized to capture engagement with the website. Dose measures were based on number of visits

to the site, time spent on the site (minutes), and total number of pages viewed. Engagement metrics to capture utilization of program components included use of the BecomeAnEX.org community and use of Separation Exercises. We chose these two features because each independently predicted abstinence in a previous evaluation [17]. We calculated total time spent on the site over the 6-month observation period as the product of minutes per visit and number of visits.

Analysis

For regression analyses, young adults were categorized into two age groups commonly used to examine tobacco use and cessation for this population: 18 to 24 years and 25 to 34 years [52-55]. Older adults were categorized as aged 35 years and older. For descriptive analyses, 18- to 24-year-olds and 25- to 34-year-olds were combined for succinctness of presentation and compared with older adults. Race and ethnicity were categorized as non-Hispanic white, non-Hispanic African American, Hispanic, and other non-Hispanic.

Descriptive analyses were used to examine differences in site utilization patterns between young adults (18-34 years) and older adults (35 years and older). Key variables of interest included number of site visits, time spent on the site in minutes, and number of page views; use of the BecomeAnEX.org community forum and Separation Exercises were examined as binary variables (none vs any). In addition to examining utilization metrics as continuous data, we created categorical variables based on the meta-analysis presented in the PHS Guideline [50] to provide a framework for interpreting the intensity of website utilization. Using the PHS Guideline for number of sessions, we categorized number of site visits as 1, 2-3, 4-8, and more than 8 visits. Using the PHS Guideline categories for total amount of contact time, we categorized time spent on the site as 3 minutes or less, 4 to 30 minutes, and 31 or more minutes. To test differences in utilization metrics by age group, we used the Wilcoxon rank-sum test for nonnormally distributed continuous variables and the chi-square test for categorical variables.

Main effects logistic or linear regressions were conducted with each of the five utilization metrics, with age group (18-24 years, 25-34 years, and 35 years and older) as the main predictor and gender and race/ethnicity as controls. For purposes of regression analyses, number of site visits was dichotomized as 1 visit (registration visit only) versus 2 or more visits; time on site was dichotomized as 3 minutes or less versus more than 3 minutes. Total pages viewed was dichotomized at the median (11 pages or fewer vs 12 or more pages), while website feature use was dichotomized as never versus any use. Given the large sample size and number of dependent measures examined (n=5), we used a criterion of $P<.01$ (.05/5) as a more conservative gauge of statistical significance.

We also conducted regressions for each outcome with age, gender, and race/ethnicity and two interactions by age and gender as well as age and race/ethnicity, with interactions considered significant at the $P<.05$ level. Models were then stratified by the three age groups and rerun.

Results

Sample Description

Young adults aged 18 to 34 years comprised 50.64% (3030/5983) of the overall sample (see Table 1). The average age of the sample overall was 37.3 years (standard error [SE] 0.16) with an average age of 21.8 years (SE 0.06) for 18- to 24-year-olds, 29.3 years (SE 0.06) for 25- to 34-year-olds, and 48.0 (SE 0.16) for older adults (see Multimedia Appendix 1). Age groups were 18 to 24 years, 16.00% (957/5983); 25 to 34 years, 34.60% (2073/5983); 31 to 49 years, 40.82% (2442/5983); and 50 years and older, 21.39% (1280/5983). The gender distribution was more evenly split for 18- to 34-year-old young adults than for adults over 35 years (54.00% [1567/3030] female and 69.02% [1998/2953] female, respectively). Among young adults, whites comprised the majority of users; however, there were fewer non-Hispanic whites and a greater proportion of Hispanics and other non-Hispanics compared with older adults. See Multimedia Appendix 1 for further breakdown of demographics for young adults aged 18 to 24 years and 25 to 34 years.

Table 1. Participant Characteristics.

		Young adults 18-34 years n=3030	Older adults 35 years and older n=2953	Full sample n=5983
Age, years, mean (SE)		26.9 (0.08)	48.0 (0.16)	37.3 (0.16)
Gender, n (%)				
	Female	1567 (54.00)	1998 (69.02)	3565 (61.50)
	Male	1335 (46.00)	897 (30.98)	2232 (38.50)
Race/ethnicity, n (%)				
	White, non-Hispanic	1753 (57.85)	2268 (76.80)	4021 (67.21)
	African American, non-Hispanic	205 (6.77)	261 (8.84)	466 (7.79)
	Hispanic	591 (19.50)	208 (7.04)	799 (13.35)
	Other, non-Hispanic	481 (15.87)	216 (7.31)	697 (11.65)

Website Utilization Differences by Age: Bivariate Analyses

The mean number of visits to the website was 5.02 (SE 0.70) overall, with a significant difference in mean visits by age (2.52 [SE 0.15] for adults aged 18 to 34 years and 7.59 [SE 1.41] for older adults; *P*<.001) (see Table 2). While a majority of both younger and older adults visited the site only once, the proportion of individuals who visited the site only once versus two times or more differed significantly by age, with 72.05% (2183/3030) of younger adults accessing the site only once compared with 56.59% (1671/2953) of older adults (*P*<.001). Younger adults also spent significantly less time on the site compared with older adults. Overall, the mean number of pages viewed was 77.11 (SE 11.98), with older adults viewing more than 2.5 times as many pages as younger adults (113.01 [SE 23.61] vs 42.00 [SE 5.44], respectively; *P*<.001). Younger adults were also significantly less likely to use the BecomeAnEX.org community and Separation Exercises features compared with older adults .Multimedia Appendix 1 shows bivariate analyses of website characteristics for each young adult group and older adults and comparisons for each group. Significant differences in utilization for the 18- to 24-year-old and 25- to 34-year-old subgroups in comparison with the older adults were similar to those described above. There were no significant differences in utilization between the 18- to 24-year-olds versus 25- to 34-year-olds, with the exception of mean time on site (28.50 minutes [SE 3.91] vs 27.12 minutes [SE 3.04] for 18- to 24-year-olds and 25- to 34-year-olds, respectively) and pages viewed (67.50 pages [SE 15.63] vs 30.41 pages [SE 3.32] for 18- to 24-year-olds and 25- to 34-year-olds, respectively).

Table 2. Bivariate analyses of website utilization metrics by age.

			Young adults 18-34 years n=3030	Older adults 35 years and older n=2953	Full sample	*P* value
Site visits						
	Mean (SE[a])		2.52 (0.15)	7.59 (1.41)	5.02 (0.70)	<.001
	Median (IQR[b])		1.00 (1.00)	1.00 (2.00)	1.00 (1.00)	
		1 time, n (%)	2183 (72.05)	1671 (56.59)	3854 (64.42)	
		2-3 times, n (%)	527 (17.39)	758 (25.67)	1285 (21.48)	
		4-8 times, n (%)	211 (6.96)	341 (11.55)	552 (9.23)	
		>8 times, n (%)	109 (3.60)	183 (6.20)	292 (4.88)	
Time on site, minutes						
	Mean (SE)		27.56 (2.42)	140.42 (32.84)	83.26 (16.27)	<.001
	Median (IQR)		5.07 (16.27)	10.98 (26.86)	7.30 (21.87)	
		≤3 minutes, n (%)	1232 (40.67)	713 (24.15)	1945 (32.52)	
		4-30 minutes, n (%)	1330 (43.91)	1497 (50.71)	2827 (47.27)	
		≥31 minutes, n (%)	467 (15.42)	742 (25.14)	1209 (20.21)	
Pages viewed						
	Mean (SE)		42.00 (5.44)	113.01 (23.61)	77.11 (11.98)	<.001
	Median (IQR)		8.00 (17.00)	14.00 (26.00)	11.00 (22.00)	
Used EX Community, n (%)			327 (10.79)	387 (13.11)	714 (11.93)	.006
Used Separation Exercises, n (%)			232 (7.66)	366 (12.39)	598 (10.00)	<.001

[a]SE: standard error

[b]IQR: interquartile range

Website Utilization Differences by Age, Gender, and Race/Ethnicity: Multivariate Analyses

Table 3 shows multivariate regressions for each of the website utilization metrics with age, gender and race/ethnicity as predictor variables. Both 18- to 24-year-olds and 25- to 34-year-olds and men were less likely to visit the website more than once, spend more than 3 minutes on the site, view 12 pages or more, use the BecomeAnEX.org community, or use the Separation Exercises compared with older adults and women. Hispanics were less likely than non-Hispanic whites to visit the website more than once, spend more than 3 minutes on the site, view 12 pages or more, or use the Separation Exercises, but they were twice as likely to use the BecomeAnEX.org community. Analyses indicated lower utilization of the website on all metrics among African Americans, but odds ratios (ORs) only reached significance for visiting the site more than once. Those identifying as other were less likely than non-Hispanic whites to spend more than 3 minutes on the site, view 12 pages or more, or use the Separation Exercises.

Table 3. Odds ratios (95% confidence intervals) of multivariate regression models of general website utilization metrics.[a]

	Site Visits[b]	Time on site[c]	Page views[d]	Used Community[e]	Used Separation Exercises[f]
Age					
Older adults: 35+	Referent	Referent	Referent	Referent	Referent
Young adults: 25-34	0.56 (0.50, 0.64)	0.56 (0.49, 0.64)	0.67 (0.59, 0.76)	0.73 (0.60, 0.88)	0.77 (0.63, 0.94)
Young adults: 18-24	0.58 (0.49, 0.68)	0.67 (0.57, 0.79)	0.72 (0.61, 0.83)	0.61 (0.48, 0.79)	0.68 (0.51, 0.89)
Gender					
Female	Referent	Referent	Referent	Referent	Referent
Male	0.74 (0.65, 0.83)	0.44 (0.39, 0.50)	0.52 (0.47, 0.59)	0.69 (0.58, 0.83)	0.51 (0.42, 0.63)
Race/ethnicity					
White, non-Hispanic	Referent	Referent	Referent	Referent	Referent
African American, non-Hispanic	0.72 (0.58, 0.88)	0.88 (0.71, 1.10)	0.82 (0.67, 0.99)	0.75 (0.53, 1.06)	0.87 (0.64, 1.19)
Hispanic	0.55 (0.46, 0.67)	0.37 (0.31, 0.44)	0.38 (0.32, 0.45)	2.09 (1.66, 2.63)	0.28 (0.18, 0.44)
Other, non-Hispanic	0.92 (0.76, 1.11)	0.63 (0.53, 0.76)	0.66 (0.55, 0.79)	1.16 (0.88, 1.54)	0.66 (0.47, 0.92)

[a]A criterion of $P<.01$ was used to determine statistical significance.

[b]Site visits: 1 visit (registration visit) versus 2 or more visits.

[c]Time on site: 3 minutes or less versus more than 3 minutes.

[d]Page views: 11 pages or fewer versus 12 pages or more.

[e]Used Community: never versus any use.

[f]Use Separation Exercises: never versus any use.

Website Utilization Differences by Gender and Race/Ethnicity: Multivariate Analyses Stratified by Age

Interactions with age and gender were significant in models for all outcomes except Separation Exercises. Table 4 shows regressions stratified by each age group. Among both 18- to 24-year-olds and 25- to 34-year-olds, men were significantly less likely than women to spend more than 3 minutes on the site, view 12 or more pages, use the BecomeAnEX.org community, or use the Separation Exercises. Men aged 25 to 34 years were also less likely to have visited the site more than once. Among older adults, men were also significantly less likely than women to spend more than 3 minutes on the site, view 12 or more pages, or use Separation Exercises. Differences in website utilization between older men and women were not as large as those between younger men and women. There were no differences in visiting the site more than once or use of the BecomeAnEX.org community between older men and women.

Interactions with age and race/ethnicity indicated significant differences for visits, viewing pages, and use of the BecomeAnEX.org community. Stratified models in Table 4 indicate that there were no differences in visits by race among the 18- to 24-year-olds. Among the 25- to 34-year-olds and those 35 years and older, Hispanics were significantly less likely to have visited the site more than once compared with non-Hispanic whites, and among those 35 years and older only, African Americans were less likely to have visited the site more than once compared with non-Hispanic whites. For 18- to 24-year-olds, Hispanics and other non-Hispanics were significantly less likely to spend more than 3 minutes on the site compared with non-Hispanic whites, while among 25- to 34-year-olds and those 35 years and older, only Hispanics were less likely to spend more than 3 minutes or view 12 or more pages compared with non-Hispanic whites. While there were no differences in the use of the BecomeAnEx.org community by race/ethnicity for older adults, 18- to 24-year-old Hispanics were 2.4 times more likely to use the community and 25- to 34-year-old Hispanics were 3.5 times more likely to visit the

community compared with their non-Hispanic white counterparts. There were no differences by race/ethnicity in use of the Separation Exercises for 18- to 24-year-olds, but 25- to 34-year-olds and those 35 years and older were less likely to use the Separation Exercises compared with their non-Hispanic white counterparts.

Table 4. Odds ratios (95% confidence intervals) of multivariate regression models of website utilization by gender, race/ethnicity, and age.[a]

	Site visits[b]	Time on site[c]	Page views[d]	Used Community[e]	Used Separation Exercises[f]
Young adults: 18-24 years					
Gender					
Female	Referent	Referent	Referent	Referent	Referent
Male	0.75 (0.56, 1.01)	0.43 (0.33, 0.57)	0.48 (0.36, 0.63)	0.51 (0.31, 0.84)	0.43 (0.25, 0.76)
Race/ethnicity					
White, non-Hispanic	Referent	Referent	Referent	Referent	Referent
African American, non-Hispanic	0.76 (0.43, 1.35)	0.68 (0.41, 1.16)	0.61 (0.36, 1.02)	1.10 (0.42, 2.91)	0.44 (0.13 1.44)
Hispanic	0.97 (0.64, 1.46)	0.53 (0.36, 0.78)	0.64 (0.43, 0.94)	2.42 (1.34, 4.39)	0.56 (0.25, 1.27)
Other, non-Hispanic	1.00 (0.67, 1.48)	0.46 (0.32, 0.68)	0.54 (0.37, 0.79)	2.34 (1.32, 4.14)	0.48 (0.21, 1.08)
Young adults: 25-34 years					
Gender					
Female	Referent	Referent	Referent	Referent	Referent
Male	0.56 (0.45, 0.69)	0.30 (0.25, 0.37)	0.36 (0.30, 0.45)	0.45 (0.32, 0.63)	0.38 (0.26, 0.56)
Race/ethnicity					
White, non-Hispanic	Referent	Referent	Referent	Referent	Referent
African American, non-Hispanic	0.75 (0.50, 1.13)	0.88 (0.60, 1.31)	0.86 (0.59, 1.24)	0.70 (0.33, 1.48)	1.08 (0.61, 1.92)
Hispanic	0.55 (0.41, 0.74)	0.32 (0.25, 0.42)	0.36 (0.27, 0.48)	3.49 (2.43, 5.00)	0.21 (0.10, 0.47)
Other, non-Hispanic	0.92 (0.67, 1.25)	0.74 (0.55, 0.98)	0.75 (0.56, 1.00)	1.59 (1.00, 2.52)	0.77 (0.45, 1.31)
Older adults: 35+ years					
Gender					
Female	Referent	Referent	Referent	Referent	Referent
Male	0.88 (0.75, 1.03)	0.63 (0.53, 0.76)	0.70 (0.59, 0.82)	0.93 (0.74, 1.19)	0.63 (0.49, 0.83)
Race/ethnicity					
White, non-Hispanic	Referent	Referent	Referent	Referent	Referent
African American, non-Hispanic	0.69 (0.53, 0.89)	0.95 (0.70, 1.29)	0.85 (0.66, 1.10)	0.71 (0.47, 1.09)	0.87 (0.58, 1.29)
Hispanic	0.44 (0.32, 0.61)	0.39 (0.29, 0.53)	0.33 (0.24, 0.45)	1.28 (0.86, 1.91)	0.26 (0.12, 0.56)
Other, non-Hispanic	0.96 (0.71, 1.29)	0.72 (0.51, 1.00)	0.72 (0.53, 0.97)	0.64 (0.39, 1.08)	0.69 (0.42, 1.14)

[a]A criterion of $P<.01$ was used to determine statistical significance.

[b]Site visits: 1 visit (registration visit) versus 2 or more visits.

[c]Time on site: 3 minutes or less versus more than 3 minutes.

[d]Page views: 11 pages or fewer versus 12 pages or more.

[e]Used Community: never versus any use.

[f]Used Separation Exercises: never versus any use.

Discussion

Principal Findings

This study compared utilization of a smoking cessation website among 18- to 24-year-old, 25- to 34-year-old, and 35 years and older smokers and examined differences by gender and race/ethnicity across age groups. Overall, both 18- to 24-year-old and 25- to 34-year-old young adults had lower levels of website engagement than older adults and were less likely to use specific features within the site. Within age groups, utilization patterns varied by gender and race/ethnicity. Women were more active on the site than men, but these gender differences were much larger in magnitude among young adults compared with adults aged 35 years and older. Minorities generally had lower levels of site utilization than white smokers and this was especially true for Hispanic smokers of any age. The exception to this pattern was use of the BecomeAnEx.org community: among 18- to 24-year-old and 25- to 34-year-old young adults, Hispanics were 2.4 to 3.5 times more likely than whites to use the BecomeAnEX.org community, whereas among older adults there were no differences in community use by race/ethnicity. There were few significant differences in utilization between the 18- to 24-year-old and 25- to 34-year-old subgroups by gender or race/ethnicity.

Among the few studies that have looked at website utilization differences between young and older adults, findings have been mixed [17,56-59]. Results from this study are somewhat counter to the Richardson et al [17] study, which found few differences in utilization between young and older adults. Differences between the findings from this study and the earlier study [17] may be due to confounding factors such as motivation to quit that were not available for the current analysis. A study by Sadasivam et al [57] found that young adult smokers were underrepresented on the Decide2quit.org website based on their representation in the general population. Another study examining Quitline callers who were offered a choice between a Web-only adjunct or a phone/Web adjunct found that Web-only participants were more likely to be younger [56]. However younger participants of either the Web-only or phone/Web option were less likely to return after the first visit [56]. Young adults have been described as hard to reach and engage with cessation treatment resources [10], and this may be true for online treatments as well.

Findings from a study by Klatt et al [60] as well as other research suggest that distinctive approaches may be needed to engage young adults, including education on how a Web-based program and other treatment modalities can improve cessation outcomes [44,58]. In addition, tailoring strategies may be needed to maintain young adult interest in website interventions. The website and associated promotional materials for this study were designed for a target audience of 25- to 49-year-olds; some of the messaging and imagery on the site may need to be adapted to resonate with a younger adult audience, particularly for the 18- to 24-year-olds. Young adults in this age range are in a period of life characterized by considerable change and instability—a phase of development in which individuals are exploring identities and seeking out a wide range of experiences prior to settling down [5]. Providing website interventions in a way that emphasizes exploration and highlights how cessation can enhance and broaden life experiences may help further engage young adult audiences versus focusing solely on the idea of quitting smoking. The research by An et al [27] which utilized an avatar host and conceptualized quitting smoking as a personal makeover suggests that such an approach may be both engaging and effective among younger adults. Despite lower utilization, it is noteworthy that over half of visitors during the 6-month period of this study were young adults—an encouraging signal that this is a viable channel to connect with this population.

Given the low utilization among young adult men, effective strategies to engage this population are critical. Health seeking is higher among women, which means that a smaller proportion of registered users are likely to be men in the first place [61]. Indeed, participants of Web-based cessation trials are more likely to be female [14]. Graham et al [62] found that banner ads targeted to men were effective in driving users to websites. However, studies have not generally focused on differences in engagement or efficacy of Web interventions by gender. Among men who seek out support online, an open question is how best to design Web-based cessation interventions that can sustain an initial level of engagement. Further, targeting online advertising to young male smokers to encourage engagement and reengagement with online cessation sites may be effective.

While young adults were less likely to use the BecomeAnEX.org community than older adults in adjusted analyses, the proportion of young adults utilizing the community was similar to that of older adults, primarily due to use by young adult Hispanics. The unusually high utilization of the BecomeAnEX.org community among Hispanic young adults may indicate an affinity for online group support for cessation among a population likely to be acculturated, native English speakers who are comfortable with online social networking. One key research question suggested by these findings is whether young adults prefer to interact with other people their same age or whether a community of current and former smokers of any age is appealing. Klatt et al [60] found that young adults who engaged with peers for online support were more likely to be abstinent at 30 days, which suggests that peer interaction may need to be an element of online cessation for young adults. Given the ubiquity of Web 2.0 tools, the daily use of social media among young adults [63], and the importance of peers and friendship networks for youth [64,65], an approach that incorporates social support and addresses social norms around smoking may resonate with this age group [23,40,45].

With the exception of use of the BecomeAnEX.org community, both young and older Hispanics were less likely than non-Hispanic whites to utilize the website. A previous evaluation of the website also found that Hispanics were less likely to visit the site compared with whites [17]. It is not clear why Hispanics were less likely to engage, because the site was designed for specific smoker populations including lower income groups and minorities, and a Spanish language version was available [66]. The high utilization of the BecomeAnEX.org community among both younger and older Hispanic adults suggests that incorporating additional options for sharing and social

networking may be one strategy for maintaining engagement among the Hispanic population. Understanding how best to increase cessation website engagement for Hispanic smokers is key to ensuring effective treatment for a group that has the lowest rate of treatment utilization of all racial/ethnic groups [31].

Both the BecomeAnEX.org community and the Separation Exercises were significantly associated with quit outcomes in unweighted analyses in a previous evaluation study of the website [17]. The current study found that use of these tools was generally low across both young and older adults. Strategies to further highlight the most effective tools, including online communities, on cessation websites may be useful in increasing engagement overall and among low utilization subgroups. Use of active online community engagement during a quit attempt can help to increase cessation by providing social support [23] and steering new users to additional website features that are effective in helping smokers quit [23,47]. Given the rising use of and comfort with social networking activity in recent years among all demographic groups [32], seeking social support from online acquaintances who are going through similar experiences may become more popular for smokers attempting to quit.

Limitations

Our ability to interpret these findings is constrained by the limited information we have about participants. Use of any tobacco cessation intervention is a function of a wide range of personal (eg, time, access) and psychosocial (eg, partner support for quitting, depression, self-efficacy for cessation) factors. Previous research in Internet smoking cessation interventions has found that changes in smoking temptations, quitting confidence, and positive and negative partner support mediated the relationship between treatment and abstinence and were strongly associated with increased website utilization [16]. Similarly, other research has found prior use of treatments and a belief that certain treatments are efficacious to be predictive of utilization [44]. Given that we did not have access to this kind of information about participants, it is not clear whether the observed age-related findings are truly a function of age or whether they reflect differences between younger and older adults on any of these unmeasured variables.

Further, utilization metrics presented here do not necessarily capture the full experience of a respondent on the site. For example, accessing the BecomeAnEX.org community does not capture differences in whether respondents simply viewed a page of the community or whether they posted or responded to a thread. Metrics such as time on site, pages viewed, or number of visits do not capture other aspects of engagement, such as how people are responding to the materials. Finally, site utilization may be shaped by website design factors including layout, website organization, and language, thus generalizability to websites with substantial design differences may be limited. While we acknowledge that these analyses are limited in their scope, this study is the first to our knowledge to document differential utilization patterns among age, gender, and race/ethnicity subgroups in an Internet cessation intervention. These findings point to important areas of inquiry to address in future research and development efforts.

This observational study was not designed to examine the links between website utilization and cessation outcomes. One meta-analysis of smoking cessation studies found that young adults were as likely to quit as older adults in studies with positive treatment outcomes [34]. However, given the nature of this observational study and the lack of cessation outcomes, we cannot conclude that lower levels of website utilization among young adults resulted in lower abstinence rates. It is possible that younger adults obtained the information and/or support they needed during their time on the site and this was sufficient in promoting some duration of abstinence.

Conclusions

Further reductions in adult smoking rates require addressing tobacco use and cessation among young adults, a population that is increasingly vulnerable to long-term smoking addiction. Given young adults' extensive use of online digital and social media, Web-based interventions are a promising intervention if younger smokers are adequately targeted and engaged. This study found overall lower levels of engagement among young adult subgroups ranging in age from 18 to 34 years compared with older adults, and patterns of use varied among age groups by race/ethnicity and gender. While findings are constrained by limited data, results suggest important areas of inquiry to address in future research and development efforts. Research focused on enhancing demand among younger smokers and men and providing effective features likely to be used once they reach a cessation site is key to helping users engage and stay motivated during a quit attempt. Incorporating features that capitalize on key aspects of young adult development, such as exploration of new experiences and the influence of peers, may also be effective in keeping young adults engaged. Identifying relevant and effective tools, including social networking apps and online community forums, to engage specific young adult subpopulations is critical to maximize the impact of Internet interventions, and this may be especially important for both young and older adult minority groups. Finally, strategies to increase utilization of effective site features among young adult users can help optimize cessation websites for an increasingly diverse user population.

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Authors' Contributions

JC conceptualized the study, conducted the analysis, and wrote the paper. AG contributed to the conceptualization and writing. VI, DV, AR, AS, SC, and RM contributed to writing and revisions. HX contributed to the analysis.

Conflicts of Interest

JC, ALG, and DMV are employees of Truth Initiative (formerly American Legacy Foundation) which runs BecomeAnEX.org, the smoking cessation website used in these analyses.

Multimedia Appendix 1

Participant characteristics for ages 18-24 years, 25-34 years, and 35 years and older.

[PDF File (Adobe PDF File), 46KB - resprot_v5i3e142_app1.pdf]

Multimedia Appendix 2

Bivariate analyses of website utilization metrics for ages 18-24 years, 25-34 years, and 35 years and older.

[PDF File (Adobe PDF File), 42KB - resprot_v5i3e142_app2.pdf]

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Abbreviations

AOR: adjusted odds ratio
IQR: interquartile range
OR: odds ratio
PHS: Public Health Service
SE: standard error

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Original Paper

Targeted Facebook Advertising is a Novel and Effective Method of Recruiting Participants into a Human Papillomavirus Vaccine Effectiveness Study

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Abstract

Background: Targeted advertising using social networking sites (SNS) as a recruitment strategy in health research is in its infancy.

Objective: The aim of this study was to determine the feasibility of targeted Facebook advertisements to increase recruitment of unvaccinated women into a human papillomavirus (HPV) vaccine effectiveness study.

Methods: Between September 2011 and November 2013, females aged 18 to 25 years, residing in Victoria, Australia, were recruited through Facebook advertisements relating to general women's health. From November 2013 to June 2015, targeted advertising campaigns were implemented to specifically recruit women who had not received the HPV vaccine. Consenting participants were invited to complete an online questionnaire and those who had ever had sexual intercourse were asked to provide a self-collected vaginal swab. The HPV vaccination status of participants was confirmed from the National HPV Vaccination Program Register (NHVPR).

Results: The campaign comprised 10 advertisements shown between September 2011 and June 2015 which generated 55,381,637 impressions, yielding 23,714 clicks, at an overall cost of AUD $22,078.85. A total of 919 participants were recruited. A greater proportion of unvaccinated women (50.4%, 131/260) were recruited into the study following targeted advertising, compared with those recruited (19.3%, 127/659) prior to showing the modified advertisement (P<.001). A greater proportion of the total sample completed tertiary education and resided in inner regional Victoria, compared with National population census data (P<.001), but was otherwise representative of the general population.

Conclusions: Targeted Facebook advertising is a rapid and cost-effective way of recruiting young unvaccinated women into a HPV vaccine effectiveness study.

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KEYWORDS

online recruitment; social media; Facebook; human papillomavirus; HPV

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted viral infection worldwide. Approximately 80% of sexually active individuals will acquire an HPV infection during their lifetime; most within a few years following sexual debut [1]. Persistent infection with high-risk or oncogenic HPV genotypes, particularly HPV 16 or 18 is a prerequisite to cervical cancer [2].

In 2007, Australia was the first country to implement a national government-funded HPV vaccination program using the quadrivalent HPV (6, 11, 16, and 18) vaccine Gardasil (4vHPV) [3-6]. The vaccine is available free-of-charge to 12 to 13 year old girls as an ongoing program and had a catch-up component for up to 26 year olds to December 2009, with vaccinations administered through schools, general practices and other community health services. Since the initiation of the program, the National HPV Vaccination Program Register (NHVPR) has documented high vaccine uptake, with coverage rates of approximately 85% of females aged 15 having received at least 1 dose, and 77% having completed the 3 dose course in 2015 [7].

Although Internet social networking sites (SNS) have been in use for over a decade, the concept of targeted advertising as a recruitment strategy in health research is still in its infancy. Approximately 93% of Australians use Facebook, including 97% of 18 to 29 year olds [8]. Of those aged 18 to 29, 79% of females use Facebook at least daily [8]. The increasing pervasiveness and utility of social media as powerful communication channels means that SNS, such as Facebook, can potentially be used to effectively engage young people in health studies. There is evidence to show that Internet-based research can yield high response rates at a considerably lesser cost than that accrued by traditional recruitment methods [9-12]. In addition, findings from pilot studies demonstrate that Facebook advertising is a feasible recruitment strategy for health studies and yields a broadly representative sample of a target population [10,13-19]. In one particular study, investigators looked at geographic variation in HPV vaccine uptake in men and women using targeted Facebook advertisements to recruit residents in Minnesota [18]. However, this has only just been utilized as a methodology in Australia in the Vaccine Against Cervical Cancer Impact and Effectiveness (VACCINE) study [20].

The VACCINE study is a cross-sectional survey in which Facebook was used to recruit participants [21]. The objective of this study was to investigate the changes in prevalence of vaccine-targeted HPV genotypes in a cohort of 4vHPV vaccine-eligible young women aged 18 to 25 years living in Victoria, Australia. Within the recruitment strategy we also modified the initial Facebook advertising campaign to specifically target and over-recruit unvaccinated women, to better understand why a free vaccine was not being embraced. We hypothesized that targeted advertising through Facebook enables faster and more efficient recruitment of vaccine-eligible women who have not yet received the HPV vaccine compared with non-targeted advertising.

Methods

The methods for this study have been published previously [21]. The study protocol was approved by the Human Research and Ethics Committee at the Royal Women's Hospital, Melbourne, Australia.

Participant Recruitment and Inclusion Criteria

Participants were recruited through advertisements published on Facebook. From September 2011 to November 2013, advertisements were set to randomly appear to Facebook users who were (1) female; (2) between the ages of 18 and 25 years; and (3) residing in Victoria, Australia.

The advertisements contained a brief headline (eg, "Women's Health Matters"), a generic picture of young women and a brief caption (Figure 1). The advertisements were subsequently modified by changing the text to target women who had not received the 4vHPV vaccine, and made visible to Facebook users from November 22, 2013 to June 2015 (Figure 2). The decision to modify these advertisements arose mid-way through the study as we wished to understand the determinants of women eligible for, but not accepting, the HPV vaccine.

Respondents could click through to the secure VACCINE Study website to read more about the study and register an expression of interest (EOI). Potential participants were contacted and screened by telephone to assess their eligibility and willingness to comply with the study requirements.

Figure 1. Example of an original advertisement from the VACCINE Study's Facebook advertising campaign.

Figure 2. Example of a modified advertisement from the VACCINE Study's Facebook advertising campaign.

Measures

Participants who verbally consented to the study were invited to provide electronic consent and to complete a self-administered, password-protected questionnaire hosted by the online survey tool SurveyMonkey. The survey questions related to demographic characteristics, sexual history and knowledge, attitudes and practices regarding HPV, the HPV vaccine, and cervical cancer screening. Participants were also requested to provide their HPV vaccination status and written or electronic consent for their HPV vaccination history to be verified with the NHVPR.

Statistical Analyses

Descriptive statistical analyses were conducted using Stata 13.1 (StatCorp LP, College Station, TX, USA). The demographics of our cohort were compared with general population data sourced from the Australian Bureau of Statistics 2011 census data [22]. Socioeconomic status was assigned using the Postal Area of Relative Socio-Economic Disadvantage 2011 [22]. The Chi-square test was used for all demographic comparisons between our sample of study and the general population, as well as within study comparisons between females recruited by general advertisements and those recruited by targeted advertisements. A 2-sided *P* value <.05 was considered statistically significant. Data were treated as missing if a question was skipped or "prefer not to answer" was selected.

Participants who received all 3 doses of the HPV vaccine were considered "vaccinated"; those who had received 1 or 2 doses were considered "under-vaccinated" and women who never received the HPV vaccine were recorded as "unvaccinated".

Results

For the duration of the entire campaign (September 2011 to June 2015), 10 advertisements resulted in 55,381,637 impressions, reaching 984,159 people, and yielding 23,714 clicks, at an overall cost of AUD $22,078.85. This translated to an average cost of AUD $24.02 per participant. The general advertisements which were implemented from September 2011 to November 2013, made 35,906,205 impressions, yielding 15,304 clicks, with an overall cost of AUD $15,381,92. The average cost per click was AUD $1.01 with a click-through rate of 0.04% per impression. From November 2013 to June 2015, 19,475,432 impressions were made, yielding 8410 clicks, with an overall cost of AUD $6696.93. The average cost per click was AUD $0.80 .

A total of 919 participants completed the online questionnaire. Among women who were recruited and completed the questionnaire following modification of the advertisements, 50.1% (131/260) were unvaccinated. In contrast, only 19.3% (127/659) of the participants who completed the questionnaire prior to modification of the advertisements had never been vaccinated (*P*<.001) (Figure 3). There were no significant differences in socio-demographics of the unvaccinated group recruited prior to targeted advertisements with those recruited post targeting (data not shown).

No significant differences were detected between the general population participating in the VACCINE study to those that were then targeted for not being vaccinated against HPV, except that for the latter group a greater proportion were born outside of Australia (19.1% vs 12.4%, *P*<.001) (Table 1).

Table 1. Demographic characteristics of participants recruited by non-targeted advertisements compared with those recruited by targeted advertisements in the VACCINE study (N=919).

Characteristic	Non targeted advertisement (n=659), n[a] (%)	Targeted advertisement (n=260), n[a] (%)	*P* value[b]
Age (years), median (Q1-Q3[c])	22 (20-23)	22 (20-24)	.08
Geographic region			
Major city	510 (77.3)	212 (81.5)	.5
Inner regional	127 (19.3)	40 (15.4)	
Outer regional/remote	21 (3.3)	8 (3.1)	
Country of birth			
Australia	574 (87.6)	208 (80.9)	<.001
Other	81 (12.4)	52 (19.1)	
Indigenous status			
Aboriginal or Torres Strait Islander	5 (0.8)	3 (1.2)	.6
Other	654 (99.2)	257 (98.8)	
Socioeconomic level (SEIFA decile)[d]			
1-5	214 (32.6)	75 (29.2)	.3
6-10	443 (67.4)	182 (70.8)	
Highest level of education completed[e]			
< Year 12	29 (4.4)	14 (5.4)	.7
Year 12	257 (39.0)	98 (37.7)	
> Year 12	365 (55.4)	145 (55.8)	
Relationship status			
Single	237 (36.0)	91 (35.0)	.7
Casual relationship	60 (9.1)	30 (11.5)	
Committed relationship	350 (53.1)	136 (52.3)	

[a]Numbers may not add up to the total due to missing data.

[b]Chi-square test was used for all demographic comparisons.

[c]Q1: 25th percentile; Q3: 75th percentile.

[d]Based on postal area code. Deciles are rankings within Victoria, Australia. The lowest 10% of areas are assigned a decile number of 1 and the highest 10% of areas are given a decile number of 10. Decile 1 is the most disadvantaged relative to the other deciles.

[e]Year 12 is the final year of high school in the Australian education system.

The age distribution of participants reflected the general population, with the median age being 22 years (Q1 25th percentile to Q3 75th percentile: 20-23) (Table 2). Compared with the 2011 census data, more women who enrolled in this study were born in Australia (86 % vs 76%, *P*<.001) and had completed tertiary education (57% vs 43%, *P*<.001). Women living in inner regional areas were over-represented (18% vs 16% of the total, *P*<.001) (Table 2).

Table 2. Demographic characteristics of participants in the VACCINE study compared with the general population in Victoria, Australia (N=919).

Demographic	Total study population[a], n (%)	Target population[b], %	*P* value[c]
Age group, years			
18-21	306 (33.3)	48.6	<0.001
22-25	613 (66.7)	51.4	
Geographic region			
Major city	722 (78.6)	80.7	0.1
Inner regional	167 (18.2)	16.3	0.001
Outer regional/remote	30 (3.3)	3.1	0.6
Country of birth			
Australia	782 (85.8)	75.5	<0.001
Other	130 (14.2)	24.5	
Indigenous status			
Aboriginal or Torres Strait Islander	8 (0.9)	0.9	1.000
Other	905 (99.1)	99.1	
Education level[d]			
Completed year 12 or below	398 (43.4)	57.4	<0.001
Completed tertiary education	519 (56.6)	42.6	

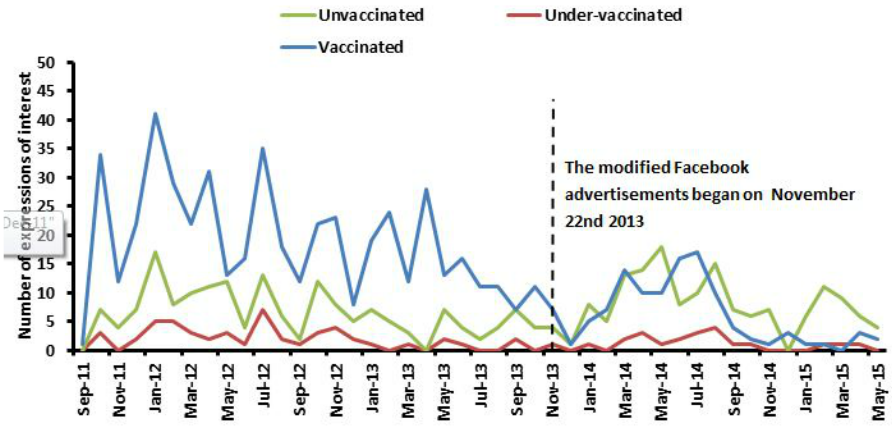
[a]Numbers may not add up to 919 due to missing data.

[b]Population data were sourced from the 2011 Australian Bureau of Statistics Census, with figures corrected for non-responses to add up to 100%.

[c]The Chi-square test was used for all demographic comparisons.

[d]Year 12 is the final year of high school in the Australian education system.

Figure 3. Participant recruitment rate based on date of expression of interest (EOI) (N=919).



Discussion

Principal Findings

Targeted Facebook advertising led to increased recruitment of young women who had not received the HPV vaccine, without employing other recruitment methods. The rationale behind over-recruiting unvaccinated women was to allow us to reliably measure any difference in the prevalence of high-risk HPV between unvaccinated and vaccinated women. We also show that recruiting through Facebook is cost-effective given that the cost per participant in this study was AUD $24.02.

Evidence from previous studies has shown that targeted Facebook advertising is effective in recruiting participants into health research [10,23,24]. In these studies, recruitment was targeted based on broad demographic characteristics such as gender, age, and location, to maximize generalizability [10,23,24]. However, there have been few studies in which Facebook advertising has been used to recruit participants with more specific characteristics [25,26]. For example, young adults who were cigarette users were sought in a study of tobacco and substance use [9,27].To attract their target audience, investigators developed Facebook advertisements which were shown to users whose profile pages contained tobacco- or

marijuana-related keywords drawn from their listed interests, activities, job titles as well as the Facebook pages they "liked" or groups to which they belonged [9]. Our study differed slightly from this approach. Instead of using keywords to define the people to whom our advertisements were displayed, we relied primarily on Facebook users to read and respond to the text in our customised advertisements.

Our study sample compared well with the general population in age. The significantly greater proportion of women born outside of Australia recruited via targeted advertisements compared with those recruited through general advertisements is intuitive as overseas students are not eligible for the HPV vaccine. Although young women who were born in Australia and/or had completed tertiary education were over-represented in the total sample; these biases are common in population-based studies [10,24,28]. This is perhaps because highly-educated people are more likely to be aware of health issues. Therefore, highly-educated people may choose to participate in health research to address their personal health concerns and/or because of altruistic motives such as the desire to contribute to medical knowledge and improving the health of others [29]. The difference in the distribution of women living in inner regional areas in our study sample was statistically significant but small compared with the general population (2%, $P<.001$); a larger sample size is required to determine whether this is meaningful.

There is an inherent risk of introducing sampling bias when targeting Facebook advertising for specific characteristics. We found that our sample was reasonably representative of the general population, except for country of birth and education level. Another potential cause of bias associated with this recruitment method is snowball or chain-referral sampling, whereby users exposed to these advertisements share information about the study on their Facebook profile page with their friends, or relatives, who may then submit an EOI. We found that 78% heard about the study from the Facebook advertisements, whereas approximately 17% either read a post on their friend's Facebook wall or were told by a friend to participate. These 17% referrals were constant pre and post changes to the advertisements. Given the small proportion who submitted an EOI without having seen the Facebook advertisements, we contend that this did not have a significant impact on our results.

Conclusion

We have demonstrated the utility of paid, targeted Facebook advertising as a contemporary and effective recruitment method. The ability to specifically target individuals with particular characteristics by tailoring Facebook advertisements enables researchers to recruit specific groups of individuals of interest into health studies.

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Conflicts of Interest

None declared.

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Abbreviations

4vHPV: Quadrivalent human papillomavirus vaccine
EOI: expression of interest
HPV: human papillomavirus
NHVPR: National human papillomavirus vaccination program register
SNS: social networking sites
VACCINE: Vaccine against cervical cancer impact and effectiveness

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Original Paper

Cloud Based Surveys to Assess Patient Perceptions of Health Care: 1000 Respondents in 3 days for US $300

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Abstract

Background: There are many challenges in conducting surveys of study participants, including cost, time, and ability to obtain quality and reproducible work. Cloudsourcing (an arrangement where a cloud provider is paid to carry out services that could be provided in-house) has the potential to provide vastly larger, less expensive, and more generalizable survey pools.

Objective: The objective of this study is to evaluate, using Amazon's Mechanical Turk (MTurk), a cloud-based workforce to assess patients' perspectives of health care.

Methods: A national online survey posted to Amazon's MTurk consisted of 33 multiple choice and open-ended questions. Continuous attributes were compared using *t* tests.

Results: We obtained 1084 responses for a total cost of US $298.10 in less than 3 days with 300 responses in under 6 hours. Of those, 44.74% (485/1084) were male and 54.80% (594/1084) female, representing 49 out of 50 states and aged 18 to 69 years.

Conclusions: Amazon's MTurk is a potentially useful survey method for attaining information regarding public opinions and/or knowledge with the distinct advantage of cost, speed, and a wide and relatively good representation of the general population, in a confidential setting for respondents.

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KEYWORDS

Mechanical Turk; MTurk; crowdsourcing; medical survey; cloud-based survey; health care perceptions

Introduction

Surveys are important research tools that allow researchers to obtain both quantitative and qualitative information from respondents that can assist health care providers and policy makers to improve education, direct research, and enhance patient care. However, obtaining generalizable and representative information in a timely and cost-efficient manner is a constant challenge in population-based surveys. Surveys have traditionally been administered in person, by phone or mail. Although this variety affords researchers greater freedom to collect data, administrative, economic and research design complications may arise, with inherent biases introduced. In-person surveys, for example, often require extensive training for interviewers; respondents may feel less comfortable

answering in-person survey questions honestly, and it is challenging to survey a population over a large geographical region [1]. Phone surveys or "cold calling" can be time consuming, limited by language barriers, and biased toward respondents who have access to landlines and are willing to participate [2]. Mail surveys, meanwhile, require extensive amounts of time and money and often have a poor response rate, which can introduce bias and affect the validity of the study [3]. One study estimated the cost per completed validated mail survey at US $17 dollars [4]. Multiple recent studies have shown that with postal surveys it can take a minimum of 8 to 12 weeks to obtain the majority of responses with multiple reminders, with some surveys taking even longer [5-7]. A Cochrane review by Edwards et al [8] investigated strategies to improve response rates to questionnaires delivered via either postal mail or electronic mail and found that although certain strategies may improve response rates, the odds of responses reduced when the study included questions of a sensitive nature.

Over the last ten years, online surveys have become more frequently used [9]. Online surveys offer significant time and cost-effectiveness in their ability to reach a large, diverse audience worldwide, while eliminating the need to send study personnel to conduct interviews, make calls or print and manually distribute survey instruments. Further, the ability to fill out a survey online creates a greater sense of anonymity among participants, thus alleviating anxiety related to answering questions honestly [10,11]. Although online surveys represent a clear improvement in efficiency, they can be costly, typically US $1-3 per respondent [12].

Online crowdsourcing services such as Amazon's Mechanical Turk (MTurk) are Internet-based marketplaces that connect businesses (termed "requesters") with individuals interested in performing Internet tasks. Requesters post tasks and workers may then choose to complete any number of available tasks for the listed monetary compensation. Amazon's MTurk, for example, accesses more than 500,000 workers from over 190 countries [13]. Concerns have been raised regarding the use of MTurk in human participant research. A study by Kuang et al [14] compared patient understanding and recognition of pictographs using MTurk versus traditional survey methods. They found that although MTurk may be complimentary to traditional surveys, the respondent population differed, with white, higher educated respondents over-represented in the MTurk sample as compared to respondents tested with in-person surveys. However, subsequent studies suggested that MTurk participants are more demographically diverse than the standard Internet population, and the data obtained are at least as reliable as those obtained via traditional methods [15]. In addition, concerns have been raised regarding the quality of work produced by MTurk participants, namely that the low median wage of MTurk workers may affect worker motivation, and ultimately, may affect the quality of work produced [16]. However, MTurk has been validated as a tool for conducting behavioral research several times over, including determining the effect of medical guidelines on behavior [17-20].

Our previous work looked at public perceptions of miscarriage and found that there are widespread misperceptions regarding the frequency and causes of miscarriage [21]. It found that patients who have had miscarriages frequently feel guilty, ashamed, and alone and suggested that revelations from friends and celebrities regarding their own losses can help assuage those feelings.

Few studies have assessed patient experiences and satisfaction with their reproductive health care. Prior surveys were in-person interviews or questionnaires, which introduced the possibility of responder biases. Such surveys, particularly when questioning respondents about highly sensitive health information, introduce responder and non-responder bias, respectively [22,23]. While some studies utilized MTurk to recruit patients to another survey site, none have used MTurk as their survey engine. To our knowledge, our previous study [21] represented the first use of a crowdsourcing service to obtain information regarding respondent attitudes, perceptions, and understanding of health issues. Here, we report on sampling and data acquisition using the crowdsourced online survey.

Methods

Setup and User Interface

We used a cloud-based, medical knowledge voluntary closed survey regarding public perceptions of miscarriage via Amazon's Web service MTurk (Multimedia Appendix 1). MTurk is an online labor market in which "requesters" have access to recruit a large number of "workers" to complete tasks. Typical tasks include transcribing audio, categorizing data, algorithm training, classifying images, reviewing databases for key information, performing online searches, tagging photos with preset words, and other tasks that are difficult to automate [24].

MTurk has templates for basic surveys that can be customized by the requester via their basic user interface (UI). The UI functions as a low-end word processing software and automatically creates a Hyper Text Markup Language (HTML) based code. The survey was tested in MTurk sandbox, which mimics a live release and allows the writers to see results in real-time without cost. Requesters can take their own survey and see the results using the same interface and server as the live version. After testing in sandbox, we ran a 100 respondent test-run that took 3 hours to complete. This allowed us to tweak any questions that were either unclear or gave ambiguous results.

Workers log in and browse Human Intelligence Tasks (HITs) by title, reward, requester or keyword to find a topic of interest. For our survey, we listed the keywords "answers, survey, experiment, medicine, questionnaire, miscarriage, simple, quick, fun, money, and pregnancy". When a worker clicks on a requester's work, the user sees a description of the work prior to accepting the HIT. In the description, we informed workers that they would not be paid for repeating the survey. There is no way to determine the percentage of workers who viewed but did not accept our HIT, but we were able to record how many people accepted our HIT but did not submit.

The system allows requesters to set qualifications for "MTurkers". Since this was a study regarding the US population, we limited respondents to only those based in the United States. Another qualification we used is the MTurker "HIT approval

rate". The approval rating qualification allows us to select workers who have proven to perform quality work on other tasks. We set the approval rating at 85%, which means that 85% or more of their previous work on various HITs was approved. This is important as it allows us to select higher "quality" workers. We required that workers had finished at least 50 other HITs to increase the likelihood of quality data collection.

HITs are listed in the order they are posted; at any given time there can be thousands of HITs available. We released the surveys in batches of 50. When a worker completes his or her task, the results are automatically sent to the requester for approval and payment. As part of the data received, there is a unique worker ID and an approval rating. The workers' approval ratings show the percentage of work approved by the requester in the last 7 days, 30 days, and lifetime of the worker. That percentage allows one to filter out anyone who has taken the survey previously and reject his or her work. This method allowed us to control for workers repeating the survey, which would skew the data.

Data Filter and Cost

We used an attention check question (ACQ) of "Have you had a fatal heart attack while watching TV" as well as a time filter. If the respondent answered yes or maybe to the ACQ or if it took a respondent less than 60 seconds to finish the 23-item survey, they were excluded from the study. Once we finished screening respondents based on the ACQ and time filters, we were able to approve or reject the results. Upon acceptance, respondents were immediately paid US $0.25 for their work. Rejected work was immediately reposted to allow for proper completion. After the survey was completed, the data was downloaded into a Microsoft Excel file for analysis. The study was approved by the Albert Einstein College of medicine institution review board (IRB).

Respondents were aware they were taking a survey regarding pregnancy, however, were unaware of any relationship with an investigator or university. The data was collected over 3 days in January of 2013. The items were not randomized and adaptive questioning was used based on respondents answer to whether they had a miscarriage. If they answered yes to miscarriage, further questions regarding their feelings after a miscarriage were added. The 23-item survey (with additional 10 added if they answered yes to the question regarding miscarriage) appeared on a single HTML page. A completeness check was not required prior to submitting and respondents were able to review their answers prior to submission. We were unable to provide a view rate, as we are unable to determine the number of people who viewed our survey but did not choose to accept. All accepted surveys were completed with a 99% item completeness rate.

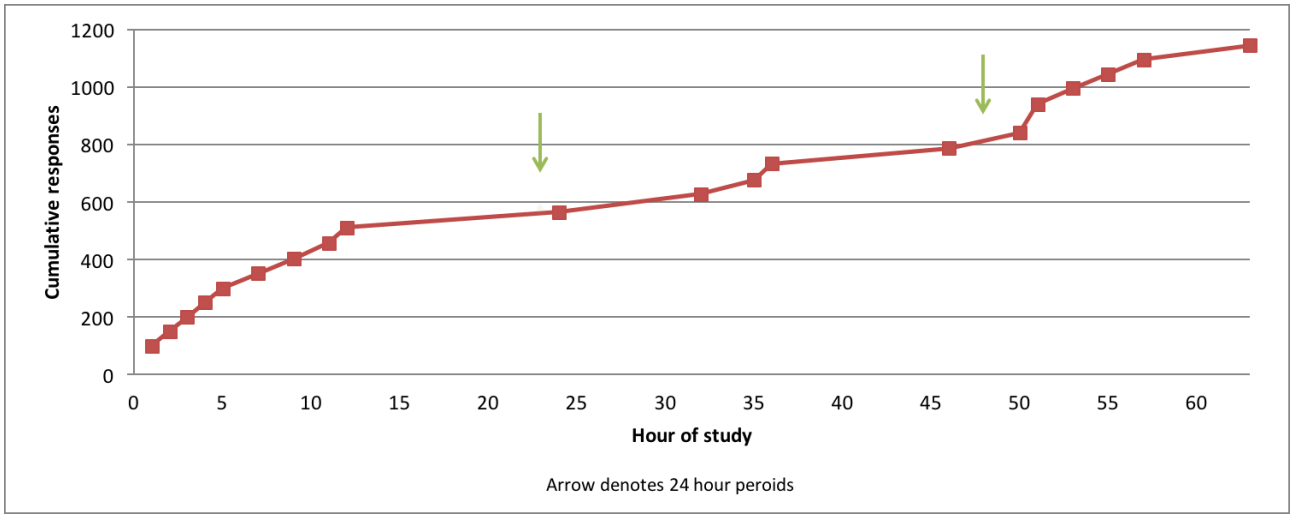
All survey data were preserved in the original format for analysis and continuous attributes were compared using *t* tests. All significance values were calculated for 2-sided 95% CIs or *P* values less than .05. Microsoft Excel (2016, Redmond, California) was used for analysis.

Results

Recruitment Time

A total of 1147 responses were collected in 2 days 14 hours and 42 minutes. On average, this translated to one survey collected every 3.3 minutes. It took 93 minutes to obtain the first 100 responses and 316 minutes to obtain the first 300 responses. The next 845 responses took 57 hours and 26 minutes to collect (Figure 1).

Figure 1. Cumulative responses over time.



Data Filter

Of the respondents, 57 repeated the survey, 6 participants answered yes to the ACQ, and no one completed the survey in less than 60 seconds. This left us with a total of 1084 usable responses (usable response rate of 94%).

Number per Batch

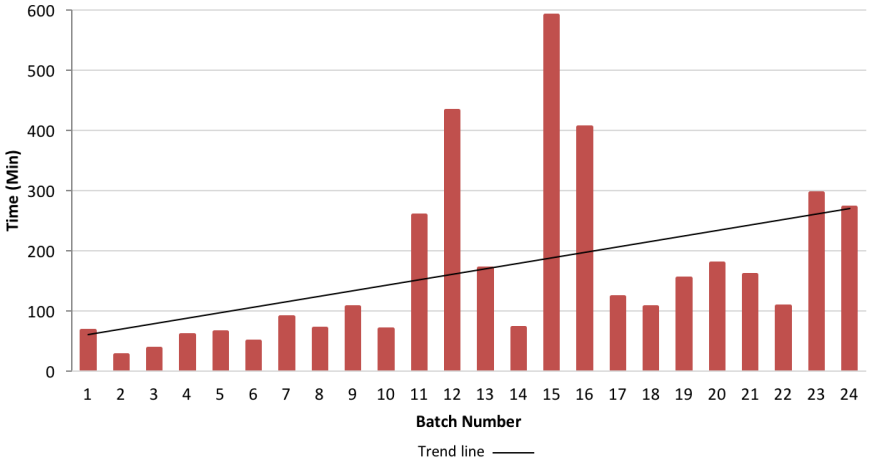
We found that if we posted batches larger than 50, the batch would take longer to finish and we would cancel the remaining surveys in that particular batch. There were no significant differences in the time to batch completion between posting a batch of 25 (156 min) versus 50 surveys (209 min) (*P*=0.5).

Batches posted between 11:00 pm and 8:30 am (Eastern Standard Time, EST) took the longest to complete. With each subsequent batch posted, the average time to completion increased. The shortest time to finish a batch was 26 minutes, and the longest was 591 minutes (Figure 2).

The mean age of the respondents was 31, with the majority of the sample between 18 to 34 years (Table 1). Of the total number participants, 44.74% (485/1084) were male and 54.80% (594/1084) female. In addition, 53.60% (580/1082) were never married, with 37.80% (409/1082) currently married. Most of our respondents were white (82.87%, 895/1080) with 6.29% (68/1080) Hispanic and 5.55% (60/1080) black. Over half the respondents (51.40%, 548/1066) reported a religious affiliation. The majority of religious people identified themselves as Christian (44.93%, 479/1066). The majority of our respondents either attended some college (39.11%, 422/1079) or graduated college (36.79%, 397/1079). As well, 10.19% (110/1079) of the respondents reported graduating high school as their highest degree earned.

The respondents represented a diverse socioeconomic status with 17.14% (17/1079) earning less than US $19,000 a year. The majority of the respondents earned less than US $60,000 (70.06%, 756/1079) with 9.73% (105/1079) earning over US $100,000 a year. We collected responses from 49 of the 50 states. California (9.45%, 102/1079), New York (6.85%, 74/1079), Florida (5.37%, 58/1079), and Pennsylvania (5.28%, 57/1079) were the four largest contributors. Arkansas, Montana and North Dakota had the fewest respondents with each contributing 1 (0.09%, 1/1079).

Figure 2. Minutes to batch completion over course of survey.



Cost

We reimbursed survey respondents US $0.25. We paid a total of US $271.00 to 1084 respondents for completing the survey. The average effective hourly rate for the respondents came out to US $3.97. Since Amazon charges a 10% fee of what is paid to the workers, our total cost for running the survey was US $298.10 or US $0.275 per respondent.

Table 1. Participant demographic characteristics (N=1084).

Characteristic		Overall sample[a], n (%)
Age, years	18-24	342 (31.69)
	25-34	438 (40.59)
	35-44	182 (16.86)
	45-54	70 (6.48)
	over 55	47 (4.35)
Gender		
	Male	485 (44.74)
	Female	594 (54.80)
Marital status	Married	409 (37.80)
	Never married	580 (53.60)
	Divorced	68 (6.28)
	Separated or widowed	25 (2.31)
Race/ethnicity	White	895 (82.87)
	Black	60 (5.55)
	Hispanic[b]	68 (6.29)
	Asian	77 (7.12)
	Other	48 (4.44)
Religion	Christian	479(44.93)
	Judaism	22 (2.06)
	Islam	11 (1.03)
	Buddhism	28 (2.63)
	Other	8 (0.08)
	Any religious affiliation	548 (51.40)
	Unaffiliated (atheist/agnostic)	518 (48.59)
Education	Attended some high school	12 (1.11)
	Graduated high school	110 (10.19)
	Attended Some college	422 (39.11)
	Graduated college	397 (36.79)
	Attended graduate school	128 (11.86)
	Attended medical school	10 (0.09)
Annual income, US dollars	<$19,999	185 (17.14)
	$20,000-39,999	312 (28.91)
	$40,000-59,999	259 (24.00)
	$60,000-79,999	132 (12.23)
	$80,000-99,999	86 (7.97)
	$100,000-249,999	94 (8.71)
	>$250,000	11 (1.01)

[a]Overall sample numbers when added together do not always equal the full sample of 1084 due to missing data points in that category.

[b]In accordance with NIH Racial and Ethnic Categories, Hispanic was a separate question, therefore the total number in this category may add up to greater than 1084.

Discussion

Principal Findings

Our study utilized Amazon's MTurk to effectively and efficiently obtain survey data from a large national pool of both men and women. We were able to obtain both quantitative and qualitative information regarding participants' knowledge of and experience with miscarriage. What makes this data unique is that we obtained quality data from over 1000 respondents over a 3-day window for under US $300. Obtaining 1000 respondents with other survey methods would cost between 4 to 69 times as much as our method depending on the survey type [4,12]. In addition, it would have taken on average weeks to months to complete the requisite number of responses [5-7].

We found that posting batches larger than 50 led to longer batch completion times, and that the best time to post was between 8:30 am to 8:30 pm EST. Based on our data, researchers should post batches during the hours in which their targeted population is awake. For example, researchers on the east coast who are targeting a west coast population should adjust their posting schedules to match the sleep/wake schedules of their expected participants.

Previously, complex technical computer skills were required to create online surveys [25]. MTurk's UI is simple to use. For those without technical skills, MTurk can be set to function similar to simple word processing programs. For those with more advanced programming skills, other more powerful programming languages may be added. MTurk, therefore, allows basic and advanced users of computer technology to easily create and distribute surveys.

Limitations

Limitations to the study include the potential for non-responder bias, as it is not possible to determine how many people previewed our survey without completing it. It is possible that those who responded felt more strongly about issues related to miscarriage. However, these limitations may exist regardless of method of survey distribution.

In addition, previous studies have suggested that the demographics of MTurk participants differed from national demographics; a paper by Paolacci et al suggested that only 47% of MTurk workers were in the United States [18]. However, our study included only those who were US based, thereby eliminating bias from international responders. As prior studies using MTurk have shown [14], race and ethnicity are not proportionately represented, with an underrepresentation of blacks and Hispanics and an overrepresentation of Asians. This may limit the generalizability of our study to the United States as a whole. In addition, respondents had attained a higher level of education than the general public, which may have led to under emphasis of misperceptions found in the general public [26]. However, participants were from 49 of 50 states with no one region over or underrepresented, and overall, the sociodemographic distribution across gender, age, religion, geographic location, and household income was consistent with 2010 national census statistics [27].

Conclusions

To our knowledge, our study is the first to examine perceptions and understanding of miscarriage among the US national population, and the first to use crowdsourced surveys to examine patient satisfaction with health care providers. Other studies have been able to obtain information from a national sample, however, data collection was costly as well as labor and time intensive. The results of our study demonstrate that MTurk is a safe, cost-effective, and time-efficient way to confidentially obtain important, sensitive information on reproductive health from a large, diverse participant population. Our study also shows that it is also possible to obtain rapid data for general health questions. While many previous studies have assessed MTurk's validity within psychological and behavioral research, our survey utilized MTurk to conduct medical research, the results of which may impact the future health care of both men and women.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Survey as published online.

[HTML File, 42KB - resprot_v5i3e166_app1.html]

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Abbreviations

ACQ: attention check question
EST: Eastern Standard Time
HTML: Hyper Text Markup Language
MTurk: Mechanical Turk
UI: user interface

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Original Paper

A Social Media Peer Group Intervention for Mothers to Prevent Obesity and Promote Healthy Growth from Infancy: Development and Pilot Trial

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Abstract

Background: Evidence increasingly indicates that childhood obesity prevention efforts should begin as early as infancy. However, few interventions meet the needs of families whose infants are at increased obesity risk due to factors including income and maternal body mass index (BMI). Social media peer groups may offer a promising new way to provide these families with the knowledge, strategies, and support they need to adopt obesity prevention behaviors.

Objective: The aim of this study is to develop and pilot test a Facebook-based peer group intervention for mothers, designed to prevent pediatric obesity and promote health beginning in infancy.

Methods: We conducted in-depth semi-structured interviews with 29 mothers of infants and focus groups with 30 pediatric clinicians, to inform the development of a theory-based intervention. We then conducted a single-group pilot trial with 8 mothers to assess its feasibility and acceptability. All participants were recruited offline at pediatric primary care practices. Participants in the pilot trial joined a private Facebook group, moderated by a psychologist, with a weekly video-based curriculum, and also had the option to meet at a face-to-face event. Within the Facebook group, mothers were encouraged to chat, ask questions, and share photos and videos of themselves and babies practicing healthy behaviors. Consistent with the literature on obesity prevention, the curriculum addressed infant feeding, sleep, activity, and maternal well-being. Feasibility was assessed using the frequency and content of group participation by mothers, and acceptability was measured using online surveys and phone interviews.

Results: Based on preferences of mothers interviewed (mean BMI 35 kg/m^2, all Medicaid-insured, mean age 27, all Black), we designed the intervention to include frequent posts with new information, videos showing parents of infants demonstrating healthy behaviors, and an optional face-to-face meeting. We developed a privacy and safety plan that met the needs of participants as

well as the requirements of the local institutional review board (IRB), which included use of a "secret" group and frequent screening of participant posts. Clinicians, 97% (29/30) women and 87% (26/30) pediatricians, preferred no direct involvement in the intervention, but were supportive of their patients' participation. In our 8-week, single group pilot trial, all participants (mean BMI 35 kg/m^2, all Medicaid-insured, mean age 28, all Black) viewed every weekly video post, and interacted frequently, with a weekly average of 4.4 posts/comments from each participant. All participant posts were related to parenting topics. Participants initiated conversations about behaviors related to healthy infant growth including solid food introduction, feeding volume, and managing stress. All 8 pilot group participants reported that they found the group helpful and would recommend it to others.

Conclusions: Our methodology was feasible and acceptable to low-income mothers of infants at high risk of obesity, and could be adapted to implement peer groups through social media for underserved populations in varied settings.

ClinicalTrial: ClinicalTrials.gov NCT01977105; https://clinicaltrials.gov/ct2/show/NCT01977105 (Archived by WebCite at http://www.webcitation.org/6iMFfOBat)

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KEYWORDS

obesity; social media; behavior change; intervention; internet; peer group; pediatrics; prevention and control; infant; mothers

Introduction

Overweight in infancy is common and associated with later obesity and adverse health outcomes [1-4]. According to national data, nearly 10% of infants and toddlers have an elevated weight for recumbent length [5]. This risk increases among those born to women with obesity, families in poverty, and racial/ethnic minorities [1,5-9]. Research suggests that infants with rapid growth during the first 2 years of life are more likely to become obese later in childhood and as adults [4,10,11]. Evidence increasingly indicates that the first 6 months of life are an especially critical time period; growth velocity during the first 4-6 months has been shown to predict obesity at ages 1, 3, 5, 10, and 20 years [2,3,12,13].

In 2011, the Institute of Medicine (IOM) emphasized the need for interventions in early childhood to prevent the subsequent development of obesity [14]. To date, however, traditional obesity prevention strategies (i.e. doctor's office or home-based parent education) have had mixed results when applied to early childhood, with high levels of treatment engagement typically needed to motivate parent behavior change [15-24]. Furthermore, very few effective interventions have been designed to meet the needs of the low-income, overweight or obese mothers whose infants are at greatest risk. The few that do exist for this population are primarily home visiting programs, which are labor-intensive, making them difficult and often expensive to scale [21-24].

Peer interventions delivered through social media represent a promising alternative to traditional peer interventions, home visiting, or pediatric office-based strategies to promote healthful behaviors and improve outcomes. In pediatrics, peer interventions have been successfully used to provide patients and families with information, support, and problem-solving skills, resulting in improved breastfeeding rates and reduced postpartum depression [25,26]. Peers have also been used to enhance the effectiveness of interventions for populations at high risk of adverse outcomes [22]. However, engaging families at high risk with in-person peer groups can be challenging because of the logistical difficulties they often confront in attending these groups [27].

Social media is a prevalent communication format that is especially well-matched to the delivery of peer interventions. Use is widespread; 90% of online young adults use social media to connect with peers [28]. A growing majority access social media using mobile phones with app capabilities (smartphones that function as computers, have Internet access, and can download apps), now owned by 85% of young adults in the United States. Mobile phones currently serve as the primary source of Internet access for nearly 1 in 5 low-income households, making them a particularly fitting intervention delivery strategy for this population [29]. Mobile phones also allow social media users to interact frequently and at their convenience, a pattern likely to facilitate engagement and delivery of a high "dose" of the intervention. Video content delivered through social media can help to overcome literacy barriers. Since social media is widely and freely accessible, interventions developed using this medium may be more readily disseminated than those requiring the adoption of new technology or frequent, face-to-face interaction.

Consistent with the American Heart Association's prioritization of social media as a tool to address obesity [30], we developed a Facebook intervention and then tested the feasibility and acceptability of this innovative approach to promote behaviors associated with healthy weight from infancy. Our intervention was designed to address the needs of families with children at highest risk of obesity. Given the potential long-term health benefits of establishing healthy growth in infancy, the need for effective interventions that keep lower-income parents engaged, and the promise of peer interventions delivered via social media, we hypothesized that this approach would be feasible and acceptable to low-income mothers.

Methods

Overview

To understand how to best implement prevention-oriented virtual peer groups with low-income mothers at high risk of having

obese children, we conducted two different research studies designed to develop, refine, and pilot-test our approach. The Children's Hospital of Philadelphia (CHOP) Institutional Review Board (IRB) determined that the intervention development study was exempt from review, and approved the pilot study.

Intervention Development Study

Study Design

We conducted in-depth, semi-structured interviews with mothers of infants (subsequently referred to as intervention development interviews), and focus groups with pediatric clinicians. We specified an *a priori* sample size of up to 30 mothers and 30 clinicians since prior research suggests that this number is sufficient to achieve saturation on themes elicited in qualitative interviews [31]. With this number as a guide, data collection and analysis continued iteratively until saturation of themes was reached.

Setting and Study Procedures

All participants were recruited from three high-volume, urban, resident teaching primary care practices in the CHOP Pediatric Research Consortium (PeRC), a 2-state practice-based research network. Through rosters generated from the electronic health record (EHR), we identified and then approached potentially eligible mothers at their infant's primary care visit, where they completed a screening questionnaire for eligibility that assessed criteria not available in the EHR. Consistent with our focus on reaching mothers of infants at high risk of developing obesity [6,7], we enrolled women who were obese with self-reported, pre-pregnancy body mass index (BMI) greater than or equal to 30 kg/m^2, and had a Medicaid-insured infant, as an indicator of income. Participating mothers were at least 18 years of age and English-speaking with a child up to 1 year old. Clinicians participating in this phase of the study were non-trainees practicing at included sites. All participants provided written informed consent.

Interview and focus group guides were developed that addressed key themes relating to the implementation strategy and content of the intervention. In interviews, mothers were also asked for their opinions on sample intervention curriculum content, delivered through brief videos. Interviews were audiotaped, transcribed, and analyzed using QSR NVIVO10 software (QSR, Cambridge, MA). We used content analysis [32,33] to identify themes that emerged regarding the curriculum, implementation strategy, and outcome measurement protocols for the planned intervention. The constant comparative method, in which newly collected data are compared with categories that have emerged from previously collected data, was used throughout the data analysis to identify emerging themes to inform the planned intervention [34]. As data collection progressed, the research team discussed emerging themes, and iteratively updated the interview guide to refine our results. A coding scheme and coding dictionary were developed. The analysis was conducted by 2 coders; double coding was used on a majority (76%, 22/29) of the transcripts to establish consistency of the coding scheme. If differences in coding arose, the coders discussed them and reached a consensus. Representative verbatim comments were selected for presentation.

Single Group Pilot Trial

Study Procedures

Incorporating findings from the intervention development study, we subsequently conducted an 8-week single-group pilot trial of an actual Facebook peer group in order to assess the feasibility and acceptability of the virtual peer group format. Eight overweight or obese mothers of Medicaid-insured newborns (<1 month) were recruited at PeRC sites using the same methods and inclusion criteria described in the intervention development study above. Further eligibility screening criteria for participation in the pilot trial included owning a mobile phone with a data plan, and the ability to take photos and videos using the phone. In addition, to focus on mothers whose needs could be addressed by the intervention, mothers were excluded from the pilot trial if they screened positive for clinical depression on the Patient Health Questionnaire-9 [35], had not received prenatal care, delivered before 37 weeks gestation, or if they had gestational diabetes, a multiple gestation pregnancy, or an infant hospitalized in the neonatal intensive care unit for 1 week or longer.

Study participation involved Facebook group activities for 8 weeks and an optional in-person meeting prior to the start of the Facebook group intervention. Participants also completed an online questionnaire at baseline and at study end, and an in-depth, semi-structured phone interview regarding their satisfaction and experiences with the group. Online surveys were completed using Research Electronic Data Capture (REDCap) hosted at CHOP. REDCap is a secure, Web-based application for data collection that provides an intuitive interface for validated data entry [36]. Baseline study measures included demographic characteristics, household food security measured using a validated 2-item questionnaire from the US Household Food Security Survey Module [37,38], and health literacy measured using the Newest Vital Sign Questionnaire [39]. In order to assess the feasibility of measuring outcomes, mothers' beliefs regarding infant feeding were measured on both the pre- and post-intervention surveys using relevant items from the Infant Feeding Style Questionnaire [40]. Surveys also included multiple choice and open-ended items measuring the acceptability of the intervention. We used interview and survey responses along with the content and rate of participant activity (posts/comments, "likes," and "seen by" counts) to identify successful aspects of the peer group and general considerations for the implementation of virtual peer groups, including the selection of measures of impact.

Initial Peer Group Design

Participants were informed that they would participate in an 8-week Facebook group focused on healthy infant growth. All were assigned to a single peer group, facilitated by a psychologist with expertise in obesity treatment. The group began with an in-person baby shower at which participants could meet other group members and the facilitator in person. Following this event, and in contrast to many previously published interventions in which social media was only a small

component [27,41-43], the entire intervention occurred online, in a Facebook group accessible only to study staff and invited participants. The group was set up as "secret," Facebook's maximum privacy setting, which restricts visibility of the group to current members. Group activities included viewing weekly educational videos posted to the group that featured mothers and infants (including many from the same community) modeling behaviors and addressing topics related to healthy infant growth. Specifically, the curriculum addressed infant feeding, sleep, activity, and maternal well-being. Participating mothers then posted their own photos, videos and experiences, provided feedback on posts by other group members and received feedback from peers and the group moderator.

This intervention design was based on Social Learning Theory [44] which emphasizes the importance of observing models in preparation for performing a behavior, then receiving positive feedback after practicing the behavior. In this case, behavioral models were provided by parents in the curriculum videos and by the group facilitator, as well as participants' own photos and videos. The facilitator provided positive feedback to participants whose posts demonstrated healthy behaviors by directly providing "likes" and comments, and encouraging other participants to do the same. In this way, the moderator role was central to this theory-based intervention.

Curriculum content was developed locally based on results from intervention development interviews with mothers and clinician focus groups, and national guidelines for pediatric prevention and health promotion [45]. Content included weekly modules that consisted of a short video, as well as a brief written summary of key points from the video (which was posted to the Facebook group both as a text post and as a downloadable PDF handout). Shorter posts throughout the week included infant "fun facts" or health tips, which, when relevant, included hyperlinks to outside resources.

As the study involved participants using their personal mobile phones to access the group, each received a US $50 monthly stipend for 2 months to offset the approximate cost of their phone data plan. Participants were told that in order to be eligible for the stipend, they needed to post or comment in the Facebook group at least once; they were encouraged to log in at least weekly, but, beyond that basic guidance, were told that they could participate in the group as much or as little as they wanted. Participants who did not access the group for over 2 weeks received a private Facebook message with a reminder from the group facilitator.

Development of the Human Subjects Plan

In order to ensure that our Facebook intervention sufficiently protected human participants, we consulted extensively with the CHOP IRB throughout the intervention development process. The IRB concluded that the intervention met the regulatory definition of minimal risk, as the activities involved posed no greater risk than those encountered in during daily life [46]. Though the risks to participants were minimal, the study safety plan employed several strategies to further minimize risk. First, access to the Facebook group was limited to individuals who had consented to participate, and the group was moderated. Second, the facilitator or study staff reviewed all posts for appropriateness of tone and content (e.g., not offensive or critical of other group members). New posts were delayed until after they had been reviewed, and posts that failed to meet the terms of the group were excluded.

From an IRB perspective, breaches of confidentiality represented the most significant risk for participants. To mitigate this risk, clear rules were established and conveyed to prospective participants as part of the informed consent process, with ground rules posted on the group page (information posted by others should be treated as confidential; others' identities should not be revealed outside the group). The consent (Multimedia Appendix 1) made clear that the confidentiality of information posted in the group could not be guaranteed.

To complement the perspectives of the IRB, both intervention development interview participants as well as pilot group members were asked to comment on the human subjects approaches proposed for the pilot group study.

Results

Study Population

A total of 29 mothers of children up to 1 year old participated in the intervention development interviews and survey; participants had a mean BMI of 35 kg/m^2, mean age of 27 years, and were all of Black race (Table 1), though race/ethnicity were not inclusion criteria for the study. As an indicator of socioeconomic status, only Medicaid-enrolled families were eligible for the study. Over half were at risk of household food insecurity [37,38]. Nearly all were current, frequent Facebook users. In addition, 30 clinicians participated in focus groups (29 women; 26 pediatricians and 4 nurse practitioners; 24 White, 3 Black, 3 Asian; mean 14 years post-training). In the pilot trial of the intervention, 8 mothers participated with a mean BMI of 35 kg/m^2, mean age 28, and all Black (Table 1). Mothers all reported an annual income of less than US $15,000, and rates of food insecurity were similar to those in the intervention development interview group. All had existing Facebook accounts at the time of enrollment, though this was not a requirement for eligibility.

Table 1. Characteristics of participating mothers in each study, measured at enrollment.

Characteristics	Interviews (N=29), n (%)	Pilot group (N=8), n (%)
Sex		
Female	29 (100)[a]	8 (100)[b]
Age, years		
18-25	13 (45)	4 (44)
26-30	12 (41)	2 (25)
≥31	4 (13)	2 (25)
Race/Ethnicity[c]		
Black	29 (100)	8 (100)
White	1 (3)	1 (13)
American Indian/Alaska Native	0 (0)	1 (13)
Hispanic/Latino	2 (%)	0 (0)
Highest education level completed		
High school or less	16 (55)	4 (50)
Some college/associate degree	10 (35)	3 (38)
Bachelors or professional degree	3 (10)	1 (13)
Annual income		
< $10,000	N/A	6 (75)
$10,000-$14,999	N/A	2 (25)
Number of children		
1	11 (38)	2 (25)
2-3	14 (48)	3 (38)
≥ 4	4 (14)	3 (38)
Weight category		
Overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2)	N/A	2 (25)[b]
Obese (BMI ≥ 30 kg/m^2)	29 (100)[a]	6 (75)[b]
Household food insecurity		
At risk	15 (52)	4 (50)
Technology use		
Have a Facebook account	25 (86)	8 (100)
Own a mobile phone	25 (86)	8 (100)[b]
Pay for mobile phone data plan	19 (66)	8 (100)[b]
Breastfeeding		
Breastfeeding only	N/A	0 (0)
Formula only	N/A	5 (63)
Both breast and formula	N/A	3 (38)
Health literacy (Newest Vital Sign)		
High likelihood or possibility of limited literacy	N/A	5 (63)
Adequate literacy	N/A	3 (38)

[a]Female sex and obesity (BMI≥ 30kg/m^2) were inclusion criteria for the intervention development interviews.

[b]Female sex, overweight or obesity (BMI≥ 25kg/m^2), and mobile phone/data plan ownership were inclusion criteria for the single-group pilot trial.

[c]Participants were instructed to select all applicable categories; hence the totals are more than 100%.

Implementation Strategies

Overview

Mothers and clinicians in the intervention development study commented on several dimensions of the intervention implementation strategy. Their responses are outlined below, followed by a description of how this information was used to develop the intervention. We then present the results and participant feedback related to study implementation from the pilot trial.

Web-Based Versus Face-To-Face Activities

In intervention development interviews, participants were asked how they would feel about participating in an online group with other mothers they had not met in person. Responses and levels of concern were quite varied. While many (59%, 17/29 mothers) were unconcerned ("That sounds perfectly fine"), for a few (10%, 3/29) it would strongly affect their willingness to participate ("[If] I don't know who they are, I won't share information with you, you know?"). Several others (31%, 9/29) had perspectives between these extremes:

> *I don't know – A little antsy, but I'd manage. I wouldn't go into so much detail about my life… I'd keep it at a certain level.*

After several mothers suggested that even one in-person event for the group would assuage their concerns about not knowing the other participants, a question about this was added to the interview guide. Of the respondents asked, 75% (15/20) said that they would like to meet in person. As one participant put it:

> *It's better to know them more direct than indirectly. You don't really know them as well on Facebook than face to face.*

Others commented that a face-to-face event would help keep them engaged and interested.

Based on this input, the pilot peer group began with an in-person event, with a baby shower theme. Of the participants, 38% (3/8) attended along with the group facilitator. One participant later commented:

> *I met [the facilitator] at the get together. It was good to meet her first and that way I was comfortable enough to talk in the group.*

Overall, participants who attended the in-person event had similar rates of participation compared to those who did not attend (median of 23 posts/comments for all participants over the course of the intervention in both groups).

Engagement Strategies

In intervention development interviews, mothers discussing the role of a peer group in their lives anticipated that the primary benefits or reasons to participate would be (1) learning new things about parenting (97%, 28/29); and (2) peer support and interaction with other mothers (93%, 27/29). When asked specifically what would be most helpful in keeping them engaged, responses reflected similar priorities. One participant replied:

> *To know each mother's experience, to know what they went through, what's been on their mind.…That would keep me involved.*

Many respondents (76%, 22/29) expressed a desire or need for support in this context, and described connecting with other mothers as a way to learn and potentially adopt better parenting behaviors. For example, in the words of one mother:

> *The support [would be the most helpful thing]. Just knowing that you have somebody like your peers that's there that can answer questions for you… [M]others telling you this is what they did and it worked for them.*

Another commented, "You would get to meet new people, learn different methods people are using to raise their kids." A first-time mother anticipated "asking questions from mothers that already had kids.

One respondent stated that if she'd had the opportunity to participate in such a peer group,

> *I would have been more confident when [my baby] came home… taking care of her, knowing what to do, because everyone has different experience and you learn from other people.*

Another engagement strategy that mothers suggested was to keep the group active with frequent posts and new, up-to-date information about parenting. Both the frequency and quality of information were considered important. Mothers requested "New topics, not the same thing over and over again, learn new things," and "Just making sure I have all the up to date, like, maybe articles and stuff like that on children and babies." Based on this feedback, groups included frequent posts of new information that augmented the curriculum.

Use of Video

When mothers were shown sample videos created for the group, several (24%, 7/29) noted that it was helpful to see actual parents and children in the videos, particularly when they demonstrated behaviors or activities. One commented:

> *I connected with everybody [in the video] because they all were interacting with their babies, it's not like they were just on there by themselves saying, "Oh this is what I do". They was always holding their babies and show them what they do.*

Mothers suggested that watching these modeled behaviors would trigger action. One said:

> *[A mother in the video] sung a song I've never heard of. I'd probably sing that with my son.*

Privacy

The vast majority of intervention development interview respondents (93%, 27/29), none of whom had ever participated in a similar intervention, reported that they would feel comfortable participating in an intervention that used a "secret" Facebook group (a privacy setting which limits group visibility and access to those invited by the moderator). For more than half (55%, 16/29), this comfort level was due specifically to the "secret" privacy setting. The mothers interviewed liked that it

would be "just moms and nobody else," and "not letting the whole world see it," so that "whatever I said would just be between a certain amount of people." Another commented that "[Facebook is] pretty good with the secret groups."

Some mothers (21%, 6/29) felt that privacy was not a concern because they did not intend to share any information that they perceived as too personal. For example, one participant stated she would not be worried about privacy because "If I'm not comfortable saying it to your face, I'm not gonna post it." Several clarified that they did not see parenting as a very private or sensitive topic: "I mean, as far as parenting, that's fine pretty much, that stuff I'd feel comfortable with sharing."

In the abbreviated pilot trial, the "secret" group setting was used. No participant reported any breach of privacy or concern about privacy, either during or after the study.

Role of the Group Facilitator

When asked about the ideal role of a group facilitator, many intervention development interview respondents (55%, 16/29) stated that they would want her to provide information or advice: "Just help answer questions, feeding, breastfeed, solid foods, I guess the leader would know all of that." Seven specified explicitly (and others implied) that they would want the facilitator to be an experienced mother, who could draw upon her own experience to provide guidance to the group. "A hands on mom has most likely been through stuff, probably can give us realistic…ideas and other ways and methods." Others said that they would want the facilitator to provide emotional support, keep group discussions on track, manage conflicts, or provide resources for low-income mothers. The group facilitator in the pilot trial was a PhD-level psychologist who was also an experienced mother with young children. She frequently posted in the group (14.4 posts per week on average), modeling healthy behaviors and providing information (in 46%, 53/115 facilitator posts), and offering emotional support and encouragement (17%, 19/115 posts), as well as guiding group discussion.

Monitoring Plan

Our monitoring plan was intended to prevent any harm to participants caused by inappropriate or offensive posts by other group members. This plan was described to mothers during intervention development interviews; all agreed that having all posts screened by the group leader before appearing on the group page would be both reasonable and helpful: "That's great, you know, some people might post things other people may not want to see." However, one noted that quick approval would be necessary to prevent the approval process from interfering with participation:

> *I think that would be fine, as long as they approve them fast. You don't wanna have to wait days for your post to be posted…. When you post something usually it's on there right away. I'd give y'all a couple of hours, maybe.*

In the pilot trial, the group facilitator and one additional member of the research staff screened and approved posts regularly throughout each day, including weekends and at night, accessing the group from mobile devices to facilitate this process. Participants did not report any problems or concerns with this approach. Group members respected ground rules established to guide interactions. In fact, during the 2-month trial, only one comment was not approved for posting by the facilitator. This comment expressed a participant's frustration with others in the group for not responding quickly to a question she had posted; the facilitator messaged the participant privately to discuss the post. The participant continued in the group with no further issues.

Involvement of Pediatric Clinicians

We asked both mothers and clinicians about the best way, if any, to involve the pediatric practice in the intervention. Mothers were asked whether they would want any of their information from the group shared with their child's pediatrician. Most were relatively comfortable with this: "I wouldn't mind. If they wanna share something with the doctor that would be fine, because I know that would be kept confidential."

When asked about information sharing in the other direction, from pediatricians to the group leader, responses were more varied. Some mothers were comfortable with "good" information being shared:

> *[I would want shared] that my baby is healthy, well taken care of, eating right, growing. All the good things.*

However, for information about problems or concerns, "It would depend on what problem," and many participants would want to approve that information on a case-by-case basis before it was shared.

In focus groups, clinicians expressed enthusiasm for the intervention, and were willing to receive and share information with the intervention team on an as-needed basis. However, clinicians preferred no direct involvement in the intervention. The intervention was designed as suggested with no direct pediatrician participation.

Feasibility of a Prevention-Oriented Peer Group

Enrollment and Access

Of the 10 eligible participants approached, 8 participants enrolled in the pilot study and successfully joined the Facebook group. One additional mother began enrollment and provided informed consent, but did not complete the enrollment survey and was unable to be contacted further; based on the limited information obtained, her characteristics were similar to the participants who enrolled successfully. Almost all of the participants reported accessing the group primarily via mobile phone; 2 used both phones and computers to access the group, and 1 reported using a tablet and a computer, but not a mobile phone. All were successfully able to view the group and create their own posts.

All 8 participants successfully completed online surveys at baseline and study end, including items assessing infant feeding beliefs and behaviors [40]. In interviews, participants reported that they understood all survey items and had no questions or concerns. Outcome data are not reported here as the objective of this study was to assess the feasibility and acceptability of our outcome measurement plan.

Engagement

The Facebook format created a record of all group activities, facilitating analysis. All active participants viewed all of the weekly videos, and the group averaged 7 posts and 6 "likes" daily. Of the participant posts, 91.8% (257/280) were text, 6.4% (18/280) were photos, and 1.8% (5/280) were videos. All participant posts were related to parenting topics. Participants initiated conversations about behaviors related to infant growth, including topics such as solid food introduction, sleep schedules (Figure 1), feeding volume, and managing stress. Consistent with the curriculum, mothers' photos and videos demonstrated responses to infant cues (Figure 2), soothing behaviors, infant play, and sleep routines. In this small sample, participation did not vary between first-time and experienced mothers.

Participants were successful in supporting one another in a virtual group format. The theme of peer support emerged strongly in surveys and interviews of the mothers in the pilot group. One participant commented that, "I felt like part of a group when I was participating and I felt like I helped someone along the way and vice versa." Reflecting how close participants in virtual peer group could become, one wrote, "…all of us as MOMS came together n [*sic*] got along so well without us even knowing each other." Another mother added that "The group wasn't really like a group of strangers talking, it was more like sisters helping each other out."

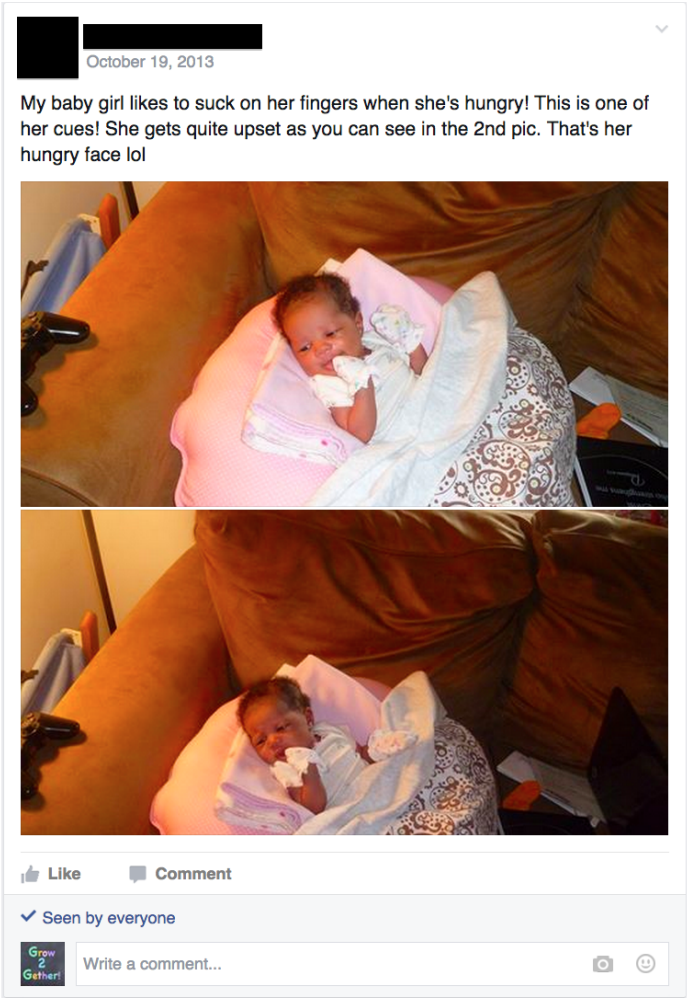
As further evidence of the peer connections established in the group, 5 of the participants reported at the end of the pilot study that they had become Facebook friends with at least one of the other group members. They also reported interactions with group members that went on outside of the group itself:

> *We exchanged numbers and friended and messaged each other on regular Facebook. We post on each other's walls and message each other.*

Another explained, "After the group was over, we all wanted to stay in contact." Participants reported that topics of discussion outside of the group generally mirrored those in the group, such as feeding and sleep schedules, although some conversations were more specific and personal, such as 2 mothers whose children were both hospitalized who messaged one another about the experience.

Figure 1. Participant-initiated conversation about infant sleep (participant information redacted, profile image shown for facilitator only).

Figure 2. Participant post showing infant hunger cues. This photo was approved for publication by the participant.



Group Impact

All 8 participants reported that they had gained knowledge from the group. In surveys, when asked if participating in the group had helped them, one commented, "I learned some new techniques for the baby," while another wrote, "Yes, new information about babies' feeding playtime activities and more, because a lot of things have changed since I had my last child 13 years ago." Others even indicated that the benefits went beyond simply learning, to shifts in attitude: "It helped me grow as a parent to different ideas."

On the survey, mothers were also asked if they had changed anything they did, or planned to, based on the group. More than half (63%, 5/8) reported that they had, primarily making adjustments to their child's feeding and sleep schedules (both of which were behavioral targets of the intervention).

Acceptability of a Prevention-Oriented Peer Group

The pilot group participants found the Facebook group highly acceptable. All (100%, 8/8) active participants agreed with the statements, "I would recommend this program," and "The program was helpful." When asked, "What did you think of the Facebook group?" responses were consistently positive, and focused on peer connections (88%, 7/8) and sharing of information as the most helpful aspects: "I think that it was amazing that I got to talk to other moms that were experiencing the same thing that I was."

> *It was nice to share with other new mothers. Even though this is baby number five for me it was nice to share some of the things I have learned over the years.*
>
> *I think it was a great group overall. I learned some good tips and got some good advice.*

While half of the participants stated that they would not want to change anything about the group, the others had the following 2 recurring suggestions: (1) to add more participants to the peer group (suggested by 3 participants), and (2) to have the 2-month long group run for a longer period of time (suggested by 4 participants).

All participants interviewed reported that they found the curriculum very helpful; all preferred information in video format (vs electronic documents or information posted directly to the Facebook group as a text comment). One elaborated:

> *I liked the videos because it was actual parents showing you how to do things. Rather than having it written out.*

Another explained:

> *The videos [were best], because I was able to see it. I'm a visual kind of person.*

Although videos were preferred, 2 participants commented that they appreciated having the information presented in multiple formats: "The videos were helpful, I liked it better with the steps written out under the video post."

> *[The facilitator] was good. Because she…posted the information in multiple ways, written out and in the videos.*

All pilot group participants had only positive feedback about the group facilitator's role. In interviews, one participant commented that, "[She] was great, very informative, gave great advice, answered all my questions, answered questions very quickly." Another said:

> *I loved her, she was very cool. Big sister type thing. I felt like I could talk to her about anything.*

Others specifically appreciated her level of involvement in the group:

> *Some leaders give you stuff to do and then are absent. She was around and attentive, anything you posted she would comment on….*

Discussion

Principal Findings

Input from low-income mothers and the clinicians who care for their children guided our development of a prevention-oriented Facebook peer group intervention that was feasible, acceptable, and engaging to participants. Based on mothers' preferences, we designed the intervention to include frequent posts with new information, videos showing parents demonstrating behaviors associated with obesity prevention, and a face-to-face group event prior to starting the Facebook group intervention. We developed a privacy and safety plan that met the needs of participants as well as the requirements of the local IRB, including use of a "secret" group and frequent screening of participant posts. In our 8-week pilot group, all participants viewed every weekly video post and interacted frequently, with each participant posting or commenting an average of 4.4 times per week. All 8 pilot group participants reported that they found the group helpful and would recommend it to others.

Comparison with Prior Work

Although our pilot group was small, rates of participation and satisfaction with the intervention were remarkably high compared with other social media-based peer group interventions in the literature. For example, an 8-week physical activity intervention delivered via Facebook group and text messages to 29 African-American women had 0.2 posts per participant per week, 22 times lower than in our group [47]. Rates of participation were nearly as low in studies of other prevention-oriented Facebook groups, including those focused on smoking, physical activity, and postpartum weight loss [48-50].

There are many potential contributing factors to the high levels of engagement in our group. Though other social media peer groups designed for demographically similar groups have not been as successful in maintaining engagement [27,47], the population participating in our intervention may have been particularly well-suited to a Facebook-based peer group, since almost all were existing frequent Facebook users and were new mothers interested in sharing photos of their children. In addition, in contrast to other interventions that split up participant interactions across multiple other platforms including text messages, phone calls, and/or other websites [27,47,51,52], Facebook was the sole delivery method of our intervention curriculum. Another unique aspect of the intervention was its focus on infant health, which may have been a more compelling topic for mothers than the maternal health outcomes targeted elsewhere [53], such as physical activity, nutrition and/or weight [27,49]. The role of the group facilitator, who, consistent with Social Learning Theory [44], provided positive reinforcement for participation and posted frequently in the group herself, may have also encouraged participants to post more often. It is possible that the US $50 monthly incentive to cover the cost of mobile phone data for active participants may have motivated some of the activity in the group. However, participants only had to post or comment in the group once to be considered "active," and all participants posted much more frequently (35 times on average).

Participants told us that protecting their privacy and safety was essential to the success of the group. Having a "secret" group setting that restricted group access to members was especially important for many participants to feel comfortable sharing information about themselves and their children. This finding has been supported by similar research; several Facebook-based interventions in the literature also used a "private" or "secret" group setting [41,54,55]. In one Facebook intervention study, a smoking cessation group was changed to a private group setting after participants expressed concerns about confidentiality [48]. Although our findings apply specifically to Facebook's current features and settings, the privacy needs of participants will certainly remain relevant to peer group success even as social media platforms and features change. In establishing safety measures, we worked carefully to balance the preferences and concerns of participants, the requirements of the IRB, and the logistical realities of the study team. For example, our procedure for monitoring posts was recommended by the IRB, and approved by mothers with the caveat that posts be screened and approved quickly. In order to meet both of these needs, we determined that more than one member of the study team would be needed to continuously screen posts, and mobile phones should be used by the team to facilitate access. Our approach may provide a model for those seeking to develop similar interventions that are acceptable to the IRB, and safe and engaging for participants.

One question that remains to be answered is the role of face-to-face meetings as a component of social media interventions. Other recent Facebook-based interventions have incorporated one or more in-person meetings [41,56], and this approach has been recommended by others as a way to increase engagement [47]. In our case, the idea was generated by mothers in intervention development interviews, and was preferred over an online chat or phone meeting by 75% (15/20) of the mothers we asked. The mothers in the pilot trial who attended the meeting reported that it was a helpful introduction that made them feel more comfortable posting to the group. This raises

the possibility that social media peer groups may be more engaging for some participants if circumstances permit a face-to-face meeting first. However, this does not appear to be the case for all participants, since only 38% (3/8) of the mothers in our group actually attended the event, and those who attended participated in the peer group at similar rates as those who did not. Furthermore, members of some online groups may be geographically distributed too broadly to meet in one location, or, especially in the case of youth and those with low income, may lack transportation [27]. Further research is needed to better understand the necessity and ideal role of offline meetings as part of social media peer group interventions.

Limitations

The primary limitation of this study is its small sample size, particularly in the pilot trial. This study was designed to develop a Facebook peer intervention; a randomized controlled trial of a longer intervention curriculum, with more participants and multiple peer groups, is currently under way. In addition, the mothers participating in this study represent a specific and narrow sample of women, whose children are at increased risk of obesity due to maternal BMI, race, and income. While this group represents a population in particular need of support, their experiences and opinions of a social media-based peer intervention may differ from those of other populations. In the pilot trial, the population was further limited to mobile phone owners; 2 mothers were excluded from participating for this reason. The majority of mothers approached did own a mobile phone, however, as do a growing majority of adults in the United States, including those with low income [29].

Furthermore, this study tested intervention delivery using Facebook groups, and it is unclear as social media evolves how the intervention may adapt to changing Facebook features or translate to other platforms. Still, the principle of delivering a moderated peer group to low-income mothers using familiar technology will likely remain relevant. Finally, this study assessed the feasibility of measuring the intended behavioral and health outcomes of the intervention. However, future studies, such as the ongoing pilot trial, are needed in order to actually understand the impact that this social media peer group intervention may have on participants' knowledge, attitudes, behaviors, and health.

Conclusions

This intervention provides a model for the design and use of private social media groups as a platform to deliver peer-based interventions to change health behaviors. Our results indicate that such groups are both feasible and acceptable, even among extremely low-income populations whose children are at high risk for obesity and other adverse health outcomes.

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Authors' Contributions

AGF, RSG, CTB, MG, TJP, RIB, SV, SNM, GKK, and MSS conceptualized and designed the study. CTB and RSG implemented the pilot group intervention. RSG and AWS acquired the data. RSG and AL analyzed the data, with guidance from AGF. RSG, AGF, AL, MG, SV, RIB, TJP, CTB, AWS, GKK, JS, and MSS interpreted the data. RSG and AGF drafted the initial manuscript, with assistance from MSS. All authors critically reviewed the manuscript and approved the final manuscript as submitted.
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Conflicts of Interest

None declared.

Multimedia Appendix 1

Pilot trial consent form.

[PDF File (Adobe PDF File), 168KB - resprot_v5i3e159_app1.pdf]

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Abbreviations

BMI: body mass index
CHOP: The Children’s Hospital of Philadelphia
EHR: electronic health record
IRB: institutional review board
PeRC: Pediatric Research Consortium
REDCap: Research Electronic Data Capture

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Original Paper

Twitter Strategies for Web-Based Surveying: Descriptive Analysis From the International Concussion Study

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Abstract

Background: Social media provides researchers with an efficient means to reach and engage with a large and diverse audience. Twitter allows for the virtual social interaction among a network of users that enables researchers to recruit and administer surveys using snowball sampling. Although using Twitter to administer surveys for research is not new, strategies to improve response rates are yet to be reported.

Objective: To compare the potential and actual reach of 2 Twitter accounts that administered a Web-based concussion survey to rugby players and trainers using 2 distinct Twitter-targeting strategies. Furthermore, the study sought to determine the likelihood of receiving a retweet based on the time of the day and day of the week of posting.

Methods: A survey based on previous concussion research was exported to a Web-based survey website Survey Monkey. The survey comprised 2 questionnaires, one for players, and one for those involved in the game (eg, coaches and athletic trainers). The Web-based survey was administered using 2 existing Twitter accounts, with each account executing a distinct targeting strategy. A list of potential Twitter accounts to target was drawn up, together with a list of predesigned tweets. The list of accounts to target was divided into 'High-Profile' and 'Low-Profile', based on each accounts' position to attract publicity with a high social interaction potential. The potential reach (number of followers of the targeted account), and actual reach (number of retweets received by each post) between the 2 strategies were compared. The number of retweets received by each account was further analyzed to understand when the most likely time of day, and day of the week, a retweet would be received.

Results: The number of retweets received by a Twitter account decreased by 72% when using the 'high-profile strategy' compared with the 'low-profile strategy' (incidence rate ratio (IRR); 0.28, 95% confidence interval (CI) 0.21-0.37, P<.001). When taking into account strategy and day of the week, the IRR for the number of retweets received during the hours of 12 AM to 5:59 AM (IRR 2.98, 95% CI 1.88-4.71, P>.001) and 6 PM to 11:59 PM (IRR 1.48, 95% CI 1.05-2.09, P>.05) were significantly increased relative to 6 AM to 11:59 AM. However, posting tweets during the hours of 12 PM to 5:59 PM, decreased the IRR for retweets by 40% (IRR 0.60, 95% CI 0.46-0.79, P<.001) compared with 6 AM to 11:59 AM. Posting on a Monday (IRR 3.57, 95% CI 2.50-5.09, P<.001) or Wednesday (IRR 1.50, 95% CI 1.11-1.11, P<.01) significantly increased the IRR compared with posting on a Thursday.

Conclusions: Surveys are a useful tool to measure the knowledge, attitudes, and behaviors of a given population. Strategies to improve Twitter engagement include targeting low-profile accounts, posting tweets in the morning (12 AM-11:59 AM) or late evenings (6 PM-11:59 PM), and posting on Mondays and Wednesdays.

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KEYWORDS

Twitter; social media; Web-based surveying; concussion; rugby

Introduction

Recruiting participants and administering surveys for research are usually conducted in person, via post, or through email [1-3]. Recruiting participants and administering surveys using these methods can be expensive and time-consuming. A potential alternative to these traditional methods is the use of social media [4-6]. Social media is the virtual interaction among users that allows for the creation, sharing, and exchange of information via websites, such as Facebook, Twitter, and YouTube. As a recruitment tool, social media provides researchers with an efficient means to reach and engage with a large and diverse audience in a short period of time. Moreover, it is relatively low cost to administer and maintain.

An example of a social media platform that can be used for recruiting participants is the Web-based social networking site known as Twitter. Within a 140 character limit, short messages (tweets) can be posted with the inclusion of a link to a website, image, or video. Users can then share the tweet (retweet) with their virtual network or community (followers). This system of posting to one network of users, and reposting to a different network of users, enables researchers to recruit using the snowball sampling method [4,6]. Traditional snowball sampling techniques use social interaction between individuals, where a participant from within the target group will recruit other participants who share the same characteristics from their own network [6]. This technique is particularly important for recruiting hard-to-reach populations [7]. In sports, athletes and trainers that deal with concussion are not easy to access [8-12]. Recruiting via Twitter may therefore offer a useful research tool to reach and engage athletes and trainers that deal with concussion.

In addition to recruiting, Web-based surveys can be administered via Twitter by posting a unique link to a questionnaire. Although using Twitter to administer Web-based surveys for research is not new [4], strategies to improve response rates are yet to be reported in the literature. Depending on the purpose, a Twitter account or Twitter post can be designed to gain maximum and focused Web-based exposure, which potentially may increase response rates. For example, targeting specific accounts by mentioning them in the posts, or wording the post to persuade followers to ‘retweet’ or click on the survey link. Furthermore, the frequency of posts, time of day, day of the week, and whether to use more than one account to post tweets are factors that may affect the Twitter Web-based exposure and surveying response rates [13,14]. Yet, the best approach to use these Twitter features for research are currently unexplored.

Therefore, the purpose of this study was to compare the potential and actual reach of 2 Twitter accounts that administered a Web-based concussion survey to rugby union (henceforth, called ‘rugby’) players and trainers using 2 distinct twitter targeting strategies. Furthermore, determine the likelihood of receiving a retweet based on the time of the day and day of the week of posting the Web-based survey.

Methods

The Web-Based Survey

A survey based on previous concussion research was developed and exported to the Web-based survey website Survey Monkey. The survey comprised of 2 questionnaires, one for players, and one for those involved in the game (eg, coaches and athletic trainers). Survey Monkey allows for the routing of questions based on a participant’s response, and early on in the survey participants had to indicate whether they were a player or an individual involved in the game in some aspect other than playing. This response then automatically directed the participant onto the appropriate questionnaire. The survey commenced with the background to the study, and a space to provide informed consent. Thereafter, 9 general demographic questions were asked (gender, age, involvement in the sport, etc). Depending on whether the participant indicated they were a player or an individual involved in the game in some aspect other than playing, Survey Monkey directed the participant onto the relevant questionnaire. The player questionnaire consisted of 16 closed questions, with the other questionnaire comprising of 12 closed questions. Space was provided at the end of some questions to allow the participant to elaborate on their answer if they so desired. The final page allowed for further comment and feedback on the overall survey experience. All participants remained anonymous throughout the completion of the questionnaire. It was assumed that participants provided accurate and honest responses. The study was approved by the University of Cape Town Human Research Ethics Committee (HREC Ref: 210/2014).

Social Media Strategy

After the link to the Web-based survey was available, the link to the survey was shared via Twitter. As no literature exists comparing different Twitter strategies to administer Web-based surveys for maximum and focused Web-based exposure, a decision was made to administer our concussion Web-based survey using 2 existing Twitter accounts, with each account executing a distinct targeting strategy. Using existing accounts also had the added benefit of having a starting base of followers. The personal accounts of the authors @Sharief_H and @SteveMellalieu were used. At the start of the study @Sharief_H had 1121 followers and @SteveMellalieu had 570 followers.

Next, a list of potential Twitter accounts to target was drawn up, and a list of predesigned tweets. The list contained International Rugby Organizations (eg, @IRBMedia, @IRBSevens), National Rugby Teams (eg, @WelshRugbyUnion, @EnglandRugby, @irfurugby), International Sport and Rugby Media (eg, @BBCSport, @BBCScrumV, @RugbyUnionNews), Professional Rugby Teams (eg, @Saracens, @CrusadersRugby), and High-Profile Professional Players (eg, @Rorylamont, @gareththomas14). The aforementioned accounts were considered ‘High-Profile’ because of their position to attract attention or publicity with a

high social interaction potential. In contrast, 'Low-Profile' accounts belonged to University teams (eg, @ikeytigers, @BathUniRugby1, @cardiffmetrfc), nonprofessional rugby clubs (eg, @swansearfc, @carmquinsrfc), and rugby coaches, trainers, scientists, and administrators (eg, @timoconnorbl, @J_Darrall_Jones, @1RugbyCoach). Note, although in most cases the 'High-Profile' accounts had more than 10,000 followers, the number of followers an account had was not the main distinguishing criterion between 'High-Profile' and 'Low-Profile' accounts. The main distinguishing criterion was the position of the account to attract attention or publicity–'High-Profile' accounts were representative of professional players/international/national organizations, whereas 'Low-Profile' accounts were nonrepresentative accounts.

Tweets were designed to include who qualified to take part in the study, a request to complete the survey, the duration of the survey, the link to the survey, character space to mention an account(s), a request to retweet, and character space for hashtags. A hashtag (preceded by a # symbol that allows for users to search topics on Twitter) was created specifically for the study - #IRCR014 (International Rugby Concussion Research 2014), and other popular hashtags such #Rugby #Concussion were also used. Textbox 1 contains a list of tweets used.

Textbox 1. A list of tweets linked to the Web-based survey.

Pls RT Play/involved in rugby union? Pls take 2min 2 complete international concussion survey. [Link to survey]

Play or involved in rugby union as a player/coach/medical/admin? Pls take few min to complete online survey on concussion [Link to survey]

Player, Coach, Medical, Manager, in rugby union? Pls take 3-4min to complete online survey on concussion [Link to survey] Pls RT #rugby

If you play or are involved in rugby union, pls take part in an International Concussion study [Link to survey] Pls RT

@XXXXXX Pls RT Are you involved in rugby union as a player/coach, or medical personnel? Pls take few min to complete online survey on concussion experiences [Link to survey]

Both accounts were at liberty to use any one of the above tweets. Administering the survey via Twitter commenced on April 2, 2014 and ended on August 3, 2014 (4 months). In the first 2 months of the study, the frequency of tweeting the survey was approximately 2 days of tweeting to targeted accounts, and then 2 days of no tweeting, alternating between the accounts. In the second 2 months, the posting occurred at least once a week to targeted accounts, alternating between the high - profile and low-profile strategy. Retweets from our own respective followers, and accounts not mentioned in the tweet post were also welcomed. For the majority of retweets received by targeted and nontargeted accounts, a reply tweet thanking the user was posted.

Analysis of Tweets

Twitter exposure data for each account were extracted using a Web-based Twitter analytics software program called Twitonomy. Twitonomy provides data on the date and time of each tweet, the composition of the tweet in terms of text, whether the tweet was a new tweet or a retweet, the platform from where the tweet was sent, the number of retweets a tweet received, and the number of favorites a tweet received. All this data can be downloaded in a Microsoft Excel sheet, over a set period, with each row in the datasheet representing a tweet. Data were downloaded and analyzed for each account separately. In the downloaded excel sheet, tweets not pertaining to the study were deleted. In addition, only tweets with the link to the survey included and where users where targeted were extracted for analyses (ie, tweets thanking users or conversational tweets about the study were excluded from the analyses). The tweet data captured in the downloaded excel sheet were validated by comparing it with the actual posted tweets for each account. Thereafter, the user(s) mentioned in each tweet were identified, and the number of followers of that user was recorded. This represented the potential reach of the tweet. If the tweet contained more than one user, the number of followers for each account mentioned was added up, and the total number of followers represented the potential reach of that tweet. The total potential reach equaled the sum total of the potential reach of each tweet. For tweets with no accounts mentioned, potential reach was recorded from the number of followers of the account posting the tweet. The number of retweets received by each post represented the actual reach of the tweet–as retweeted posts meant that the followers of the targeted account(s) would actually see the post on their timeline feed. The number of retweets received by each account was further analyzed in order to understand when the most likely time of day and day of the week a retweet would be received. To analyze time, the 24 hours of the day were categorized into periods of 6 hours, specifically 12 AM to 5:59 AM, 6 AM to 11:59 AM, 12 PM to 5:59 PM, and 6 PM to 11:59 PM. The date of the tweet was used to determine the day of the week.

Descriptive statistics are reported to compare potential reach, actual reach, and time and day of the week 'retweets' were received between the high-profile and low-profile strategy. In addition, a Student *t* test was used to compare potential reach and actual reach between the high-profile and low-profile strategy. Statistical significance was set at $P<.05$. For *t* test comparisons, the mean number of followers and standard deviations for each strategy are reported. Cohen's *d* effect sizes were calculated to determine the magnitude of the difference between the two strategies. Effect sizes of <0.2, 0.2-0.6, 0.6-1.2, and 1.2-2 were considered trivial, small, moderate, and large, respectively [15].

To determine the best strategy, and the most likely time of day and day of the week a retweet was received based on the number of posts, Poisson regression analyses was used. Poisson regression allows for the determination of the relationship between predictor variables (in this case, strategy, time of day, and day of the week) and the counts of events (outcome variable) while taking into account exposure (number of posted tweets).

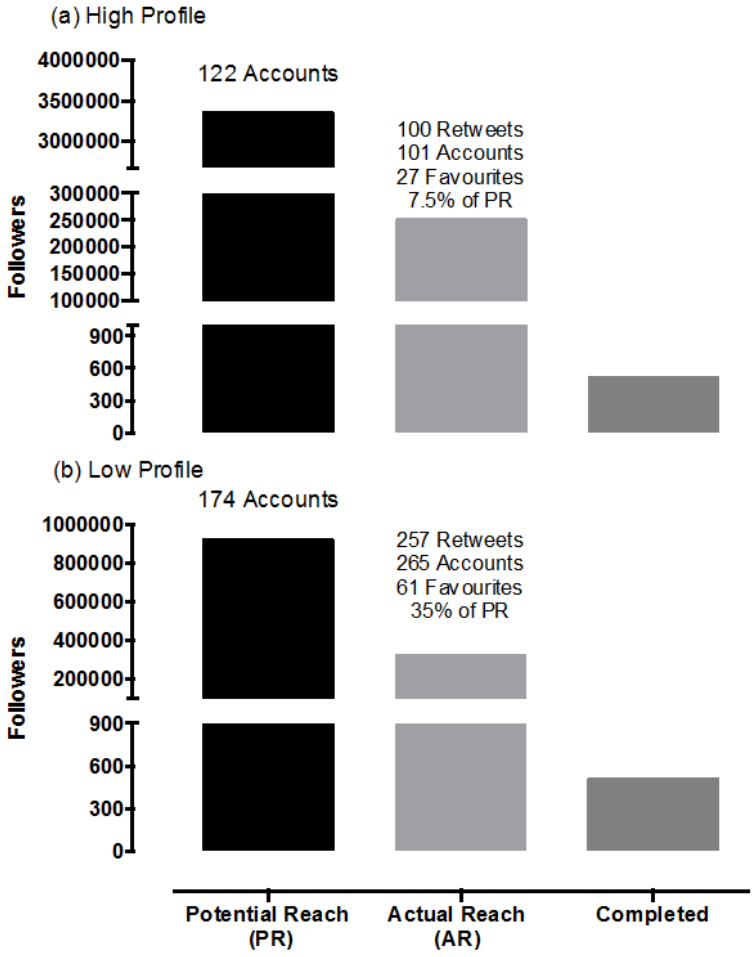
The outcome variable for this Poisson regression was number of retweets received. First, a Poisson regression model was performed for each predictor variable separately (ie, one for strategy, time of day, and day of the week). Thereafter, a model with time of day and day of the week as the predictor variables was adopted. The final model contained all three predictor variables in one model. To perform this analysis, predictor variables were computed relative to a referent or base variable. For strategy, the referent variable was the low-profile strategy; for time of day, the referent variable was 6 AM to 11:59 AM; and for day of the week, the referent variable was Thursday. Incidence rate ratio (IRR) and 95% confidence intervals (CI) were reported for each predictor variable. The standard interpretation for the Poisson regression model is that for a unit change in the predictor variable (relative to its referent variable), the incidence rate is expected to change by its respective parameter estimate (IRR), while holding all other variables in the model constant.

Results

Descriptive

Over 4 months, 507 questionnaires were completed. The primary involvements of the respondents are reported in Table 1. The high-profile strategy tweeted 146 posts (including 'thank you for retweets') and mentioned 122 accounts with a potential reach of 3,352,223 followers. The high profile strategy received 100 retweets from 101 accounts, which totaled an actual reach of 249,836 followers (Figure 1). This represented 7.5% (n=249,836) of the potential reach. Of the high-profile tweets, 27 were saved as favorites. In comparison, the low-profile strategy tweeted 164 posts (including 'thank you for retweets') and mentioned 174 accounts with a potential reach of 921,421 followers. The low - profile strategy received 257 retweets from 265 accounts, which totaled to an actual reach of 323,796 followers. This represented 35% of the potential reach. Of the low-profile strategy, 61 tweets were favorited. The high-profile strategy had a higher potential reach than the low-profile strategy (difference 2,430,802 followers), but the low-profile strategy had a higher actual reach (difference 73,960 followers).

Figure 1. The number of followers high profile and low profile accounts could potentially have reached, actually reached, and the number of followers that completed Web-based questionnaires.



High-Profile Strategy Versus Low-Profile Strategy

The potential reach of the high-profile strategy (27477±64819) was significantly different (*P*<.001) to the low-profile strategy (5295±9979), although the magnitude of this difference was small (effect size=0.52). On average, the actual reach of the high-profile strategy (2473±6686) was significantly different (*P*<.01) to the low-profile strategy (1221±2424). The magnitude of this difference however, was small (effect size=0.31).

Table 1. The primary involvements of the respondents to the Web-based survey (n=472).

Primary Involvement[a]	%	n
Player	46%	219
Former player (retired)	13%	59
Coach	13%	62
Referee/official	4%	19
Administrator	2%	8
Team manager	2%	9
Physiotherapist/athletic trainer	6%	30
Sports physician	1%	5
General practitioner	0%	1
Support staff (sports scientist, S&C coach, nutritionist, psychologist, analyst)	4%	18
Parent	3%	12
Other	6%	30

[a]35 respondents did not answer this question.

Poisson Regression

Predictor Variables Modelled Independently From Each Other

The number of retweets received by a Twitter account decreased by 56% when using the 'high- profile strategy' compared with the 'low-profile strategy' (IRR 0.44, 95% Cl 0.35-0.55, *P*<.001). For time of day, the number retweets received during 12 AM to 5:59 AM (IRR 1.08, 95% Cl 0.74-1.57, *P*>.05), 6 PM to 11:59 AM (IRR 1.03, 95% Cl 0.75-1.41, *P*>.05) did not significantly change compared with 6 AM to 11:59 AM. However, posting tweets during 12 PM to 5:59 PM, decreased the IRR for retweets by 34% (IRR 0.66, 95% Cl 0.51-0.85, *P*=.001) compared with 6 PM to 11:59 AM. The IRR was 3.30 (95% Cl 2.33-4.66, *P*<.001), and 1.48 (95% Cl 1.10-1.99, *P*<.01) times higher for retweets when posting on a Monday and Wednesday, respectively.

Time of Day and Day of the Week Model

When time of day and day of the week were factored into one model, posting tweets during 12 PM to 5:59 PM, decreased the IRR for retweets by 23% (IRR 0.77, 95% Cl 0.59-0.99, *P*<.05) compared with 6 AM to 11:59 AM. Monday (IRR 3.24, 95% Cl 2.27-4.62, *P*<.001) and Wednesday (IRR 1.50, 95% Cl 1.12-2.03, *P*<.01) remained the best days to post tweets.

Strategy, Time of Day, and Day of the Week Model

In the full model, the number of retweets received by a Twitter account decreased by 72% when using the 'high-profile strategy' compared with the 'low-profile strategy' (IRR 0.28, 95% Cl 0.21-0.37, *P*<.001). When taking into account strategy and day of the week, the IRR for the number retweets received during 12 AM to 5:59 AM (IRR 2.98, 95% Cl 1.88-4.71, *P*>.001) and 6 PM to 11:59 PM (IRR 1.48, 95% Cl 1.05-2.09, *P*>.05) increased relative to 6 AM to 11:59 AM. However, posting tweets during 12 PM to 5:59 PM, decreased the IRR for retweets by 40% (IRR 0.60, 95% Cl 0.46-0.79, *P*<.001) compared with 6 AM to 11:59 AM. Posting on Monday (IRR 3.57, 95% Cl 2.50-5.09, *P*<.001) or Wednesday (IRR 1.50, 95% Cl 1.11-1.11, *P*<.01) significantly increased the IRR compared with Thursday.

Discussion

Principal Results

The study yielded 4 main results: (1) this is the first study comparing the Web-based exposure of two Twitter strategies for Web-based surveying, (2) the low-profile strategy was more likely to receive retweets when the number of tweets was taken into account, (3) the time of day with the least potential to elicit retweets was between 12 PM and 5:59 PM, and (4) the day of the week with the highest potential to elicit retweets was a Monday and Wednesday.

High-Profile Strategy Versus Low-Profile Strategy

This is the first study comparing the social media exposure of two Twitter strategies for Web-based surveying. Twitter strategies for this study were based on the accounts each strategy targeted in a tweet. Although the high-profile strategy had a significantly higher mean potential and actual reach than the low-profile strategy, the magnitude of this difference was small. Furthermore, the low-profile strategy was more likely to receive retweets when the number of tweets was taken into account. High-profile Twitter accounts that are representative of a professional organization may be governed by the rules of the organization, and therefore less inclined to engage and retweet posts they are mentioned in. In contrast, low-profile Twitter

accounts may be more liberal in their Twitter engagement, and willing to share tweets for research purposes.

Time of Day and Day of the Week

The time of day with the least potential to elicit retweets was between 12 PM and 5:59 PM, and days with the highest potential to elicit retweets were a Monday and Wednesday. Interestingly, the time of day and the day of the week with the highest potential to elicit retweets in this study differ to the recommendations offered for business marketing. According to Zarrella [14], retweets for business marketing purposes are highest for tweets posted between 3 PM and 5 PM and on Thursdays and Fridays [14]. Although the results show that the potential to receive a retweet may differ throughout the day and on different days of the week, it should be acknowledged that Twitter has a global community across all time zones, and the dynamic and emerging nature of posting tweets and retweeting makes it difficult to recommend an exact time and day to post a Web-based survey. With that said, because this is the first study to explore the relationship between time and day of posting a Web-based survey on Twitter and its potential to elicit a retweet, the results reported here can be used as a guideline.

Determinants of Retweets

Retweeting, arguably, is the most important feature of Twitter, as this allows for the propagation of information. Retweeting is considered a behavior of selecting and diffusing information [16]. In view of this, a number of studies have been conducted to determine why Twitter users retweet certain posts compared with others [16-18]. Based on this work, determinants of retweeting can be divided into two categories–content and contextual [18]. In brief, content features relate to the composition of the tweet–whether the information in the tweet is positive, objective, or contains a verb or not. For example, Suh et al [18] showed that adding a link or hashtag to a tweet increases the probability of a retweet. Contextual features relate to the number of followers a user has, the trustworthiness of the user, the expertise of the user, and knowing information about one's followers. For example, Rudat et al [16] showed that users that knew more about their followers adapted their retweets to serve the needs or expectations of their followers. In light of the above literature, and considering both accounts in this study used similar content, some contextual differences between the 2 accounts used is this study may explain why the low-profile strategy was more likely to receive retweets.

Although personal accounts were used for posting tweets and administering the survey, the name of the account that executed the low-profile strategy is called 'Rugby Science', whereas the name of the account that executed the high-profile strategy was 'Stephen Mellalieu'–the author's name. Contextual features such as trustworthiness and expertise, based on the name of the account 'Rugby Science' may have influenced retweeting behavior, as this was a Rugby study. This highlights a caveat in the current study, but may offer a recommendation for future Web-based surveying (ie, align the name of the account posting the survey, to the area of study).

Limitations

Even though the objective of this study was achieved, we were unable to determine the relationship between the Twitter strategy used, and the number of completed questionnaires. The Twitter analytics software program used in this study was sufficient to analyze reach and retweet data. Presently, Twitter offers its own analytical services that allows for the analyses of the number of users that viewed and engaged with each tweet, and the number of users that click the link posted in a tweet (if a link is provided). Even though this will provide data on the number of users that clicked on the link to the survey, whether the user completed the questionnaire cannot be determined. For future work in this area, a potential solution to this limitation would be to add a question to the questionnaire, asking from which Twitter account was the link to the survey accessed. A final noteworthy limitation of this study is that the identity of each participant could not be verified. To address this limitation, contact details of the participant's current club or team should be obtained in the survey, and subsequently contacted to verify their identity.

Conclusion

Surveys are a useful tool to measure the knowledge, attitudes, and behaviors of a given population. As a recruitment tool, social media provides researchers with an efficient means to reach and engage with a large and diverse audience in a short period of time. Moreover, it is relatively low cost to administer and maintain. Twitter allows for the virtual social interaction among a network of users that enables researchers to recruit and administer Web-based surveys using the snowball sampling method. Strategies to improve Twitter engagement include, targeting low-profile accounts, posting tweets in the morning (12 AM-11:59 AM) or late evenings (6 PM-11:59 PM), and posting on Mondays and Wednesdays.

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Authors' Contributions

SH was part of conceptualizing the study, collected data, and led the write-up of the study. SM was part of conceptualizing the study, collected data, and edited the manuscript. PD assisted in analyzing the data, and editing.

Conflicts of Interest

None declared.

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Abbreviations

CI: confidence interval
IRR: incidence rate ratio

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Original Paper

Use of Web 2.0 Social Media Platforms to Promote Community-Engaged Research Dialogs: A Preliminary Program Evaluation

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Abstract

Background: Community-engaged research is defined by the Institute of Medicine as the process of working collaboratively with groups of people affiliated by geographic proximity, special interests, or similar situations with respect to issues affecting their well-being. Traditional face-to-face community-engaged research is limited by geographic location, limited in resources, and/or uses one-way communications. Web 2.0 technologies including social media are novel communication channels for community-engaged research because these tools can reach a broader audience while promoting bidirectional dialogs.

Objective: This paper reports on a preliminary program evaluation of the use of social media platforms for promoting engagement of researchers and community representatives in dialogs about community-engaged research.

Methods: For this pilot program evaluation, the Clinical and Translational Science Office for Community Engagement in Research partnered with the Social Media Network at our institution to create a WordPress blog and Twitter account. Both social media platforms were facilitated by a social media manager. We used descriptive analytics for measuring engagement with WordPress and Twitter over an 18-month implementation period during 2014-2016. For the blog, we examined type of user (researcher, community representative, other) and used content analysis to generate the major themes from blog postings. For use of Twitter, we examined selected demographics and impressions among followers.

Results: There were 76 blog postings observed from researchers (48/76, 64%), community representatives (23/76, 32%) and funders (5/76, 8%). The predominant themes of the blog content were research awareness and dissemination of community-engaged research (35/76, 46%) and best practices (23/76, 30%). For Twitter, we obtained 411 followers at the end of the 18-month evaluation period, with an increase of 42% (from 280 to 411) over the final 6 months. Followers reported varied geographic location (321/411, 78%, resided in the United States); 99% (407/411) spoke English; and about half (218/411, 53%) were female. Followers produced 132,000 Twitter impressions.

Conclusions: Researchers and community stakeholders use social medial platforms for dialogs related to community-engaged research. This preliminary work is novel because we used Web 2.0 social media platforms to engage these stakeholders whereas prior work used face-to-face formats. Future research is needed to explore additional social media platforms; expanded reach to other diverse stakeholders including patients, providers, and payers; and additional outcomes related to engagement.

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KEYWORDS

Web 2.0; social media; platforms; analytics; community; engagement; stakeholders; WordPress; Twitter; Facebook

Introduction

Community Engagement

A 2013 Institute of Medicine report [1] report highlighted the need to promote the engagement of diverse patients, community representatives, and other stakeholders as active partners in the full spectrum of translational research. Community engagement expands research beyond the scientist-participant context by creating opportunities for meaningful, collaborative, trusting partnerships with researchers and diverse members of the community including but not limited to study participants. Community-engaged research is defined as "the process of working collaboratively with groups of people who are affiliated by geographic proximity, special interests, or similar situations with respect to issues affecting their well-being" [2]. This definition of community engagement serves as the starting place to consider novel ways to engage those interested in biomedical research. Traditional community engagement involves face-to-face outreach such as attendance at health fairs [2]. This process is restricted by geographic location and limited resources and is often characterized as a one-way communication channel. Recent approaches such as science cafes and engagement studios promote bidirectional dialogs between researchers and community members but are limited to face-to-face communication formats [3-5]. These formats promote engagement by facilitating dialogs about health needs of communities, and in turn, researchers bring perspectives on current work that addresses these needs (ie, colearning). However, community engagement biomedical research teams need new communication methods to reach and engage a larger audience. Virtual online communities could also be developed and fostered to promote community engagement [1,6-8]. This paper reports on the preliminary evaluation of the use of social media platforms for promoting engagement of researchers and community representatives in bidirectional dialogs. This work is innovative for engaging community members and researchers in dialogs using online social media platforms and has not been done previously.

Web 2.0 Technologies

Web 2.0 transformed health communication patterns. Web 2.0 refers to a collection of electronic, Web-based applications and technologies that "facilitate interactive information sharing, user-centered design and collaboration" [9]. Web 2.0 technologies encompass a large class of information and technological tools, including blogs and social networking sites. Web 1.0 Internet-based technologies are limited to the passive viewing of content created by others [9]. In contrast, through Web 2.0 technologies users can interact and collaborate with each other in a social media dialog as cocreators of user-generated content in a virtual community. With their high level of interactivity, Web 2.0 technologies have potential for increasing the depth and reach of engagement among stakeholders [10].

Web 2.0 Social Media Platforms

Social media tools include blogging, microblogging, social networks, and curation [11]. For example, WordPress is a free, open-source blogging tool that allows users to create webpages. Over 60.1 million new posts with 61.5 million new comments appear each month, leading to the creation of 19.1 billion pages with 409 million views [12]. Twitter offers users a different type of blogging experience called microblogging. Twitter has 288 million active monthly users with 500 million Tweets (microblogs) posted per day in more than 33 different languages [13]. Facebook, another popular social networking tool, has 936 million active users daily with 1.44 billion active monthly users [14]. Diverse individuals use social media including racial/ethnic minorities and those aged 65 years and older [15,16]. From two community health needs assessments jointly conducted by Mayo Clinic and public health partners in 2014 [17] and 2016 [18] we learned that community members prefer to receive information about health and research through social media platforms . In addition, social media platforms such as Twitter are used by researchers. As early as 2007, 77% of life scientists reported they used social media and, of these, 85% said these communications impacted their decision making [19,20].

Objective

The Center for Clinical and Translational Science's Office for Community Engagement in Research partnered with the Social Media Network at Mayo Clinic to develop and implement a social media communication plan to promote community engagement at our institution. The initial target stakeholder audiences for the social media communication plan were researchers and community representatives. Consistent with the Institute of Medicine report [1], we wanted to support and promote the use of community engagement by the workforce (ie, researchers). In addition, we targeted community representatives to increase public support for research to improve population health. For this pilot program evaluation, we created and evaluated the use of two social media platforms, Twitter and a WordPress blog, for engaging researchers and community representatives in online dialogs and community engagement educational curricula. If these platforms showed promise, our long-term goal was to develop an extensive social media plan with additional applications (eg, Facebook, Storify, and podcasts) [14,21,22], expanded targeted stakeholder

audiences (eg, providers, payers, policy makers) [1,15], and engagement outcomes. This paper describes a preliminary program evaluation of the use of social media tools to engage researchers and community representative stakeholders.

Methods

Target Audience/Stakeholders

The audience or stakeholders targeted in this pilot program evaluation were researchers and community representatives (ie, the public). Researchers were targeted broadly along the full spectrum of clinical and translational science.

Developing the Social Media Platforms

A key feature of our social media plan involved ensuring ease-of-use of the social media tools we selected. We took into account the Centers for Disease Control and Prevention recommendations for developing health communications [23] and specifically for engaging stakeholders through social media platforms [24] that suggested blogs and Facebook for our target audiences. We developed a WordPress blog but chose to also use Twitter based on our Mayo Clinic Social Media Network's experience with engaging providers, researchers, and patients at our institution on health topics through this platform [15]. Blogs and Twitter forums have been successful elsewhere for connecting patients, physicians and other healthcare providers, patient and family advocacy groups, and researchers to discuss topics of interests [25].

The social media integration framework [26] provided the conceptual basis for developing the blog and Twitter social media platforms. Based on this conceptual framework, social media changes the traditional communication process through (1) exposure, (2) feedback, (3) connection, and (4) exchange. *Exposure* involves providing information to users—a blog posting by a researcher about an upcoming community outreach event, for example. While exposure begins the process of engagement, it is limited to single one-way sources of communication typical of Web 1.0 technologies. *Feedback* involves two-way communication such as a community representative responding or commenting on a researcher's blog posting based on past experiences, opinions, and perceptions. *Connection* involves new users dialoging with one another (ie, third parties) through, for example, tweets and retweets. Finally, *exchange* involves sharing through posting of pictures, stories, testimonials, videos, podcasts, and other forms of media based on user or consumer-generated content. Sharing through stories or testimonies has been found to enhance emotional engagement and attentional focus of social media users [8]. The processes of connection and exchange promote sustainability of social media platforms [26]. Using this conceptual framework, the information flowing is not limited to one way in which stakeholders only receive messages but instead is an interactive process that places stakeholders in the center on an equal level of information exchange. This allows opportunities for bidirectional dialogs or two-way communication for community engagement using virtual communities.

WordPress Blog

We created a WordPress blog in the spring of 2014 to increase our Web presence allowing for dynamic interactions between researchers and stakeholders [27]. The blog serves as an information hub (exposure) to explain how we engage the community in research. It allows us to archive posts in an easily accessed way for our audiences. At least two blogs are posted per week.

In addition to traditional blog posts allowing for exposure (information flow), feedback, and connecting, the WordPress site contains opportunities for sharing via video testimonials and podcasts, links to Mayo Clinic research resources, and information on how to register for educational training opportunities. Testimonials were provided by researchers conducting community-engaged research at Mayo Clinic and elsewhere. Other testimonials were sought such as a community research partner explaining the benefits of participating in research. The links to Mayo Clinic resources related directly to connecting Mayo Clinic investigators with community-engaged research liaisons available to provide mentoring and support to help study teams increase their level of engagement. Another resource available through the blog is access to the Community Engagement in Research Advisory Board. This community advisory is made of 15 community members and seeks to ensure that research conducted by and with Mayo Clinic fits the needs of the larger community. The blog also serves as portal to online educational opportunities for researchers and community to increase awareness on the principles and best practices of community engagement.

Twitter

Twitter is an online social networking service that enables users to send and read short 140-character messages called Tweets [13]. Users can read and post Tweets. Twitter involves all of the processes by which social media can increase communication including exposure, feedback, connecting and sharing. We created a Twitter account (@mayoclinic_cenr) in August 2014 to connect researchers and stakeholders. Our research staff does purposeful microblogging to raise awareness of community-engaged research. Our staff uses the account to do live Tweets from conferences and community events. We also participate in Twitter chats hosted by other stakeholders and share newly published research and other resources related to community-engaged research.

Social Media Facilitation

The research team developed and implemented a plan for WordPress blog postings and Tweets and identified a social media manager to facilitate the plan. The facilitator is bilingual (Spanish and English) and has a degree in business. This individual received training in social media development, facilitation, and analytics by the Mayo Clinic Social Media Network. The facilitator worked with the Network, other faculty, and staff to develop social media guidelines consistent with the overall social media plan at Mayo Clinic [15]. Guidelines for blog posts and Tweets are as follows: (1) post new blogs and Tweets at least once per week, (2) when attending a live event Tweet during the event to show active engagement, (3) have

planned Tweets to send in the morning related to providing information to the followers on community engagement activities, (4) create a hashtag for the use of all social media activities (#EngagementTheNorm), (6) review and repost content from other community engagement stakeholders, and (7) stay connected with internal stakeholders relating to their needs on community-engaged research to provide updates on our research activities to the broader community. Other members of our research team posted Tweets and Blog posts as appropriate.

Content Selection

Content for the blog and Twitter related directly to the overall capacity-building goals of our research program. These goals include increase awareness and sharing of community-engaged and collaborative research activities, develop best practices on community-engaged research in biomedical research, encourage community members and stakeholders to participate in online training on community engagement, and provide opportunities to connect around topics of shared interests to make community engagement the norm in biomedical research. These areas remained in the fore when determining the most appropriate content to share. We connected with existing collaborative partners (researchers and community members) to share information from their social media platforms and newsletters on topics of interests to our followers. This level of dynamic community engagement with other collaborative partners generated more traffic to our social media platforms.

Promotion of the Social Media Platforms

The WordPress blog and Twitter account were promoted through the Office of Community-Engaged Research website, Mayo Clinic Public Affairs website for our Clinical and Translational Service Award, Mayo Clinic Social Media Network, colleagues from the community, and peers at other academic-medical centers.

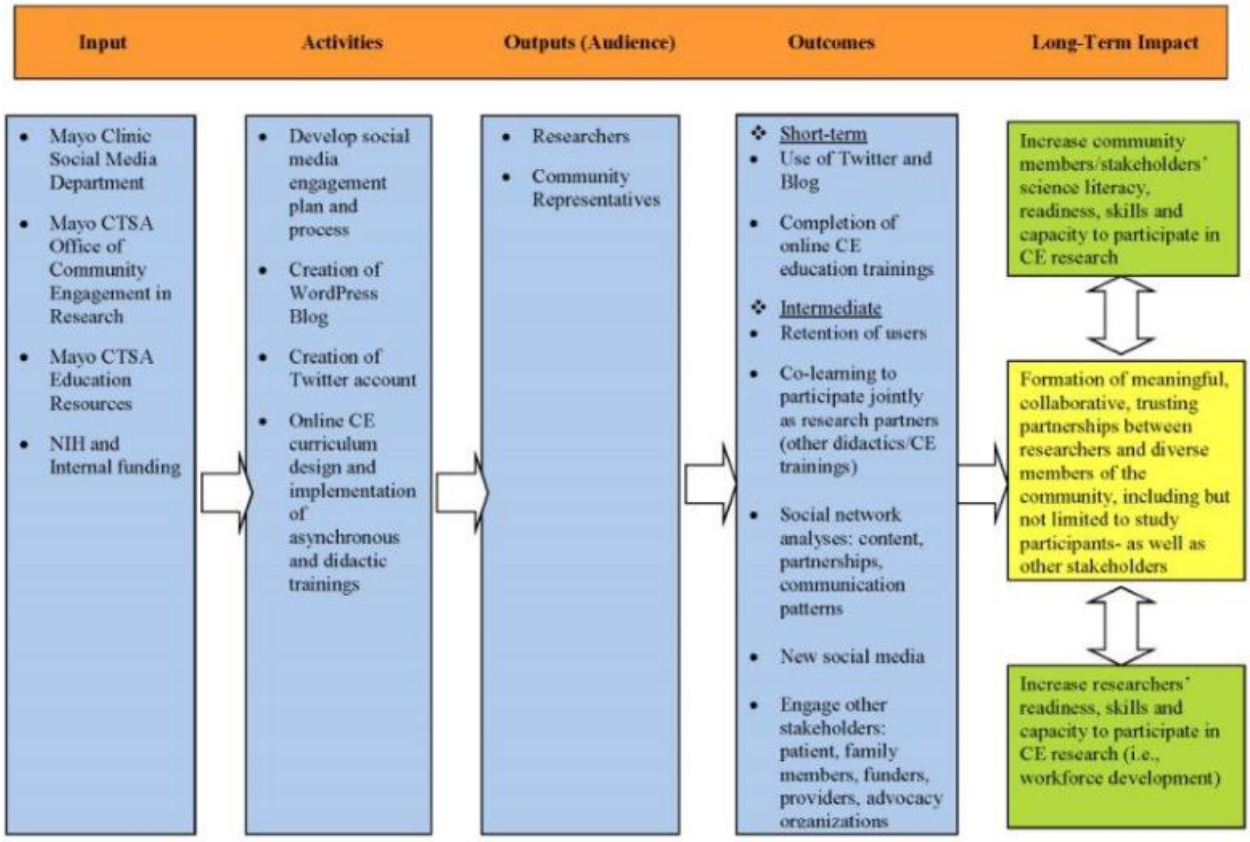
Evaluation Framework

In this preliminary evaluation we sought to summarize the use of our social media platforms as the initial step in evaluating engagement of our targeted audience. Figure 1 presents a logic model for the potential impact of social media platforms on engagement, including short, intermediate, and long-term outcomes. Proximate outcomes include use of Twitter and the blog and enrollment in our online community engagement educational curriculum among both stakeholder audiences targeted. Intermediate outcomes include increasing skills among both community representatives and researchers to build capacity for jointly conducting community-engaged research as equal partners [1]. Long-term outcomes include formation of meaningful, collaborative and trusting partnerships between researchers and diverse members of the community, including but not limited to study participants.

For this initial pilot program evaluation, a number of descriptive analytics were implemented to summarize the use of our social media platforms. Each was evaluated over an 18-month period (2014-2016). We used blog post tracking to assess use of the WordPress blog and type of user (community representative, researcher, or other). Content analysis [28] was used to generate the major themes from blog postings. Coding was done jointly by authors MVS and JBB until consensus was reached.

We used standard Twitter Analytics to determine use of this social media platform [13]. Basic Twitter Analytics are free and are linked and downloaded directly from an established Twitter account. Analytics downloaded were: (1) impressions (the number of times a user may see a tweet), engagements (the number of times a person interacts with a tweet), engagement rate (number of engagements divided by the number of impressions), and other methods of interactions with tweets such as retweets, replies, likes, user profile clicks, URL clicks, and hashtag clicks. A limited set of demographics was also available from Twitter Analytics. Data from Twitter Analytics was downloaded to an Excel spreadsheet. We used the data analysis software SPSS version 22 to calculate means and standard deviations (SDs) for selected Twitter activities.

Figure 1. Evaluation framework.



Results

WordPress Blog

Over an 18-month period, we created 76 blog posts. Two-thirds of the posts were from researchers (48/76, 64%). Postings from the community represented 32% (23/76) and funders represented 8% (5/76) of all posts. From content analysis of blog postings, five themes emerged. Table 1 presents themes from the blog. The predominant theme was community-engaged research awareness and dissemination (35/76, 46%). This theme related to increasing knowledge about and findings from community-engaged research. Best practices posts (23/76, 30%) related to lessons learned about how to increase community engagement in research. Overall awareness of community engagement posts included information presented from other community engagement sources and the blogging community (15/76, 20%). Education and training posts (9/76, 12%) were linked to the creation of the new online curriculum on community engagement offered by Mayo Clinic. Community engagement events (9/76, 12%) increased awareness of activities that stakeholders could participate in either online (webinars) or in a local community. Fourteen video testimonials related to community-engaged research projects funded internally and by external partners were also posted on the blog, spanning multiple themes.

Table 1. WordPress blog themes from 76 postings over an 18-month period (2014-2016).

Blog theme	n (%)[a]	Illustrative content
Research awareness and dissemination	35 (46)	Title of post (testimonial from a community partner, see Multimedia Appendix 1): What to do and what to avoid when doing outreach.
Best practices	23 (30)	Title of post (from a researcher, see Multimedia Appendix 2): How do you address community's needs if they are different than your original project?
Overall awareness	15 (20)	Title of post (Mayo podcast [29,30], see Multimedia Appendix 3): How to navigate health care.
Education and training	9 (12)	Title of post (from a researcher, see Multimedia Appendix 4): A New Year's resolution you can accomplish!
Events	9 (12)	Title of post (from a community representative, see Multimedia Appendix 5): Mark your calendar if you want to outreach to the Latino community –Partnership with Alliance of Chicanos Hispanics and Latin Americans.

[a]Percentages do not equal 100 as some postings reflected multiple themes and categories are not exclusive.

Twitter

At the start of the evaluation period we had no followers. Over an 18-month period, we acquired 411 followers, with one new follower added nearly daily. From 12 to 18 months, we increased the number of followers by 42% (from 240 to 411). Table 2 presents selected demographics of the 411 followers.

Table 2. Selected demographic characteristics of Twitter followers (N=411) over an 18-month period (2014-2016).

Characteristic		n (%)[a]
Gender identity		
	Female	218 (53.0)
	Male	193 (47.0)
Language		
	English	407 (94.2)
	Spanish	16 (3.7)
	French	3 (<1.0)
	Portuguese	3 (<1.0)
	Arabic	3 (<1.0)
Country		
	United States	321 (78.1)
	Canada	25 (6.1)
	United Kingdom	8 (1.9)
	Australia	8 (1.9)
	Mexico	5 (1.2)
North American region		
	Minnesota	103 (32.1)
	Florida	16 (5.0)
	California	13 (4.0)
	Illinois	13 (4.0)
	New York	10 (3.1)
	Ontario, CA	10 (3.1)
	Massachusetts	10 (3.1)
	Virginia	6 (1.9)
	Wisconsin	6 (1.9)
	Pennsylvania	6 (1.9)
Top interests		
	Business and news	292 (71.0)
	Health, mind, and body	284 (69.1)
	Politics and current events	267 (65.0)
	Science news	263 (64.0)
	Biotech and biomedical	230 (56.0)
	Tech news	230 (56.0)
	Technology	185 (45.0)
Device type		
	Desktop or laptop computer	325 (79.1)
	iOS device	185 (45.0)
	Android device	95 (23.1)

[a]For some categories, percentages do not equal 100 due to multiple responses being possible.

Table 3. Twitter use (N=411) for an 18-month period (2014-2016).

Twitter Analytics	Mean (SD)
Impressions	184.29 (734.36)
Engagements	4.05 (6.58)
Engagement rate	0.27 (0.33)
Retweets	0.42 (1.00)
Replies	0.14 (0.48)
Likes	0.58 (1.02)
User profile clicks	0.36 (0.83)
URL clicks	0.56 (1.50)
Hashtag clicks	0.15 (0.56)

Table 3 shows the level of interactions with the Twitter microblogs and our followers. Followers produced 132,000 Twitter impressions.

Twitter followers were engaging with our content with new discussions/topics generated. Although we did not systematically collect content data for Tweets, examination of some of the topic areas indicated a health focus—cancer, diabetes, blood pressure, substance use, and mental health—and information on upcoming community outreach events addressing these health topics.

Preliminary Impact of Social Media on Engagement With Online Community Engagement in Research Curriculum

Twitter was used to promote free educational training opportunities on community-engaged research offered by our research team that were hosted on the WordPress blog. We tweeted when new trainings were available on the blog. As noted above, the blog apparently served to increase awareness of our community-engaged research educational online curriculum (Table 1). Twitter was also used to promote this free online curriculum that was offered to community members and researchers. In February 2015, we had 40 learners complete this online training. After that time, we increased promotion of these trainings by creating a Tweet pin and promoting our educational opportunities during Tweet chats. At the end of the 18-month evaluation period, our learner base more than tripled with 182 learners. Of these learners, 19 were community members and 163 were researchers.

Discussion

Principal Findings

Increasing attention has focused on engagement of stakeholders to enhance research translation [1,2]. This preliminary program evaluation examined if researchers and community representatives would use social media platforms to dialog and interact around community-engaged research. The main finding was that researchers and community stakeholders use social media platforms to engage in dialogs. We were able to engage with these stakeholders by posting at least two blogs per week and more frequent Tweets. A potential concern was that only researchers would use these platforms, but about one-third (23/76, 32%) of the blog postings were from community representatives. It should also be noted that from Twitter Analytics (Table 2), the main interests of our followers were business and news; health, mind, and body; and politics and current events. Prior studies used traditional forms of community engagement between researchers and stakeholders including face-to-face outreach [2-5]. These strategies are limited by available resources and geographic location. Our findings are innovative because we used social media platforms to promote discussions between researchers and community representatives with a large geographical reach. Using Twitter Analytics gave us a bit of insight on our audience of Twitter followers that might use social media platforms to dialog about community-engaged research. Of note, we attracted a geographically diverse audience from the United States and other countries which speaks to the potential reach of Web 2.0 technologies for community-engaged research. Through content analysis we explored the types of information exchange on the blog which produced novel data, particularly with respect to increasing knowledge about and findings from community-engaged research. Benefits our staff observed were that the social media platforms provided a new method for dissemination of research findings, raised awareness of scientific leaders in community-engaged research, and helped develop a core network of diverse communities communicating about health research. Our preliminary results further indicate that social media platforms can potentially impact engagement of community members and other stakeholders in online community engagement educational trainings.

Limitations

A key limitation to our work was the use of Twitter and WordPress analytics. The demographic data are extremely limited in scope, and we are not able to examine some areas of interests and trends beyond basic awareness of our posts. In particular, we did not assess the racial/ethnic or socioeconomic characteristics of our blog users or Twitter followers. Moreover, although we were able to assess the type of blog user (eg, researcher, community representative, or other stakeholder), we did not collect these data for our Twitter followers. We did not determine what type of researchers across the full spectrum of clinical and translational science engaged with the social media. We are therefore unable to compare our samples with general population characteristics to assess representativeness.

Another drawback: the WordPress blog readers did not post comments on the blog posts although this feature is available. We also made it possible for blog readers to contact us directly with feedback and suggestions. However, these features were not specifically promoted, which could have helped to increase dynamic engagement with our Web 2.0 social media platforms [31]. Information was not available on number of Twitter followers over various time intervals that would have allowed us to examine trends in the data, although we did observe a 42% increase in the number of followers over the final 6 months after creating the Twitter account. We did not assess if we retained users or long-term engagement [6]. Furthermore, we did not obtain complete data on the content of Tweets which would have provided useful information on the types of dialogs engaged in by various stakeholders. Encouragingly, a limited evaluation of some of the Tweet content generated indicated a health and wellness focus and sharing of upcoming information on community outreach events addressing health topics.

Another limitation is that we did not vary engagement activities in a clear experimental framework. Moreover, we do not have baseline data from which to compare our results. In addition, this preliminary evaluation is limited by the use of only two social media platforms, and other very popular technologies exist such as Facebook. Another drawback is that we only targeted specific stakeholders of researchers and community representatives. Moreover, resources were limited for promoting the use of the social media platforms to researchers and the community and thus their potential use may be underestimated.

Future Directions

This work suggests several directions for future research. We plan to extend the reach of our approach by using additional social networking tools such as Facebook, Instagram, and podcasts. We will utilize innovative platforms including crowdsourcing to assess public views on research topics as a form of engagement. Moreover, we plan to use tools such as Storify.com to moderate social media–based conversations related to community-engaged research. Future research is also needed to expand the targeted stakeholder audiences to patients, providers, and payers [1,15]. To extend the reach of our social media platforms for community-engaged research, creative and targeted efforts are needed to reach racially and socioeconomically diverse stakeholders. We will develop an integrated communications plan which is essential to promoting community-engaged research [32]. Future promotions such as flyers and billboards will include a QR code linking to the social media platforms. As a preliminary evaluation, our purpose was to engage researchers and community representatives in discussions about community-engaged research. Future research might select specific populations with known sociodemographics and measure engagement with social media platforms, comparing demographics of those who use the applications versus those who do not.

Our platforms were nondirective, and certain topics or questions such as health needs among community representatives were not explored. One study of a Twitter-based intervention for smoking cessation [33] used a hybrid approach combining a traditional social media approach of spontaneous, real-time automated messages that encouraged discussions of focused topics with online community building [6,7], promoting sustainability. This approach could be evaluated in future evaluations.

Our preliminary results suggest that the potential impact of social media to promote engagement of community members and other diverse stakeholders in community engagement educational trainings needs further evaluation. We now have a baseline level of participation in our online community engagement educational curriculum using Twitter and the blog; future evaluations can test impact of different social media platforms and promotion strategies. In particular, we need to expand our efforts to promote our education and training in community-engaged research among community members.

Studies are warranted to evaluate use of social media platforms for impact on outcomes specified in Figure 1. Survey research is needed to assess retention of users and long-term engagement [6]. Furthermore, the application of social network analysis is a promising and innovative approach for assessing engagement outcomes in future work [6]. Social network analysis could be used to examine trends in the content of the social media dialogs, demonstrate relationships and connections between members (eg, influential users, patterns of communication), and identify gaps in our communication plan for reaching diverse groups of community representatives and researchers.

Conclusion

In conclusion, researchers and community member stakeholders use social media platforms for dialogs related to community-engaged research. Moreover, social media platforms could engage these stakeholders to participate in community engagement educational trainings. Based on this preliminary program evaluation, Web 2.0 technologies hold great promise for engaging stakeholders in clinical and translational science research.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

What to do and what to avoid when doing outreach.

[JPG File, 66KB - resprot_v5i3e183_app1.jpg]

Multimedia Appendix 2

How do you address community's needs if they are different than your original project?

[JPG File, 52KB - resprot_v5i3e183_app2.jpg]

Multimedia Appendix 3

How to navigate health care.

[JPG File, 34KB - resprot_v5i3e183_app3.jpg]

Multimedia Appendix 4

A New Year's resolution you can accomplish!

[JPG File, 61KB - resprot_v5i3e183_app4.jpg]

Multimedia Appendix 5

Mark your calendar if you want to outreach to the Latino community –Partnership with Alliance of Chicanos Hispanics and Latin Americans.

[JPG File, 55KB - resprot_v5i3e183_app5.jpg]

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Abbreviations

SD: standard deviation

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Corrigenda and Addenda

Acknowledgements Correction of: Using Behavioral Intervention Technologies to Help Low-Income and Latino Smokers Quit: Protocol of a Randomized Controlled Trial

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The authors of "Using Behavioral Intervention Technologies to Help Low-Income and Latino Smokers Quit: Protocol of a Randomized Controlled Trial" (JMIR Res Protoc 2016;5(2):e127) would like to change the Acknowledgements section of their paper to the following:

"This project was partially supported by funds provided by The Regents of the University of California, Tobacco-Related Diseases Research Program, Grant Number No. 24RT-0027. The opinions, findings, and conclusions herein are those of the authors and not necessarily represent those of The Regents of the University of California, or any of its programs.

Programming and development of the web app for this project is being carried out by the Center for Behavioral Intervention Technologies at Northwestern University Feinberg School of Medicine."

The originally published acknowledgement has only the first sentence.

This correction has been made in the online version of the paper on the JMIR Research Protocols website on September 23, 2016, together with publishing this corrigendum.

A correction notice has been sent to PubMed, and the publication was resubmitted to Pubmed Central and other full-text repositories.

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Corrigenda and Addenda

Addendum to: Can Internet-Based Sexual Health Services Increase Diagnoses of Sexually Transmitted Infections (STI)? Protocol for a Randomized Evaluation of an Internet-Based STI Testing and Results Service

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Following the advice of the Trial Steering Committee, the authors of "Can Internet-Based Sexual Health Services Increase Diagnoses of Sexually Transmitted Infections (STI)? Protocol for a Randomized Evaluation of an Internet-Based STI Testing and Results Service" (JMIR Res Protoc 2016;5[1]:e9) are adding additional information about their primary and secondary analyses, as well as their respective outcomes, to provide readers with more details on the study.

Primary Analysis

For the primary analysis we will use multivariate imputation using chained equations (MICE) which uses the observed predictors of outcome and the predictors of loss to follow up to impute missing outcome data, thus attempting to correct for any potential bias caused by missing data under the assumption that data are 'missing at random'.

Missing data will occur if:

1. Participants do not complete a 6-week follow up questionnaire (or submit an incomplete questionnaire), and attend a different health service (ie, not a clinic in Lambeth and Southwark or SH:24).
2. Participants who report testing for an STI but whose patient records we are unable to access (because they did not test in a clinic in Lambeth or Southwark or SH24 and they did not tell us where they tested so we were unable to obtain data from the clinic where they were tested).
3. Participants who are diagnosed with an STI but there is no record of them attending any clinic in Lambeth and Southwark for treatment and they did not tell us where they obtained treatment so we were unable to obtain data regarding whether or not they were treated.

We will impute each of the incomplete outcome variables using multivariate imputation using chained equations. Sexuality is also incomplete but is a baseline variable, so a missing category will be used. The propensity score for randomised allocation will be estimated for all participants using a logistic regression model with randomised group as the response, and gender, age

(years), number of sexual partners in the last 12 months, sexual orientation and ethnicity as covariates. The imputation model will then contain randomised group as a covariate and will be weighted by the inverse of the estimated propensity score. The imputation model for any incomplete variable will then condition on other incomplete variables. In particular, the conditional model to impute testing according to clinic data will include self-reported testing; and the model to impute treated STI will include diagnosis of STI. One hundred imputed datasets will be generated. Multiple imputation inference will then proceed via Rubin's rules [1].

We will account for baseline factors (gender, age, number of sexual partners in last 12 months, sexuality and ethnicity) by weighting on the inverse propensity score, which we will estimate by logistic regression. This will allow us to obtain more precise estimates and confidence intervals with the correct coverage.

Secondary Analyses

Sensitivity to Missing Outcome Data

We will perform a sensitivity analysis to explore departures from MAR assumptions. We will multiply impute missing outcome data, using inverse probability weighting on the estimated propensity score and with allocated group and whether or not participants report having been tested as covariates. The odds of STI diagnosis and the odds of a completed STI test for missing participants will be varied to be ¼, ½, 2 and then 4 times larger than the MAR analyses.

The risk difference and risk ratios weighted by inverse propensity score will be reported alongside proportions.

Subgroup Analyses

In order to explore heterogeneity of the intervention effect on our primary outcomes, we will test for interaction at a 5% level of significance to assess whether effectiveness varies by:

- Gender
  - Male
  - Female
- Ethnicity
  - White
  - Asian/Asian British
  - Black/African/Caribbean/Black British
  - All other groups (Mixed/Multiple ethnic groups/Other ethnic group)
- Sexuality
  - Men who have sex with men
  - All other groups
- Age group
  - 16-19 years
  - 20-24 years
  - 25-30 years
- Control group
  - Time period when SH:24 website available exclusively to intervention group participants
  - Time period when SH:24 website unblocked

We will test for linear interaction for deprivation (centiles of overall UK Indices of Multiple Deprivation ranks) using a log binomial model. These analyses will be conducted in the complete cases under a missing-at-random assumption. As with the primary analyses, they will be weighted by the inverse of the estimated propensity score. When a subgroup variable is one that appears in the propensity score (defined above), we will re-estimate the propensity score omitting the subgroup variable.

Intervention effect estimates by subgroups will be presented in a forest-type plot. Given that the study is not powered to test for interactions, these analyses will be treated as exploratory and the statistical significance of the interactions will be interpreted with caution.

Secondary Outcomes

The primary analysis of the following secondary outcome will follow the same principles as the analysis of our co-primary outcomes described above:

- The proportion of participants who are prescribed treatment in each arm

For our time-to-event secondary outcomes we will conduct the following analyses:

We will use survival analysis to estimate time from randomisation to (1) test completion and (2) treatment. For each measure we will estimate the restricted mean survival time (RMST) setting the restricted mean time t*=6 weeks (42 days) for time to test and t*= 3 months (84 days) for time to treatment.

This will be estimated from a "3df/1df" Royston–Parmar model and the difference in restricted mean survival time will be estimated.

Process Outcomes

For the following process outcomes we will summarise:

- The proportion of STI tests taken that are positive in each arm
- The median survival time from diagnosis to treatment in each arm
- The proportion of the intervention group who deem the intervention to be acceptable
- The proportion of the intervention group who adhere to an appropriate testing pathway
- The proportion of participants who complete an STI test, by service type
- The proportion of participants who are diagnosed with an STI, by service type

These estimates will be summarised by arm but there will be no comparison of groups.

Acceptability will be constructed as a binary variable, derived from 4 questions. A score of 8 will be coded as 1 (acceptable); a score <8 will be coded as 0 (not acceptable).

Did you feel that your personal information was kept confidential by this service?

A. Yes (2), B. Yes to some extent (1) C. No (0)

Did you have trust in the clinical expertise of this service

A. Yes (2), B. Yes to some extent (1) C. No (0)

Would you use this service again if you needed to?

A. Yes definitely (2) B. Yes, probably (1) C. No (0)

Would you recommend this service to a friend?

A. Yes definitely (2) B. Yes, probably (1) C. No (0)

Reference

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Protocol

Designing an Adverse Drug Event Reporting System to Prevent Unintentional Reexposures to Harmful Drugs: Study Protocol for a Multiple Methods Design

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Abstract

Background: Adverse drug events (ADEs) are unintended and harmful events related to medication use. Up to 30% of serious ADEs recur within six months because culprit drugs are unintentionally represcribed and redispensed. Improving the electronic communication of ADE information between care providers, and across care settings, has the potential to reduce recurrent ADEs.

Objective: We aim to describe the methods used to design Action ADE, a novel electronic ADE reporting system that can be leveraged to prevent unintentional reexposures to harmful drugs in British Columbia, Canada.

Methods: To develop the new system, our team will use action research and participatory design, approaches that employ social scientific research methods and practitioner participation to generate insights into work settings and problem resolution. We will develop a systematic search strategy to review existing ADE reporting systems identified in academic and grey literature, and analyze the content of these systems to identify core data fields used to communicate ADE information. We will observe care providers in the emergency departments and on the wards of two urban tertiary hospitals and one urban community hospital, in one rural ambulatory care center, and in three community pharmacies in British Columbia, Canada. We will also conduct participatory workshops with providers to understand their needs and priorities related to communicating ADEs and preventing erroneous represcribing or redispensing of culprit medications. These methods will inform the iterative development of a preliminary paper-based reporting form, which we will then pilot test with providers in a real-world setting.

Results: This is an ongoing project with results being published as analyses are completed. The systematic review has been completed; field observations, focus groups, and pilot testing of a preliminary paper-based design are ongoing. Results will inform the development of software that will enable clinically useful user-friendly documentation and communication of ADEs.

Conclusions: We take this approach with the recognition that information technology-based solutions in health care often fall short of expectations as a result of designers' failure to account for organizational and work practice considerations, and the needs of end-users. We describe how integrating qualitative methods into an iterative participatory design process (planned in partnership with end-users) will allow us to address specific clinical needs, conceptualize linkages between systems, integrate the reporting system into clinicians' workflow, and design the system to optimize its uptake into practice.

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KEYWORDS

adverse drug event; adverse drug reaction reporting systems; health services research; action research; qualitative research; user-centered design; methods; focus groups; systematic review

Introduction

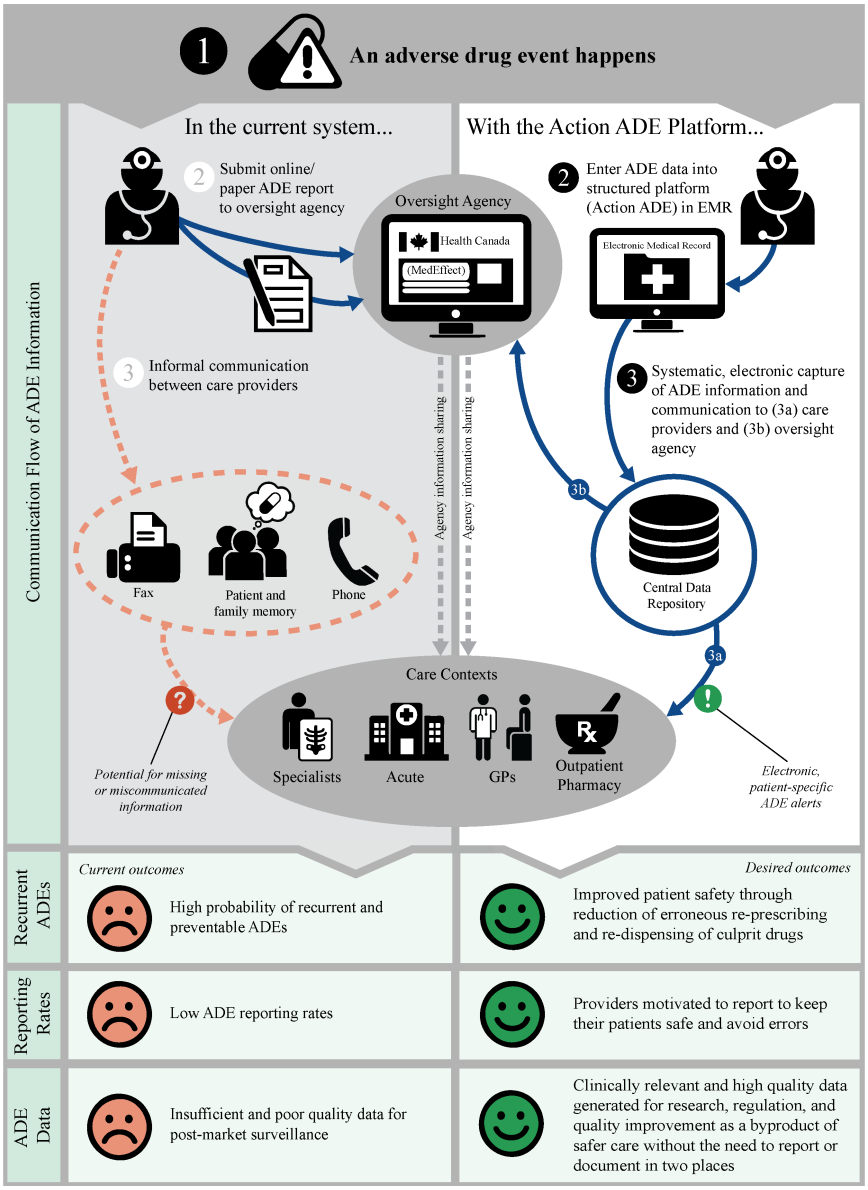
Adverse drug events (ADEs) are unintended and harmful events associated with medication use, and represent a leading cause of ambulatory and emergency department visits and unplanned hospital admissions [1-4]. Prospective studies have consistently identified 30-70% of clinically significant ADEs as preventable [4-6], making the development, implementation, and evaluation of effective preventative strategies a public health priority [7]. To date the development of effective preventative strategies has been challenged by a lack of robust epidemiological data on patient and system-level risk factors for ADEs as well as the heterogeneity of clinical events observed. However, a prospective study enrolling a cohort of elderly patients admitted to hospital for an ADE indicated that a surprising 27% of patients were unintentionally reexposed to the culprit drug (the drug that caused the index ADE) within only six months of the initial event [8]. Similarly, Australian data indicate that up to 30% of ADEs requiring hospital admission consist of repeat events [9]. These data indicate that health systems interventions aimed at reducing repeat ADEs, regardless of their categorization or severity, may represent a high-yield area for prevention.

Poor documentation and lack of communication of ADE information between care providers, and across health care settings, are likely to contribute to frequent represcribing and redispensing of culprit drugs [10]. When examining health systems in which patients have multiple prescribers, it is clear that medical records are often fragmented and linkages between electronic resources remain inadequate. Crucial information regarding ADEs and high-risk medical conditions (eg, long QT syndrome) may remain elusive to care providers that prescribe and dispense drugs [10]. ADE documentation within electronic medical records (EMRs) has historically been limited to allergies, even though the majority of ADEs are not related to allergies (eg, medication-induced delirium, bleeding events) [3-4]. Most EMRs have not developed standardized, structured, user-friendly, and succinct data entry options for these types of events [11]. Even if information on ADEs is present within an EMR, it can be easily overlooked, as the information is often in lengthy free-text formats, buried within historical notes, and cannot be used to generate automated alerts that might remind the care provider of prior ADEs at the point of prescribing. Finally, these fields have not been configured to facilitate communication between care providers within, or across, health care settings (eg, between family physicians and community pharmacists).

Electronic ADE documentation currently occurs within online reporting systems hosted by organizations external to care delivery (eg, the United States Food and Drug Administration). Such reporting websites collect ADE data for post-market surveillance and research. Although this documentation is structured and somewhat standardized across systems, it is cumbersome and time-consuming to enter such information into existing systems. The resulting reports are used for research and regulatory purposes only, and cannot be accessed to support clinical care decisions or communication between health professionals [12]. ADE reporting within these websites is disconnected from the needs of clinical care providers, and clinicians rarely report such events, as immediate patient care-related activities supersede the data request of external agencies [13].

If ADE reporting can be refocused to meet the documentation, communication, and patient safety needs of the clinicians who diagnose and treat ADEs at the point-of-care, and *hold* information about these events, clinicians may be more willing to document harmful events. Transforming the purpose of structured formal ADE reporting, from generating health data to improving clinical care by preventing recurrent events, may not only improve patient safety, but may yield *more* representative and higher quality reporting (and thereby generate more robust ADE data). Our main goal is therefore to design a patient-oriented and provider-centered ADE reporting system that is fully integrated into an EMR. Ideally, this system will be used by clinicians to facilitate ADE documentation and information flow between care providers and across health sectors (eg, between ambulatory care settings, hospitals, and community pharmacies) to prevent unintentional reexposures to harmful drugs (see Figure 1). A secondary goal is to use the structured ADE reports to generate improved health data on both known and novel ADEs for drug safety surveillance and research. We are not aiming to circumvent or replace the activities of pharmacosurveillance agencies, but rather to provide such agencies and other researchers with a novel source of rich ADE data. The objective of this paper is to describe the methods we plan to use to design the ADE reporting system, which we call *Action ADE*.

Figure 1. Adverse drug event information flow - existing versus with Action ADE.

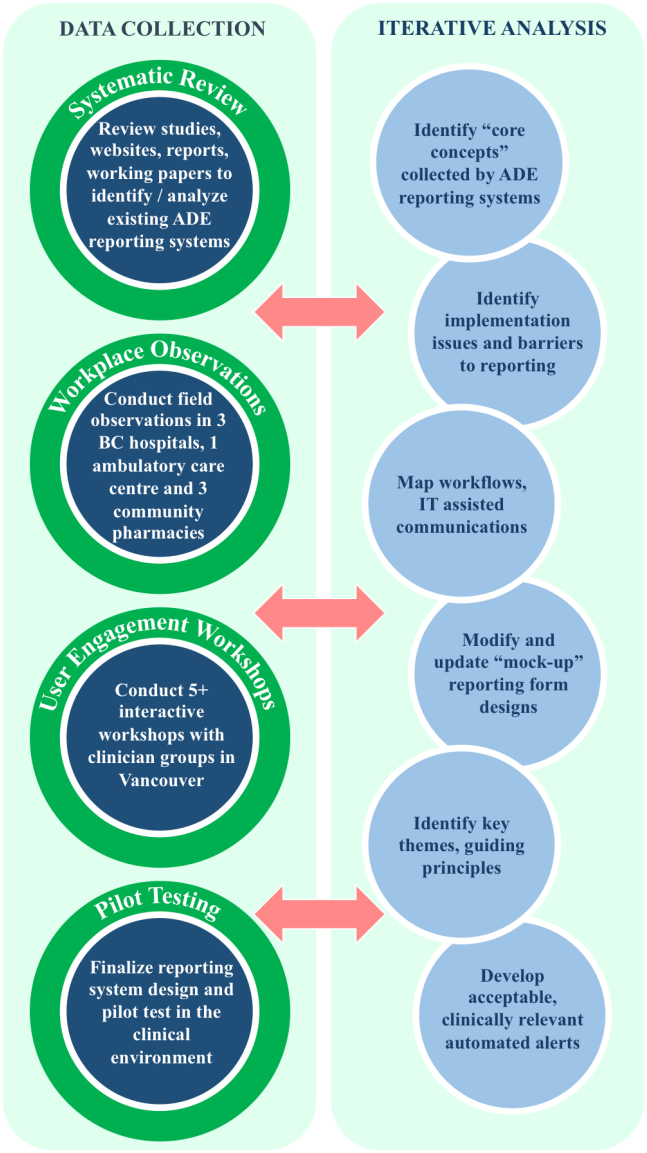


Methods

Approach

We will use action research and participatory design principles to develop a novel electronic ADE reporting interface. Action research involves teams of researchers and practitioners that incorporate various methods (eg, workplace observations, interviews, and focus groups) to integrate the perspectives of practitioners into innovative solutions for practical problems [14]. Incorporating principles of participatory design will allow us to ensure that our design reflects *observed actual* rather than *assumed* practices [15,16]. We anticipate that this approach will allow us to maximize the system's user-friendliness, utility, and uptake into clinical practice. Figure 2 outlines the data collection and analysis activities that are planned for this study.

Figure 2. Planned data collection and analysis activities.



Systematic Review

Our first step will be to complete a systematic review of existing ADE reporting systems [12,17]. Our goal is to identify how (and precisely which) ADE data are currently being solicited, and in what format and sequence ADE data are being collected. These findings will provide us with a foundation from which to propose a complete set of data fields for a future reporting system, to ensure that all relevant fields are considered.

We will begin by completing an environmental scan of the literature and developing a systematic search strategy. We will complement a bibliographic reference database search with a grey literature search, including a search of websites of pharmacovigilance organizations, to identify current ADE reporting systems internationally. The search will include qualitative and quantitative studies, government reports, working papers, and websites describing or hosting reporting systems for ADEs in humans. Reporting systems that focus only on errors or allergies will be excluded, along with registries that are specific to a single medication or class of medications, or a single disease state. Two authors will independently review all sources for inclusion and exclusion criteria, and then abstract data from all included systems. The extracted data will be exported into visual thinking software *Inspiration 9.2* to allow us to visualize and sort information pertaining to the data fields, structure, and dictionaries used by each system. When using *Inspiration 9.2*, each extracted data field will appear as a single bubble containing the label of the individual data field within the reporting system, and the number of times we encountered the same data field across systems. We will then sort the individual data fields into overarching reporting concepts and, in a second iteration, all duplicate (or very similar) data fields will be eliminated. During a third sort, relationships and hierarchies between the reporting fields and concepts will be identified.

This process will allow us to distill a compendium of data fields from individual reporting systems into a list of *core fields* which are currently used to communicate ADE content in existing reporting systems. We will then develop a preliminary ADE reporting form, using all core fields that we have identified.

Observational Fieldwork

In parallel to our systematic review, we will conduct observational fieldwork to observe physicians and pharmacists in settings with patients who commonly experience ADEs. This approach will allow us to gain an understanding of clinical workflow, the work environment, how ADEs are diagnosed, documented, and become reportable, and barriers to reporting. Furthermore, this approach is useful for understanding users' actual needs, and the context in which the technology will be integrated, rather than relying on intuition and untested assumptions [18-20]. For example, we might gain insight into the collaborative nature of ADE diagnosis, make tacit elements of work explicit, and show the differences between how work is conceptualized as opposed to how it actually unfolds in real-life (eg, using spontaneous problem-solving processes) [15]. In addition, our fieldwork will allow us to observe the roles of relevant actors and artefacts that might otherwise go unnoticed and not be considered in our design, especially those resources used to gather and document information that contributes to medication management decisions.

Our team will conduct observations in the emergency departments and on the wards of two urban tertiary hospitals and one urban community hospital, in one rural ambulatory care center, and in three community pharmacies in British Columbia, Canada. Researchers will shadow clinical pharmacists, nurses, and physicians at various times of the day (and days of the week) to account for changing levels of activity and work procedures over time. Study participants will include a convenience sample of practitioners recruited through the contacts of the practicing clinicians on our team, and those on shift at the time of scheduled data collection shifts. Our observations will focus on (1) the setting, (2) patient presentations in which ADEs are suspected, managed, and documented, (3) artifacts that mediate the work (eg, medication reconciliation forms), (4) activities that constitute work (eg, obtaining a medication history), and (5) information flow between clinicians. Two researchers will independently code observation notes using the qualitative data analysis software *NVivo 10*, and iteratively review the data with attention to emerging trends and concepts. Upon initial review, our team will develop a formal coding structure while ensuring consistency between coders. As coding progresses, we anticipate the need to discuss emerging findings in team meetings, and will use analytic exercises, including situational maps (a set of visual thinking exercises for interrogating qualitative data [21]), workflow diagrams, information flow maps, and event summaries to explore our findings.

Participatory Workshops

Our team will synthesize information from our systematic review and field observations to create a preliminary ADE reporting form. This form will take into account all relevant data fields identified in our systematic review, the sequence in which documentation can best be adapted to the workflow observed in our fieldwork, and required linkages to other information sources. We will generate the preliminary form using *Microsoft Visual Basic for Applications* so that it has the appearance of a computer screenshot. This template will enable clinicians to imagine how the reporting interface might look. The first iteration of the form will be a *maximum* form containing data fields that reflect all core reporting concepts that were encountered in our systematic review. We will use this template as a starting point to engage with clinician end-users, in order to obtain feedback and refine the form.

We will conduct a minimum of five participatory workshops with different clinician groups (emergency physicians, family physicians, hospitalists or internists, hospital pharmacists, and community pharmacists) in which we will present ADE cases along with the preliminary ADE form, in order to stimulate discussion. These workshops will create opportunities for bottom-up collaborative design, in which future end-users can choose between design alternatives, highlight perceived challenges and opportunities, propose solutions, and point to issues that we may not have identified. Unlike observational or interview settings, workshops will allow participants to develop their views in concert with their peers through discussion, challenging their personal assumptions and introducing perspectives that they may not have previously considered [22].

We will hold workshops during lunchtime professional rounds for groups practicing in hospitals, and advertise via posters and email invitations. For participants practicing outside of hospitals, we will hold workshops in the evenings and recruit clinicians through verbal communication, posters, and email invitations. Each workshop will begin with an informal survey of the participants to gather information on their practice setting, the information systems they use, and the participants' concerns related to ADE documentation and communication. Using the forms and a wide range of ADE cases from our observations as examples, we will ask participants to highlight the data they feel must be documented, and where and how it should be documented. We will note aspects of the form that they find useful or problematic, and ideas about how the form might be improved. After each workshop, we will revise the ADE form to incorporate the end-users' feedback, in order to create the next version of the form that will be presented in the following workshop. We will create a log of changes to the form, including a rationale for each change. Workshops will continue until the form is acceptable to the groups involved, and no novel suggestions or concerns are being raised.

Paper-Based Pilot Testing

Once a mature paper-based design is established, we will pilot the form in the clinical setting prior to building it in electronic format. Our main goal is to test the content, functionality, and clarity of the form. We will observe how reporters access information sources while completing the form to understand the links between our form and other electronic systems. This approach will allow us to address required revisions that could not be anticipated during the workshops, and consider linkages between systems that must be established prior to the electronic build. We anticipate that paper-based pilot testing will allow us to propose a more mature design, and introduce revisions at lower cost, than if revisions were required after all programming costs have been incurred.

We will conduct semi-structured interviews and use *lightweight ethnography* (a methodology that allows for collection of specific and relevant information, while accepting that a

complete understanding of a work setting may not be needed [23]) to observe clinicians completing the forms. This approach is ideally suited for pilot studies, as it can rapidly and efficiently provide guidelines for technology design.

Study participants will consist of a convenience sample of clinical pharmacists that will be recruited through team contacts, specifically via verbal communication and email invitations. During 2-4 hour shifts, a research assistant will shadow participants in two hospital settings that commonly encounter patients with ADEs. The research assistant will provide pharmacists with a paper version of the ADE reporting form and ask them to complete it should they encounter an ADE. The research assistant will observe the participants completing the form, and collect additional information about the ADE, workflow, and any comments and impressions about the reporting form. Coding and analysis of qualitative data from field notes will be conducted in the same manner as the observational fieldwork. We will produce descriptive statistics to summarize the completeness of data entry regarding individual data fields and the form as a whole.

Development of Automated Alerts

Once a paper-based ADE reporting form has been established, with a robust set of data fields making up the *input* into the reporting system, we will develop our system's *output*. Output screenshots are those through which an ADE will be flagged when attempts are made to represcribe or redispense a culprit drug (or drug of the same class). The output will be integrated into the patients' EMR, and communicated to and stored in PharmaNet, British Columbia's electronic outpatient drug dispensing database. By storing alerts in patients' PharmaNet profiles, we will be able to communicate alerts to care providers (with access to PharmaNet) who practice outside of the institution in which the ADE was diagnosed. Such providers include family physicians, who usually practice in offices without access to hospital EMRs, as well as community pharmacists who must enter dispensed drugs into PharmaNet for reimbursement purposes.

Alert functions can be valuable tools in health care. However, when alerts are too frequent, not specific enough (eg, flagging many clinically irrelevant events), or integrated poorly into clinical information systems, they may impede and complicate clinical work, or contribute to alert fatigue. Alert fatigue occurs when clinicians are bombarded with irrelevant or obvious alerts that they learn to bypass, override, or ignore [24]. Thus, we will avoid generic alerts that are not specific to individual patients (eg, drug interactions) by generating alerts for serious and confirmed ADEs that will only be flagged for the specific patient in whom the ADE was reported, and only when the culprit drug or drug class is represcribed or redispensed.

To ensure that ADE alerts communicate the correct information in a timely and appropriate manner, we will use workplace observations and participatory workshops (as previously described) with an emphasis on providers in outpatient settings, who would receive ADE alert outputs (eg, family physicians and community pharmacists). The same methods will be used for recruitment, scheduling of data collection shifts, and analyses, and will focus on the content and display of ADE information, and when/how alerts should be integrated into clinical workflow. Using the ADE data elements from our ADE reporting form (ie, the input), and our workplace observations, we will design preliminary ADE alerts (ie, the output). Participatory workshops will facilitate the creation of preliminary ADE alerts, and participants will highlight the data that they feel is required, along with any display modification suggestions or issues with missing information. We will note any ideas that might improve the alerts, and after each workshop we will revise the ADE alerts to incorporate the end-users' feedback, in order to optimize the form that will be presented in the following workshop. Again, workshops will be held until the ADE alerts are acceptable to the groups involved, and no novel suggestions or concerns are being raised.

Results

This is an ongoing project, with results being published as analyses are completed. The systematic review of existing ADE reporting systems has been completed and published [12]. Further data collection (field observations, focus groups, and pilot-testing) has begun, preliminary analyses are underway, and results are to be expected in 2016-2017. These results will inform the design of a clinically useful and user-friendly platform for communicating ADEs. The platform will be systematically evaluated beginning in 2017.

Discussion

Study Rationale

Existing ADE reporting systems have been designed at a distance from use, with limited clinician end-user input. Current systems have focused on the data needs of organizations engaged in medication safety surveillance, rather than the information needs of clinical care providers who diagnose and treat patients with ADEs. Research from multiple jurisdictions has consistently revealed that clinicians are simply not using these systems, as the act of reporting is perceived as irrelevant to clinical care delivery, and systems are cumbersome to use and not integrated into current electronic information systems [25]. As a result, the vast majority of ADEs (even serious events) remain unreported, and are not reflected in current health data that are used by pharmacovigilance and research organizations that examine drug safety. Preventable ADEs go unaddressed, to the detriment of patients, the health care system, and taxpayers.

Our work addresses a methodological gap in the way that ADE reporting systems (and other health information technology systems) have been conceptualized, designed, and implemented. Given the recognized limitations of the current state of ADE reporting, innovations have been proposed by others. However, these innovations preserve the data-centric orientation of the current system. Some studies, for example, have suggested using administrative data or mining EMRs for signals to identify harmful events [26,27], although validation studies have indicated that these methods have poor sensitivity for identifying relevant ADE outcomes [28,29]. Other studies have pointed to the value of expanding the role of patient reports, yet there has been little formal evaluation of patient reporting, and reporting

rates among patients remain low [30,31]. Studies that have examined underreporting and initiatives to improve reporting have rarely scrutinized systems issues, instead focusing on the users. The results of these studies attribute shortcomings to poor user knowledge, attitudes, workplace culture, professional priorities, incentives, and media influence [13,32]. Studies have generally failed to question the current data-centric orientation of reporting systems, examine system shortcomings, or propose ways to redesign reporting so that it may complement and facilitate components of clinical care, in addition to meeting the data needs of external organizations.

In contrast to previous studies and prior interventions that attempted to address underreporting, we suggest that it is not the end-users that need to be *fixed* through more education, enticement, or enforcement, but rather that the work practices and technologies that support their work need to be altered. The conscious work of end-users cannot be replaced by analyzing traces of data left as documentation within medical records that were never specifically intended to capture robust ADE information [28,29]. Instead, we stress the need to rethink the rationale and systems designed for reporting ADEs. If clinicians are going to supply the information-reporting that systems seek to capture, we must prioritize the design of such systems so that they work for clinicians, enabling them to meet their care delivery goals of safer and more efficient care for patients.

Medical disciplines have generated little or no discussion about what, if any, research evidence should be used to inform the design of information technology systems that may have a profound impact on health services delivery. The use of qualitative observational data (including information from end-user engagement) in designing information technologies has gained popularity in the last 25 years in computer and information sciences [33]. Despite the promise that such approaches hold, their uptake in medical communities has been slow, and is likely related to assumptions that frame the design of health information technologies as exclusively a *technical* problem [19,34,35]. The claims for technologies such as EMRs, automated decision support, or computerized physician order entry–that they will increase efficiency, support decision-making, reduce errors, and standardize information–are often taken as self-evident [19]. The benefits are simply presumed to follow logically from implementation, and coupled with this assumption is the notion that staff and clinical practices will *adapt* to new technology [34].

In practice, however, the success of a new technology often hinges on how well it is integrated into organizational and clinical practice, and whether it meets the needs of end-users [19,34,35]. In order to optimize user-friendliness, functionality, and uptake, methods are needed to bring rigor, robustness, and accountability to this process. Importantly, these methods must allow for meaningful engagement with clinician-users in the design, evaluation, and implementation phases, and should include observational methods to identify differences between actual and perceived work practices. The methods we outline in this paper offer an example of how qualitative research methods may be integrated in an iterative fashion to meet this need. Elements of a systematic review can be used to ensure that an information technology design begins from a complete account of systems in existence (including non-electronic formats). From this starting point, designers may choose from a variety of observational and participatory design methods to generate further evidence to inform system design. This approach may be used to reinvent existing information systems that, over time, have become part of a *de facto* and perhaps antiquated infrastructure [36].

Limitations

Careful methodical design does not guarantee uptake into clinical practice. Therefore, our work must continue after the intervention has been introduced, and include evaluation and refinement of the design, and knowledge dissemination to end-users. To foster successful uptake, we must first support the design stages with training, education, program evaluation, and refinement of the interface. Second, the introduction of any reporting system will be perceived as an additional burden of documentation on clinicians, whose priority remains patient care. Accordingly, the introduction and adaptation to a new electronic documentation platform is likely to be met with some resistance, and any added documentation must be minimized. We hope that our collaborative approach will help mitigate this resistance by making this documentation practical for clinicians and their patients, and help clinicians meet patient safety goals. Third, shifting communication between practitioners regarding ADEs to an automated platform carries the risk of reducing verbal communication. While verbal communication about ADEs is presently inadequate, we need to be attentive to how an intervention might negatively affect collaborative practice to the extent that it currently exists. Fourth, the dissemination of unverified ADE information among care providers introduces a number of concerns, such as data reliability (eg, false positives), patient privacy, and provider liability. These serious issues must be evaluated during and after implementation, along with our assumptions that the *Action ADE* system might improve reporting rates, prevent recurrent events, and provide higher-quality data.

These concerns will be the foci of future phases of our work that will be devoted to the implementation and evaluation of the system. Finally, our research will be undertaken in the health care environment in British Columbia, Canada, with specific provider groups, and will be influenced by specific contexts that will be encountered. Successful integration of this tool into other settings will require consideration of (and adaptation to) local exigencies and concerns, will require collaboration with teams in other settings, and involve tailored education and implementation. To address these issues, we plan to carry out work in additional communities of practice to ensure that our design is relevant across multiple health care environments.

Conclusion

In this paper, we have outlined an action research and participatory approach to designing a novel, provider-centric reporting tool to capture and share information about ADEs experienced by patients, in order to reduce the likelihood of ADE recurrence. This approach may be useful in enhancing patient safety, while generating robust and representative data on ADE outcomes for drug safety and effectiveness research and regulation. As policies and practices shift to accommodate

new federal laws that mandate the reporting of all serious adverse drug reactions in Canada, our work may offer a model for how technological innovation in health care systems design can be planned in partnership with health providers.

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Conflicts of Interest

None declared.

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Abbreviations

ADE: adverse drug event
EMR: electronic medical record

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Original Paper

Telemedicine in Neonatal Home Care: Identifying Parental Needs Through Participatory Design

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Abstract

Background: For the majority of preterm infants, the last weeks of hospital admission mainly concerns tube feeding and establishment of breastfeeding. Neonatal home care (NH) was developed to allow infants to remain at home for tube feeding and establishment of breastfeeding with regular home visits from neonatal nurses. For hospitals covering large regions, home visits may be challenging, time consuming, and expensive and alternative approaches must be explored.

Objective: To identify parental needs when wanting to provide neonatal home care supported by telemedicine.

Methods: The study used participatory design and qualitative methods. Data were collected from observational studies, individual interviews, and focus group interviews. Two neonatal units participated. One unit was experienced in providing neonatal home care with home visits, and the other planned to offer neonatal home care with telemedicine support. A total of 9 parents with preterm infants assigned to a neonatal home care program and 10 parents with preterm infants admitted to a neonatal unit participated in individual interviews and focus group interviews, respectively.

Results: Three overall themes were identified: being a family, parent self-efficacy, and nurse-provided security. Parents expressed desire for the following: (1) a telemedicine device to serve as a “bell cord” to the neonatal unit, giving 24-hour access to nurses, (2) video-conferencing to provide security at home, (3) timely written email communication with the neonatal unit, and (4) an online knowledge base on preterm infant care, breastfeeding, and nutrition.

Conclusions: Our findings highlight the importance of neonatal home care. NH provides parents with a feeling of being a family, supports their self-efficacy, and gives them a feeling of security when combined with nursing guidance. Parents did not request hands-on support for infant care, but instead expressed a need for communication and guidance, which could be met using telemedicine.

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KEYWORDS

preterm infant; telemedicine; participatory design; neonatal home care

Introduction

Overview

Birth below 37 weeks of pregnancy requires admission to a neonatal intensive care unit (NICU), which can have long-term impacts on the family. A growing body of literature recognizes the importance of family-centered care (FCC) in the NICU [1]. However, having an infant in the NICU is still stressful because mothers have difficulty bonding with their infants and have feelings of not being a parent [2-3]; also, parents must divide

their time between the NICU and home [4], especially when there are other children in the family [5]. For the majority of preterm infants, the last weeks in the NICU involve tube feeding and establishment of breastfeeding [4-5]. Establishment of breastfeeding is challenging, lasts several weeks, and cannot be accelerated because it depends on infant maturity [4-5]. Neonatal home care (NH) was developed to meet FCC requirements and optimize family conditions at this time [4,6-9]. NH allows infants to remain at home for tube feeding and establishment of breastfeeding [9]; this occurs with regular home visits from neonatal nurses until the infant can eat and gain weight without supplemental tube feeding, meeting criteria for discharge. NH seems to increase breastfeeding rates [8,10], increase parent self-confidence, support early family formation [11], and provide the benefits of FCC [9]. Thus, NH can provide a desirable transition from the NICU to home for preterm infants and their parents. However, for hospitals covering large regions, home visits may be challenging, time consuming, and expensive and alternative approaches must be explored. In the current health care environment, the need to reduce overall costs despite increasing admissions has led to treatments moving from the hospital to the home, and telemedicine provides a further opportunity to reduce costs [12]. Decreasing costs in the neonatal field is crucial [13-14] and early discharge is one approach. This study was the first to investigate whether telemedicine could provide a viable alternative to home visits. Despite little research on telemedicine in the neonatal field [15], one study has shown telemedicine to offer a communication platform between the NICU and the home and to provide parental satisfaction [6].

Aim

The aim of this study was to identify parental needs when preterm infants receive NH with telemedicine support.

Methods

Design

User involvement in health care research is important [16], especially when developing new health technologies, such as telemedicine. Such involvement is imperative to ensure that these technologies meet the needs of the users [17-20]. This study employed a participatory design (PD) approach. PD is typically carried out in three phases [17-18]; this article reports on interviews and focus group interviews from Phase 1. The next steps will be to develop a telemedicine solution (Phase 2), addressing the needs identified in this study, and to implement that solution (Phase 3), which will be the topic of future papers.

Setting and Participants

Parents with preterm infants admitted to two NICUs (see Table 1)—Hvidovre Hospital (HH) and Hans Christian Andersen Children's Hospital (HCA)—participated in this study (see Table 2). HH has experience in providing NH with home visits and HCA planned to offer NH with telemedicine support.

Table 1. Characteristics of neonatal intensive care units involved in the study.

Characteristics	Hvidovre Hospital	Hans Christian Andersen Children's Hospital
Associated hospital	Copenhagen University Hospital	Odense University Hospital
Location	Capital region	Region of Southern Denmark
Type of unit	Neonatal intensive care unit	Neonatal intensive care unit
Neonatal home care experience	Experienced in providing neonatal home care with home visits	Planning to offer neonatal home care with telemedicine

Data Collection

Observational studies, individual interviews, and focus group interviews were conducted. The observational studies monitored the dynamic and actions during NH home visits, following recommendations from Spradley [21]. Based on the observational study, a semistructured interview guide inspired by Malterud [22] and Kvale [23] was developed to interview parents of preterm infants assigned to NH from the NICU at HH. These interviews aimed to identify parent experiences with NH and home visits, including the meeting content and meaning. The four themes of the interviews were as follows: home visits, parent self-efficacy, nutrition/breastfeeding, and family life. From December 2014 through January 2015, the first author (KG) interviewed parents in their homes while their preterm infants received NH.

Parallel to the interviews, two focus group interviews were conducted with parents whose preterm infants were admitted to the NICU at HCA who fulfilled the inclusion criteria for NH, which were as follows: (1) stable infant without need to monitor vital signs, (2) minimum age equivalent of 34 weeks, and (3) tube feeding required. Both primiparous and multiparous parents were included in the focus group interviews. The focus group interviews aimed to identify norms, ideas, and practices [22]. Themes were as follows: the last weeks in the unit, nutrition/breastfeeding, and needs when receiving NH supported by telemedicine.

The first (KG) and fourth (JC) authors led the focus group interviews. Field notes were taken by the fourth author (JC) during the interviews. All interviews were recorded and fully transcribed by the first author (KG). A total of 9 parents participated in an individual interview, and 10 parents participated in focus group interviews (see Table 2). Interviews lasted 34-70 minutes, and focus group interviews lasted 86-99 minutes.

Analysis

Interview data were analyzed using Malterud's systematic text condensation [24], which consists of four steps (see Table 3) as follows: (1) read transcripts repeatedly to identify themes, (2) identify and code units of meaning, (3) identify subgroups of codes from step 2 and develop condensates from them, and

(4) describe experiences based on the condensates [24]. To have multiple perspectives during the first process of the analysis, the first (KG) and second (AB) authors individually extracted themes from the individual interview and focus group interview transcripts. These themes were triangulated and a consensus was reached. The first author (KG) completed steps 2-4, and the final product was approved by all authors.

Table 2. Demographic data for parents and infants (n=19).

Demographic information	Hvidovre Hospital (n=9)	Hans Christian Andersen Children's Hospital (n=10)
Mothers, n (%)	5 (56)	7 (78)
Mothers' age in years, range	25-41	24-36
First-time mothers, n (%)	3 (33)	4 (44)
Mothers' education, n (%)		
Student	0 (0)	1 (11)
10-13 years	2 (22)	2 (22)
>13 years	3 (33)	4 (44)
Fathers, n (%)	4 (44)	3 (33)
Fathers' age in years, range	28-40	26-36
First-time fathers, n (%)	2 (22)	3 (33)
Fathers' education, n (%)		
Student	0 (0)	2 (22)
10-13 years	2 (22)	0 (0)
>13 years	2 (22)	1 (11)
Infants' information, range		
Gestational age(weeks+days)	28+5-34+4	30+4-35+3
Birth weight (grams)	1100-2375	875-2550

Table 3. Example of the analytical process[a].

Setting and initial themes	From themes to codes		Subcategories	Overall category
	Quotes	Codes		
Hans Christian Andersen Children's Hospital				
Family conditions	"Out here you are a part-time family and that's the way it will be" (Father #5).	Families were separated during their infant's admission and it affected their perception of being a new family.	Separation of families	Being a family
Being away from home	"It lasted for so long [breastfeeding establishment], because everything went so slowly. We had been here for so long that we could do all the things the nurses did, so you felt you wasted your time and would have benefitted from being home" (Mother # 6).	Families felt staying in the neonatal unit during breastfeeding establishment was a waste of time and that made them long for home.	Longing for home	Being a family
Hvidovre Hospital				
Paternal role	"When I got there [to the NICU[b]] the time was so short that is was a lot of work for a one-hour visit. I'm now a dad rather than being a helper. Definitely" (Father #1).	Fathers experienced that NH[c] gave them possibilities of fathering their infants.	Room for fatherhood	Being a family
Daily life	"Obviously, we can do our own things; we are not just sitting in the hospital. Now we can carry on, do what we want and get on with our lives" (Father).	Families experienced a return to their daily life. Further NH brings calmness to the family being at home instead of in the hospital. They feel it is better to be home.	Own surroundings brings comfort	Being a family

[a]The four-step analytical process [24]: (1) withdrawing themes, (2) identifying meaning of units and coding them, (3) identifying different subgroups, and (4) description of experiences based on the subcategories.

[b]NICU: neonatal intensive care unit.

[c]NH: neonatal home care.

Ethics

According to the Declaration of Helsinki, respondents received written and oral information about the study and provided signed consent. They could withdraw consent at any time with no consequences for future treatment of themselves or their infants. The study was approved by the Danish Data Protection Agency (2008-58-0035). The study was presented to the local ethics committee, but their review was deemed to not be required by Danish law.

Results

Analysis of the individual interviews and focus group interviews identified the following three categories: being a family, parent self-efficacy, and nurse-provided security.

Being a Family

Parents expressed that the admission of their preterm infant to the NICU negatively affected being a new family, because they felt separated; only mothers were allowed to stay 24 hours per day with their infant. As one father stated, "Out here you are a part-time family and that's the way it will be." Many mothers were frustrated that their husbands could not spend the night, because they needed their support and wanted to share the experience.

Parents felt that staying in the neonatal unit with a healthy preterm infant for tube feeding and establishment of breastfeeding was not necessary:

> *It [establishment of breastfeeding] lasted for so long because everything went so slowly. We had been here for so long that we could do all the things the nurses did, so you felt you wasted your time and would have benefitted from being home.* [Mother #6]

Finally, parents felt trapped by the physical environment of the neonatal unit where strict hygiene rules required them to ask nurses for diapers, washcloths, and other basics required for infant care. This gave them a feeling of dependency on the nurses, which they disliked.

Parents with a preterm infant assigned to NH expressed that the NH supported their perception of being a family. There were overall positive effects of NH, including a feeling of calm for the entire family. One father stated the following:

> *Obviously, we can do our own things; we are not just sitting in the hospital. Now we can carry on, do what we want and get on with our lives.* [Father #1]

Parents were relieved to be in charge and not to have to adapt to hospital rules. For families with other children, NH allowed them to get back to being a normal family. For men, NH provided the opportunity to father their infants, becoming more

familiar with their noises and cries, which they did not observe while their infants were in the hospital. One father stated the following:

> *I had no time with my daughter [in the NICU] because when I got there, the time was so short that it was a lot of work for a one-hour visit. I'm now a dad rather than being a helper.*

Parent Self-Efficacy

Parents with infants in the NICU felt that the constant presence of nurses negatively affected their decision making. When nurses entered the room to help the parents, it made parents doubt their competence instead of supporting their self-efficacy. One mother stated the following:

> *Today, for example, when they [twins] needed a bath, a nurse came in and said, "Shouldn't I help you?" It makes me insecure. Can't I do that myself?*

Parents receiving NH experienced an increase in their self-efficacy by being at home and parent-infant bonding was further strengthened:

> *Being home means that you bond with your child because when you are in the hospital among professionals, you get the feeling that they are more capable of caring for him, and that others are better at taking care of your child is a terrible feeling. Here at home, we are absolutely the best at caring for him, which gives us a totally different feeling.* [Mother #2]

Nurse-Provided Security

Parents with infants in the NICU were happy with guidance from nurses when establishment of breastfeeding was prolonged. One mother stated the following:

> *There has been someone [a nurse] that has guided me all the way and said that it was okay, that breastfeeding establishment takes time.* [Mother #2]

Nurses also provided parents with a reassurance of normality:

> *I think it was important to know. Some kind of normality in such an abnormal situation.* [Mother #1]

Similarly, for parents of infants receiving NH, home visits from neonatal nurses gave them a feeling of security that the infant was doing fine:

> *If she didn't come, then I might look at him and say doesn't his belly looks a little dilated? The way that a professional sees him and says he is doing fine, is so fantastic.* [Mother #3]

Frequent professional eyes on the infants reassured parents that their infant was developing normally. For this reason, the parents suggested the use of a telemedicine device to serve as a "bell cord," giving 24-hour access to the neonatal unit. One father stated the following:

> *A video connection would be good if we needed the nurse to see some red spots on the baby or help with the tube, but it could also be by email, if you had a question for which you didn't need the answer right away, but just within a couple of hours.* [Father #3]

Timely email communication with the neonatal unit gives parents the opportunity to communicate when needed. This, combined with an online knowledge base regarding preterm infant care, especially breastfeeding and nutrition, would provide security and self-efficacy.

Discussion

Principal Findings

This study supports the use of NH because it gives parents the feeling of being a family and promotes their self-efficacy. NH provides parents with the guidance they need from the nurses when they do not require hands-on support.

Studies have demonstrated the importance of FCC when preterm infants are admitted to the NICU, showing positive effects on parent-infant relationships and parents' experience of being involved in infant care [1,25]. Despite the NICU at HCA performing FCC, parents experienced a lack of involvement and questioned their own decision-making regarding infant care; the hospital environment and presence of health care professionals affected parents' thinking and actions. It has been shown that the NICU milieu can be a barrier for parent-infant bonding [26], contrary to NH [9-11]. Statements from parents with an infant receiving NH support the findings from Turner et al [26]: they experienced growing independence, increased decision-making, and a feeling of the infants as their children. When parents are successful in decision-making, it increases their self-efficacy [27] and they experience increased empowerment. The noisy, busy environment of the NICU is a barrier for establishment of breastfeeding [26] and is stressful for parents. Studies suggest that establishment of breastfeeding might benefit from NH [8-10], and parental responsibility for infant feeding and general care reduces parental stress [28].

Our findings revealed that nurse guidance of infant care, rather than hands-on support, provided a feeling of security. This supports telemedicine as an alternative to hospital admission. Gund found that video-conferencing could reduce the need for home visits and was less stressful than home visits [6]. However, Lindberg found that video-conferencing could not replace ordinary care [29]. This inconsistency may be explained by the 4-year time difference between these two studies, during which our adaption to technology has increased rapidly. The methods used in these prior studies are not in accordance with recommendations for implementing telemedicine in clinical practice today [30-31], since the users' needs were not identified before using telemedicine. Identifying needs of users before developing a telemedicine device can reduce the risk of implementation failure in clinical practice [31]. However, the findings in this study were in accordance with recommendations, and the development of a telemedicine device covering all parental needs is feasible.

Study Limitations

This study had a small sample size. Infant gestational age and birth weight varied, and the parents represented a heterogeneous group varying in age, education, and primiparous versus multiparous status. Individual interviews and focus group interviews were conducted until data saturation was reached

[22] and took place during NH and infant admission to the NICU, preventing recall bias.

Conclusions

These data highlight the importance of NH for preterm infants. NH provides parents with a feeling of being a family and supports their self-efficacy. Parents do not request hands-on support for infant care but feel safe with nurse-provided security. Parents also outlined the need for a technological "bell cord" if NH is to be supported by telemedicine, which would consist of the following: possibility for video-conferencing, timely written email communication, and a knowledge base of information regarding infant nutrition and breastfeeding.

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Authors' Contributions

KG obtained the required approvals for the study, recruited participants at HCA, conducted individual interviews and focus group interviews, and performed data analysis. JC participated in an observational study in the NICU and in the focus group interviews. AB participated in the first step of the analysis and, together with GZ, supervised KG throughout the study and agreed on the analysis and framework.

Conflicts of Interest

None declared.

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Abbreviations

FCC: family-centered care
HCA: Hans Christian Andersen Children's Hospital
HH: Hvidovre Hospital
NH: neonatal home care
NICU: neonatal intensive care unit
PD: participatory design

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